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	Application Number	
	Filing Date	
	First Named Inventor	Sydney Brenner
	Art Unit	
	Examiner Name	
	Attorney Docket Number	CGLC-020CON2

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	2	2007/018601	WO	A1	2007-02-15	RUBICON GENOMICS INC		☐

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	3	1841879	EP	A2	2007-10-10	POPULATION GENETICS TECHNOLOGI		☐
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	1	YAN, et al., "Rapid one-step construction of hairpin RNA", Biochemical and Biophysical Research Communications, (2009), 383:464-8.	☐
	2	PCT/IB2010/002243, International Search Report and Written Opinion, mailed February 9, 2011, 13pgs.	☐
	3	LAIRD, et al., "Hairpin-bisulfite PCR: Assessing epigenetic methylation patterns on complementary strands of individual DNA molecules" (2004) PNAS 101; 204-209.	☐
	4	USHIJIMA et al., "Detection and interpretation of altered methylation patterns in cancer cells" (2005) Nature reviews 5; 223-231.	☐
	5	IMBURGIO et al., "Studies of Promoter Recognition and Start Site Selection by T7 RNA Polymerase Using a Comprehensive Collection of Promoter Variants" (2000) Biochemistry 39; 10419-10430.	☐

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie, Reg. No. 48,920/	Date (YYYY-MM-DD)	2013-04-09
Name/Print	James S. Keddie	Registration Number	48920

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Electronic Patent Application Fee Transmittal	
Application Number:	
Filing Date:	
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	Sydney Brenner
Filer:	James Samuel Keddie
Attorney Docket Number:	CGLC-020CON2
Filed as Small Entity	

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Pages:				
Claims:				
Miscellaneous-Filing:				
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Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
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Electronic Acknowledgement Receipt

EFS ID:	15470267
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	Sydney Brenner
Customer Number:	93726
Filer:	James Samuel Keddie
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Attorney Docket Number:	CGLC-020CON2
Receipt Date:	09-APR-2013
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Application Type:	Utility under 35 USC 111(a)

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1		CGLC-020_Appln_fr_parent.pdf	311265 [illegible]	yes	43

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	Document Description	**Start**	**End**
	Specification	1	39
	Claims	40	42
	Abstract	43	43

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	Specification	2	2
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	Applicant Arguments/Remarks Made in an Amendment	6	7

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9	Information Disclosure Statement (IDS) Form (SB08)	CGLC-020CON2_IDS.pdf	613042 d0119ce7b1cc9069048d40a7811f5129fbcbadcb	no	5
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COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

BACKGROUND

We have previously described methods that enable tagging each of a population of fragmented genomes and then combining them together to create a 'population library' that can be processed and eventually sequenced as a mixture. The population tags enable analysis software to parse the sequence reads into files that can be attributed to a particular genome in the population. One limitation of the overall process stems from limitations of existing DNA sequencing technologies. In particular, if fragments in the regions of interest of the genome are longer than the lengths that can be sequenced by a particular technology, then such fragments will not be fully analyzed (since sequencing proceeds from an end of a fragment inward). Furthermore, a disadvantage of any sequencing technology dependent on fragmentation is that sequence changes in one part of a particular genomic region may not be able to be linked to sequence changes in other parts of the same genome (e.g., the same chromosome) because the sequence changes reside on different fragments. (See Figure 5 and its description below).

The present invention removes the limitations imposed by current sequencing technologies as well as being useful in a number of other nucleic acid analyses.

SUMMARY OF THE INVENTION

Aspects of the present invention are drawn to processes for moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide, also referred to as a "reflex method" (or reflex process, reflex sequence process, reflex reaction, and the like). In certain embodiments, the reflex method results in moving a region of interest into functional proximity to specific domain elements present in the polynucleotide (e.g., primer sites and/or MID). Compositions, kits and systems that find use in carrying out the reflex processes described herein are also provided.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is best understood from the following detailed description when read in conjunction with the accompanying drawings. It is emphasized that, according to common practice, the various features of the drawings are not to scale. Indeed, the

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dimensions of the various features are arbitrarily expanded or reduced for clarity. Included in the drawings are the following figures:

Figure 1: Panel A is a schematic diagram illustrating moving a first domain from one site to another in a nucleic acid molecule using a reflex sequence. Panel B is a schematic diagram depicting the relative position of primer pairs (A_n-B_n primers) that find use in aspects of the reflex process described herein.

Figure 2 shows an exemplary embodiment of using binding partner pairs (biotin/streptavidin) to isolate single stranded polynucleotides of interest.

Figure 3 is a schematic diagram illustrating an exemplary embodiment for moving a primer site and a MID to a specific location in a nucleic acid of interest.

Figure 4 shows a schematic diagram illustrating an exemplary use of the reflex process for generating a sample enriched for fragments having a region of interest (e.g., from a population of randomly fragmented and asymmetrically tagged polynucleotides).

Figure 5 shows a comparison of methods for identifying nucleic acid polymorphisms in homologous nucleic acids in a sample (e.g., the same region derived from a chromosomal pair of a diploid cell or viral genomes/transcripts). The top schematic shows two nucleic acid molecules in a sample (1 and 2) having a different assortment of polymorphisms in polymorphic sites A, B and C (A1, B1, C1 and C2). Standard sequencing methods using fragmentation (left side) can identify the polymorphisms in these nucleic acids but do not retain linkage information. Employing the reflex process described herein to identify polymorphisms (right side) maintains linkage information.

Figure 6: Panel A is a schematic showing expected structures and sizes of nucleic acid species in the reflex process; Panel B is a polyacrylamide gel showing the nucleic acid species produced in the reflex process described in Example 1.

Figure 7: Panel A is a schematic showing the structure of the nucleic acid and competitor used in the reflex process; Panel B is a polyacrylamide gel showing the nucleic acid species produced in the reflex process described in Example 1.

Figure 8 shows a flow chart of a reflex process (left) in which the T7 exonuclease step is optional. The gel on the right shows the resultant product of the reflex process either without the T7 exonuclease step (lane 1) or with the T7 exonuclease step (lane 2).

Figure 9 shows an exemplary reflex process workflow with indications on the right as to where purification of reaction products is employed (e.g., using Agencourt beads to remove primer oligos).

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Figure 10 shows the starting material (left panel) and the resultant product generated (right panel) using a reflex process without using a T7 exonuclease step (as described in Example II). The reflex site in the starting material is a sequence normally present in the polynucleotide being processed (also called a "non-artificial" reflex site). This figure shows that the 755 base pair starting nucleic acid was processed to the expected 461 base pair product, thus confirming that a "non-artificial" reflex site is effective in transferring an adapter domain from one location to another in a polynucleotide of interest in a sequence specific manner.

Figure 11 shows a schematic and results of an experiment in which the reflex process is performed on a single large initial template (a "parent" fragment) to generate five different products ("daughter" products) each having a different region of interest (i.e., daughter products are produced having either region 1, 2, 3, 4 or 5).

Figure 12 shows a schematic and results of experiments performed to determine the prevalence of intramolecular rearrangement during the reflex process (as desired) vs. intermolecular rearrangement (MID switching).

Figure 13 shows a diagram of exemplary workflows for preparing material for and performing the reflex process.

DEFINITIONS

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Still, certain elements are defined for the sake of clarity and ease of reference.

Terms and symbols of nucleic acid chemistry, biochemistry, genetics, and molecular biology used herein follow those of standard treatises and texts in the field, e.g. Kornberg and Baker, DNA Replication, Second Edition (W.H. Freeman, New York, 1992); Lehninger, Biochemistry, Second Edition (Worth Publishers, New York, 1975); Strachan and Read, Human Molecular Genetics, Second Edition (Wiley-Liss, New York, 1999); Eckstein, editor, Oligonucleotides and Analogs: A Practical Approach (Oxford University Press, New York, 1991); Gait, editor, Oligonucleotide Synthesis: A Practical Approach (IRL Press, Oxford, 1984); and the like.

"Amplicon" means the product of a polynucleotide amplification reaction. That is, it is a population of polynucleotides, usually double stranded, that are replicated from one or more starting sequences. The one or more starting sequences may be one or more copies of the same sequence, or it may be a mixture of different sequences. Amplicons

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may be produced by a variety of amplification reactions whose products are multiple replicates of one or more target nucleic acids. Generally, amplification reactions producing amplicons are "template-driven" in that base pairing of reactants, either nucleotides or oligonucleotides, have complements in a template polynucleotide that are required for the creation of reaction products. In one aspect, template-driven reactions are primer extensions with a nucleic acid polymerase or oligonucleotide ligations with a nucleic acid ligase. Such reactions include, but are not limited to, polymerase chain reactions (PCRs), linear polymerase reactions, nucleic acid sequence-based amplification (NASBAs), rolling circle amplifications, and the like, disclosed in the following references that are incorporated herein by reference: Mullis et al, U.S. patents 4,683,195; 4,965,188; 4,683,202; 4,800,159 (PCR); Gelfand et al, U.S. patent 5,210,015 (real-time PCR with "TAQMAN™" probes); Wittwer et al, U.S. patent 6,174,670; Kacian et al, U.S. patent 5,399,491 ("NASBA"); Lizardi, U.S. patent 5,854,033; Aono et al, Japanese patent publ. JP 4-262799 (rolling circle amplification); and the like. In one aspect, amplicons of the invention are produced by PCRs. An amplification reaction may be a "real-time" amplification if a detection chemistry is available that permits a reaction product to be measured as the amplification reaction progresses, e.g. "real-time PCR" described below, or "real-time NASBA" as described in Leone et al, Nucleic Acids Research, 26: 2150-2155 (1998), and like references. As used herein, the term "amplifying" means performing an amplification reaction. A "reaction mixture" means a solution containing all the necessary reactants for performing a reaction, which may include, but not be limited to, buffering agents to maintain pH at a selected level during a reaction, salts, co-factors, scavengers, and the like.

The term "assessing" includes any form of measurement, and includes determining if an element is present or not. The terms "determining", "measuring", "evaluating", "assessing" and "assaying" are used interchangeably and includes quantitative and qualitative determinations. Assessing may be relative or absolute. "Assessing the presence of" includes determining the amount of something present, and/or determining whether it is present or absent. As used herein, the terms "determining," "measuring," and "assessing," and "assaying" are used interchangeably and include both quantitative and qualitative determinations.

Polynucleotides that are "asymmetrically tagged" have left and right adapter domains that are not identical. This process is referred to generically as attaching adapters asymmetrically or asymmetrically tagging a polynucleotide, e.g., a polynucleotide

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fragment. Production of polynucleotides having asymmetric adapter termini may be achieved in any convenient manner. Exemplary asymmetric adapters are described in: U.S. Patents 5,712,126 and 6,372,434; U.S. Patent Publications 2007/0128624 and 2007/0172839; and PCT publication WO/2009/032167; all of which are incorporated by reference herein in their entirety. In certain embodiments, the asymmetric adapters employed are those described in U.S. Patent Application Ser. No. 12/432,080, filed on April 29, 2009, incorporated herein by reference in its entirety.

As one example, a user of the subject invention may use an asymmetric adapter to tag polynucleotides. An "asymmetric adapter" is one that, when ligated to both ends of a double stranded nucleic acid fragment, will lead to the production of primer extension or amplification products that have non-identical sequences flanking the genomic insert of interest. The ligation is usually followed by subsequent processing steps so as to generate the non-identical terminal adapter sequences. For example, replication of an asymmetric adapter attached fragment(s) results in polynucleotide products in which there is at least one nucleic acid sequence difference, or nucleotide/nucleoside modification, between the terminal adapter sequences. Attaching adapters asymmetrically to polynucleotides (e.g., polynucleotide fragments) results in polynucleotides that have one or more adapter sequences on one end (e.g., one or more region or domain, e.g., a primer site) that are either not present or have a different nucleic acid sequence as compared to the adapter sequence on the other end. It is noted that an adapter that is termed an "asymmetric adapter" is not necessarily itself structurally asymmetric, nor does the mere act of attaching an asymmetric adapter to a polynucleotide fragment render it immediately asymmetric. Rather, an asymmetric adapter-attached polynucleotide, which has an identical asymmetric adapter at each end, produces replication products (or isolated single stranded polynucleotides) that are asymmetric with respect to the adapter sequences on opposite ends (e.g., after at least one round of amplification/primer extension).

Any convenient asymmetric adapter, or process for attaching adapters asymmetrically, may be employed in practicing the present invention. Exemplary asymmetric adapters are described in: U.S. Patents 5,712,126 and 6,372,434; U.S. Patent Publications 2007/0128624 and 2007/0172839; and PCT publication WO/2009/032167; all of which are incorporated by reference herein in their entirety. In certain embodiments, the asymmetric adapters employed are those described in U.S. Patent Application Ser. No. 12/432,080, filed on April 29, 2009, incorporated herein by reference in its entirety.

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"Complementary" or "substantially complementary" refers to the hybridization or base pairing or the formation of a duplex between nucleotides or nucleic acids, such as, for instance, between the two strands of a double stranded DNA molecule or between an oligonucleotide primer and a primer site on a single stranded nucleic acid. Complementary nucleotides are, generally, A and T (or A and U), or C and G. Two single stranded RNA or DNA molecules are said to be substantially complementary when the nucleotides of one strand, optimally aligned and compared and with appropriate nucleotide insertions or deletions, pair with at least about 80% of the nucleotides of the other strand, usually at least about 90% to 95%, and more preferably from about 98 to 100%. Alternatively, substantial complementarity exists when an RNA or DNA strand will hybridize under selective hybridization conditions to its complement. Typically, selective hybridization will occur when there is at least about 65% complementary over a stretch of at least 14 to 25 nucleotides, preferably at least about 75%, more preferably at least about 90% complementary. See, M. Kanehisa Nucleic Acids Res. 12:203 (1984), incorporated herein by reference.

"Duplex" means at least two oligonucleotides and/or polynucleotides that are fully or partially complementary undergo Watson-Crick type base pairing among all or most of their nucleotides so that a stable complex is formed. The terms "annealing" and "hybridization" are used interchangeably to mean the formation of a stable duplex. "Perfectly matched" in reference to a duplex means that the poly- or oligonucleotide strands making up the duplex form a double stranded structure with one another such that every nucleotide in each strand undergoes Watson-Crick base pairing with a nucleotide in the other strand. A stable duplex can include Watson-Crick base pairing and/or non-Watson-Crick base pairing between the strands of the duplex (where base pairing means the forming hydrogen bonds). In certain embodiments, a non-Watson-Crick base pair includes a nucleoside analog, such as deoxyinosine, 2, 6-diaminopurine, PNAs, LNA's and the like. In certain embodiments, a non-Watson-Crick base pair includes a "wobble base", such as deoxyinosine, 8-oxo-dA, 8-oxo-dG and the like, where by "wobble base" is meant a nucleic acid base that can base pair with a first nucleotide base in a complementary nucleic acid strand but that, when employed as a template strand for nucleic acid synthesis, leads to the incorporation of a second, different nucleotide base into the synthesizing strand (wobble bases are described in further detail below). A "mismatch" in a duplex between two oligonucleotides or polynucleotides means that a pair of nucleotides in the duplex fails to undergo Watson-Crick bonding.

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"Genetic locus," "locus," or "locus of interest" in reference to a genome or target polynucleotide, means a contiguous sub-region or segment of the genome or target polynucleotide. As used herein, genetic locus, locus, or locus of interest may refer to the position of a nucleotide, a gene or a portion of a gene in a genome, including mitochondrial DNA or other non-chromosomal DNA (e.g., bacterial plasmid), or it may refer to any contiguous portion of genomic sequence whether or not it is within, or associated with, a gene. A genetic locus, locus, or locus of interest can be from a single nucleotide to a segment of a few hundred or a few thousand nucleotides in length or more. In general, a locus of interest will have a reference sequence associated with it (see description of "reference sequence" below).

"Kit" refers to any delivery system for delivering materials or reagents for carrying out a method of the invention. In the context of reaction assays, such delivery systems include systems that allow for the storage, transport, or delivery of reaction reagents (e.g., probes, enzymes, etc. in the appropriate containers) and/or supporting materials (e.g., buffers, written instructions for performing the assay etc.) from one location to another. For example, kits include one or more enclosures (e.g., boxes) containing the relevant reaction reagents and/or supporting materials. Such contents may be delivered to the intended recipient together or separately. For example, a first container may contain an enzyme for use in an assay, while a second container contains probes.

"Ligation" means to form a covalent bond or linkage between the termini of two or more nucleic acids, e.g. oligonucleotides and/or polynucleotides, in a template-driven reaction. The nature of the bond or linkage may vary widely and the ligation may be carried out enzymatically or chemically. As used herein, ligations are usually carried out enzymatically to form a phosphodiester linkage between a 5' carbon of a terminal nucleotide of one oligonucleotide with 3' carbon of another oligonucleotide. A variety of template-driven ligation reactions are described in the following references, which are incorporated by reference: Whiteley et al, U.S. patent 4,883,750; Letsinger et al, U.S. patent 5,476,930; Fung et al, U.S. patent 5,593,826; Kool, U.S. patent 5,426,180; Landegren et al, U.S. patent 5,871,921; Xu and Kool, Nucleic Acids Research, 27: 875-881 (1999); Higgins et al, Methods in Enzymology, 68: 50-71 (1979); Engler et al, The Enzymes, 15: 3-29 (1982); and Namsaraev, U.S. patent publication 2004/0110213.

"Multiplex Identifier" (MID) as used herein refers to a tag or combination of tags associated with a polynucleotide whose identity (e.g., the tag DNA sequence)

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can be used to differentiate polynucleotides in a sample. In certain embodiments, the MID on a polynucleotide is used to identify the source from which the polynucleotide is derived. For example, a nucleic acid sample may be a pool of polynucleotides derived from different sources, (e.g., polynucleotides derived from different individuals, different tissues or cells, or polynucleotides isolated at different times points), where the polynucleotides from each different source are tagged with a unique MID. As such, a MID provides a correlation between a polynucleotide and its source. In certain embodiments, MIDs are employed to uniquely tag each individual polynucleotide in a sample. Identification of the number of unique MIDs in a sample can provide a readout of how many individual polynucleotides are present in the sample (or from how many original polynucleotides a manipulated polynucleotide sample was derived; see, e.g., U.S. Patent No. 7,537,897, issued on May 26, 2009, incorporated herein by reference in its entirety). MIDs can range in length from 2 to 100 nucleotide bases or more and may include multiple subunits, where each different MID has a distinct identity and/or order of subunits. Exemplary nucleic acid tags that find use as MIDs are described in U.S. Patent 7,544,473, issued on June 6, 2009, and titled "Nucleic Acid Analysis Using Sequence Tokens", as well as U.S. Patent 7,393,665, issued on July 1, 2008, and titled "Methods and Compositions for Tagging and Identifying Polynucleotides", both of which are incorporated herein by reference in their entirety for their description of nucleic acid tags and their use in identifying polynucleotides. In certain embodiments, a set of MIDs employed to tag a plurality of samples need not have any particular common property (e.g., Tm, length, base composition, etc.), as the methods described herein can accommodate a wide variety of unique MID sets. It is emphasized here that MIDs need only be unique within a given experiment. Thus, the same MID may be used to tag a different sample being processed in a different experiment. In addition, in certain experiments, a user may use the same MID to tag a subset of different samples within the same experiment. For example, all samples derived from individuals having a specific phenotype may be tagged with the same MID, e.g., all samples derived from control (or wildtype) subjects can be tagged with a first MID while subjects having a disease condition can be tagged with a second MID (different than the first MID). As another example, it may be desirable to tag different samples derived from the same source with different MIDs (e.g., samples derived over time or derived from different sites within a tissue). Further, MIDs can be generated in a

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variety of different ways, e.g., by a combinatorial tagging approach in which one MID is attached by ligation and a second MID is attached by primer extension. Thus, MIDs can be designed and implemented in a variety of different ways to track polynucleotide fragments during processing and analysis, and thus no limitation in this regard is intended.

"Nucleoside" as used herein includes the natural nucleosides, including 2'-deoxy and 2'-hydroxyl forms, e.g. as described in Kornberg and Baker, DNA Replication, 2nd Ed. (Freeman, San Francisco, 1992). "Analogs" in reference to nucleosides includes synthetic nucleosides having modified base moieties and/or modified sugar moieties, e.g. described by Scheit, Nucleotide Analogs (John Wiley, New York, 1980); Uhlman and Peyman, Chemical Reviews, 90: 543-584 (1990), or the like, with the proviso that they are capable of specific hybridization. Such analogs include synthetic nucleosides designed to enhance binding properties, reduce complexity, increase specificity, and the like. Polynucleotides comprising analogs with enhanced hybridization or nuclease resistance properties are described in Uhlman and Peyman (cited above); Crooke et al, Exp. Opin. Ther. Patents, 6: 855-870 (1996); Mesmaeker et al, Current Opinion in Structual Biology, 5: 343-355 (1995); and the like. Exemplary types of polynucleotides that are capable of enhancing duplex stability include oligonucleotide N3'→P5' phosphoramidates (referred to herein as "amidates"), peptide nucleic acids (referred to herein as "PNAs"), oligo-2'-O-alkylribonucleotides, polynucleotides containing C-5 propynylpyrimidines, locked nucleic acids ("LNAs"), and like compounds. Such oligonucleotides are either available commercially or may be synthesized using methods described in the literature.

"Polymerase chain reaction," or "PCR," means a reaction for the in vitro amplification of specific DNA sequences by the simultaneous primer extension of complementary strands of DNA. In other words, PCR is a reaction for making multiple copies or replicates of a target nucleic acid flanked by primer sites, such reaction comprising one or more repetitions of the following steps: (i) denaturing the target nucleic acid, (ii) annealing primers to the primer sites, and (iii) extending the primers by a nucleic acid polymerase in the presence of nucleoside triphosphates. Usually, the reaction is cycled through different temperatures optimized for each step in a thermal cycler instrument. Particular temperatures, durations at each step, and rates of change between steps depend on many factors well-known to those of ordinary skill in the art, e.g. exemplified by the references: McPherson et al, editors, PCR: A Practical Approach and PCR2: A Practical Approach (IRL Press, Oxford, 1991 and 1995, respectively). For example, in a conventional

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PCR using Taq DNA polymerase, a double stranded target nucleic acid may be denatured at a temperature >90°C, primers annealed at a temperature in the range 50-75°C, and primers extended at a temperature in the range 72-78°C. The term "PCR" encompasses derivative forms of the reaction, including but not limited to, RT-PCR, real-time PCR, nested PCR, quantitative PCR, multiplexed PCR, and the like. Reaction volumes range from a few hundred nanoliters, e.g. 200 nL, to a few hundred μL, e.g. 200 μL. "Reverse transcription PCR," or "RT-PCR," means a PCR that is preceded by a reverse transcription reaction that converts a target RNA to a complementary single stranded DNA, which is then amplified, e.g. Tecott et al, U.S. patent 5,168,038, which patent is incorporated herein by reference. "Real-time PCR" means a PCR for which the amount of reaction product, i.e. amplicon, is monitored as the reaction proceeds. There are many forms of real-time PCR that differ mainly in the detection chemistries used for monitoring the reaction product, e.g. Gelfand et al, U.S. patent 5,210,015 ("TAQMAN™"); Wittwer et al, U.S. patents 6,174,670 and 6,569,627 (intercalating dyes); Tyagi et al, U.S. patent 5,925,517 (molecular beacons); which patents are incorporated herein by reference. Detection chemistries for real-time PCR are reviewed in Mackay et al, Nucleic Acids Research, 30: 1292-1305 (2002), which is also incorporated herein by reference. "Nested PCR" means a two-stage PCR wherein the amplicon of a first PCR becomes the sample for a second PCR using a new set of primers, at least one of which binds to an interior location of the first amplicon. As used herein, "initial primers" in reference to a nested amplification reaction mean the primers used to generate a first amplicon, and "secondary primers" mean the one or more primers used to generate a second, or nested, amplicon. "Multiplexed PCR" means a PCR wherein multiple target sequences (or a single target sequence and one or more reference sequences) are simultaneously carried out in the same reaction mixture, e.g. Bernard et al, Anal. Biochem., 273: 221-228 (1999)(two-color real-time PCR). Usually, distinct sets of primers are employed for each sequence being amplified.

"Quantitative PCR" means a PCR designed to measure the abundance of one or more specific target sequences in a sample or specimen. Quantitative PCR includes both absolute quantitation and relative quantitation of such target sequences. Quantitative measurements are made using one or more reference sequences that may be assayed separately or together with a target sequence. The reference sequence may be endogenous or exogenous to a sample or specimen, and in the latter case, may comprise one or more competitor templates. Typical endogenous reference sequences include segments of transcripts of the following genes: β-actin, GAPDH, β_2-microglobulin, ribosomal RNA, and the like. Techniques for

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quantitative PCR are well-known to those of ordinary skill in the art, as exemplified in the following references that are incorporated by reference: Freeman et al, Biotechniques, 26: 112-126 (1999); Becker-Andre et al, Nucleic Acids Research, 17: 9437-9447 (1989); Zimmerman et al, Biotechniques, 21: 268-279 (1996); Diviacco et al, Gene, 122: 3013-3020 (1992); Becker-Andre et al, Nucleic Acids Research, 17: 9437-9446 (1989); and the like.

"Polynucleotide" or "oligonucleotide" is used interchangeably and each means a linear polymer of nucleotide monomers. Monomers making up polynucleotides and oligonucleotides are capable of specifically binding to a natural polynucleotide by way of a regular pattern of monomer-to-monomer interactions, such as Watson-Crick type of base pairing, base stacking, Hoogsteen or reverse Hoogsteen types of base pairing, wobble base pairing, or the like. As described in detail below, by "wobble base" is meant a nucleic acid base that can base pair with a first nucleotide base in a complementary nucleic acid strand but that, when employed as a template strand for nucleic acid synthesis, leads to the incorporation of a second, different nucleotide base into the synthesizing strand. Such monomers and their internucleosidic linkages may be naturally occurring or may be analogs thereof, e.g. naturally occurring or non-naturally occurring analogs. Non-naturally occurring analogs may include peptide nucleic acids (PNAs, e.g., as described in U.S. Patent 5,539,082, incorporated herein by reference), locked nucleic acids (LNAs, e.g., as described in U.S. Patent 6,670,461, incorporated herein by reference), phosphorothioate internucleosidic linkages, bases containing linking groups permitting the attachment of labels, such as fluorophores, or haptens, and the like. Whenever the use of an oligonucleotide or polynucleotide requires enzymatic processing, such as extension by a polymerase, ligation by a ligase, or the like, one of ordinary skill would understand that oligonucleotides or polynucleotides in those instances would not contain certain analogs of internucleosidic linkages, sugar moieties, or bases at any or some positions. Polynucleotides typically range in size from a few monomeric units, e.g. 5-40, when they are usually referred to as "oligonucleotides," to several thousand monomeric units. Whenever a polynucleotide or oligonucleotide is represented by a sequence of letters (upper or lower case), such as "ATGCCTG," it will be understood that the nucleotides are in 5'→3' order from left to right and that "A" denotes deoxyadenosine, "C" denotes deoxycytidine, "G" denotes deoxyguanosine, and "T" denotes thymidine, "I" denotes deoxyinosine, "U" denotes uridine, unless otherwise indicated or obvious from context. Unless otherwise noted the terminology and atom numbering conventions will follow those disclosed in Strachan and Read, Human Molecular Genetics 2 (Wiley-Liss, New York,

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1999). Usually polynucleotides comprise the four natural nucleosides (e.g. deoxyadenosine, deoxycytidine, deoxyguanosine, deoxythymidine for DNA or their ribose counterparts for RNA) linked by phosphodiester linkages; however, they may also comprise non-natural nucleotide analogs, e.g. including modified bases, sugars, or internucleosidic linkages. It is clear to those skilled in the art that where an enzyme has specific oligonucleotide or polynucleotide substrate requirements for activity, e.g. single stranded DNA, RNA/DNA duplex, or the like, then selection of appropriate composition for the oligonucleotide or polynucleotide substrates is well within the knowledge of one of ordinary skill, especially with guidance from treatises, such as Sambrook et al, Molecular Cloning, Second Edition (Cold Spring Harbor Laboratory, New York, 1989), and like references.

"Primer" means an oligonucleotide, either natural or synthetic, that is capable, upon forming a duplex with a polynucleotide template, of acting as a point of initiation of nucleic acid synthesis and being extended from its 3' end along the template so that an extended duplex is formed. The sequence of nucleotides added during the extension process is determined by the sequence of the template polynucleotide. Usually primers are extended by a DNA polymerase. Primers are generally of a length compatible with their use in synthesis of primer extension products, and are usually are in the range of between 8 to 100 nucleotides in length, such as 10 to 75, 15 to 60, 15 to 40, 18 to 30, 20 to 40, 21 to 50, 22 to 45, 25 to 40, and so on, more typically in the range of between 18-40, 20-35, 21-30 nucleotides long, and any length between the stated ranges. Typical primers can be in the range of between 10-50 nucleotides long, such as 15-45, 18-40, 20-30, 21-25 and so on, and any length between the stated ranges. In some embodiments, the primers are usually not more than about 10, 12, 15, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, or 70 nucleotides in length.

Primers are usually single-stranded for maximum efficiency in amplification, but may alternatively be double-stranded. If double-stranded, the primer is usually first treated to separate its strands before being used to prepare extension products. This denaturation step is typically affected by heat, but may alternatively be carried out using alkali, followed by neutralization. Thus, a "primer" is complementary to a template, and complexes by hydrogen bonding or hybridization with the template to give a primer/template complex for initiation of synthesis by a polymerase, which is extended by the addition of covalently bonded bases linked at its 3' end complementary to the template in the process of DNA synthesis.

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A "primer pair" as used herein refers to first and second primers having nucleic acid sequence suitable for nucleic acid-based amplification of a target nucleic acid. Such primer pairs generally include a first primer having a sequence that is the same or similar to that of a first portion of a target nucleic acid, and a second primer having a sequence that is complementary to a second portion of a target nucleic acid to provide for amplification of the target nucleic acid or a fragment thereof. Reference to "first" and "second" primers herein is arbitrary, unless specifically indicated otherwise. For example, the first primer can be designed as a "forward primer" (which initiates nucleic acid synthesis from a 5' end of the target nucleic acid) or as a "reverse primer" (which initiates nucleic acid synthesis from a 5' end of the extension product produced from synthesis initiated from the forward primer). Likewise, the second primer can be designed as a forward primer or a reverse primer.

"Primer site" (e.g., a sequencing primer site, and amplification primer site, etc.) as used herein refers to a domain in a polynucleotide that includes the sequence of a primer (e.g., a sequencing primer) and/or the complementary sequence of a primer. When present in single stranded form (e.g., in a single stranded polynucleotide), a primer site can be either the identical sequence of a primer or the complementary sequence of a primer. When present in double stranded form, a primer site contains the sequence of a primer hybridized to the complementary sequence of the primer. Thus, a primer site is a region of a polynucleotide that is either identical to or complementary to the sequence of a primer (when in a single stranded form) or a double stranded region formed between a primer sequence and its complement. Primer sites may be present in an adapter attached to a polynucleotide. The specific orientation of a primer site can be inferred by those of ordinary skill in the art from the structural features of the relevant polynucleotide and/or context in which it is used.

"Readout" means a parameter, or parameters, which are measured and/or detected that can be converted to a number or value. In some contexts, readout may refer to an actual numerical representation of such collected or recorded data. For example, a readout of fluorescent intensity signals from a microarray is the address and fluorescence intensity of a signal being generated at each hybridization site of the microarray; thus, such a readout may be registered or stored in various ways, for example, as an image of the microarray, as a table of numbers, or the like.

"Reflex site", "reflex sequence" and equivalents are used to indicate sequences in a polynucleotide that are employed to move a domain intramolecularly from its initial location

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to a different location in the polynucleotide. The sequence of a reflex site can be added to a polynucleotide of interest (e.g., present in an adapter ligated to the polynucleotide), be based on a sequence naturally present within the polynucleotide of interest (e.g., a genomic sequence in the polynucleotide), or a combination of both. The reflex sequence is chosen so as to be distinct from other sequences in the polynucleotide (i.e., with little sequence homology to other sequences likely to be present in the polynucleotide, e.g., genomic or sub-genomic sequences to be processed). As such, a reflex sequence should be selected so as to not hybridize to any sequence except its complement under the conditions employed in the reflex processes herein described. As described later in this application, the complement to the reflex sequence is inserted on the same strand of the polynucleotide (e.g., the same strand of a double-stranded polynucleotide or on the same single stranded polynucleotide) in a particular location so as to facilitate an intramolecular binding event on such particular strand. Reflex sequences employed in the reflex process described herein can thus have a wide range of lengths and sequences. Reflex sequences may range from 5 to 200 nucleotide bases in length.

"Solid support", "support", and "solid phase support" are used interchangeably and refer to a material or group of materials having a rigid or semi-rigid surface or surfaces. In many embodiments, at least one surface of the solid support will be substantially flat, although in some embodiments it may be desirable to physically separate synthesis regions for different compounds with, for example, wells, raised regions, pins, etched trenches, or the like. According to other embodiments, the solid support(s) will take the form of beads, resins, gels, microspheres, or other geometric configurations. Microarrays usually comprise at least one planar solid phase support, such as a glass microscope slide.

"Specific" or "specificity" in reference to the binding of one molecule to another molecule, such as a labeled target sequence for a probe, means the recognition, contact, and formation of a stable complex between the two molecules, together with substantially less recognition, contact, or complex formation of that molecule with other molecules. In one aspect, "specific" in reference to the binding of a first molecule to a second molecule means that to the extent the first molecule recognizes and forms a complex with another molecule in a reaction or sample, it forms the largest number of the complexes with the second molecule. Preferably, this largest number is at least fifty percent. Generally, molecules involved in a specific binding event have areas on their surfaces or in cavities giving rise to specific recognition between the molecules binding to each other. Examples of specific binding include antibody-antigen interactions, enzyme-substrate interactions, formation of

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duplexes or triplexes among polynucleotides and/or oligonucleotides, biotin-avidin or biotin-streptavidin interactions, receptor-ligand interactions, and the like. As used herein, "contact" in reference to specificity or specific binding means two molecules are close enough that weak noncovalent chemical interactions, such as Van der Waal forces, hydrogen bonding, base-stacking interactions, ionic and hydrophobic interactions, and the like, dominate the interaction of the molecules.

As used herein, the term "T_m" is used in reference to the "melting temperature." The melting temperature is the temperature (e.g., as measured in °C) at which a population of double-stranded nucleic acid molecules becomes half dissociated into single strands. Several equations for calculating the T_m of nucleic acids are known in the art (see e.g., Anderson and Young, Quantitative Filter Hybridization, in Nucleic Acid Hybridization (1985). Other references (e.g., Allawi, H.T. & SantaLucia, J., Jr., Biochemistry 36, 10581-94 (1997)) include alternative methods of computation which take structural and environmental, as well as sequence characteristics into account for the calculation of T_m.

"Sample" means a quantity of material from a biological, environmental, medical, or patient source in which detection, measurement, or labeling of target nucleic acids is sought. On the one hand it is meant to include a specimen or culture (e.g., microbiological cultures). On the other hand, it is meant to include both biological and environmental samples. A sample may include a specimen of synthetic origin. Biological samples may be animal, including human, fluid, solid (e.g., stool) or tissue, as well as liquid and solid food and feed products and ingredients such as dairy items, vegetables, meat and meat by-products, and waste. Biological samples may include materials taken from a patient including, but not limited to cultures, blood, saliva, cerebral spinal fluid, pleural fluid, milk, lymph, sputum, semen, needle aspirates, and the like. Biological samples may be obtained from all of the various families of domestic animals, as well as feral or wild animals, including, but not limited to, such animals as ungulates, bear, fish, rodents, etc. Environmental samples include environmental material such as surface matter, soil, water and industrial samples, as well as samples obtained from food and dairy processing instruments, apparatus, equipment, utensils, disposable and non-disposable items. These examples are not to be construed as limiting the sample types applicable to the present invention.

The terms "upstream" and "downstream" in describing nucleic acid molecule orientation and/or polymerization are used herein as understood by one of skill in the art. As such, "downstream" generally means proceeding in the 5' to 3' direction, i.e., the direction in which a nucleotide polymerase normally extends a sequence, and "upstream" generally

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means the converse. For example, a first primer that hybridizes "upstream" of a second primer on the same target nucleic acid molecule is located on the 5' side of the second primer (and thus nucleic acid polymerization from the first primer proceeds towards the second primer).

It is further noted that the claims may be drafted to exclude any optional element. As such, this statement is intended to serve as antecedent basis for use of such exclusive terminology as "solely", "only" and the like in connection with the recitation of claim elements, or the use of a "negative" limitation.

DETAILED DESCRIPTION OF THE INVENTION

The invention is drawn to compositions and methods for intramolecular nucleic acid rearrangement that find use in various applications of genetic analysis, including sequencing, as well as general molecular biological manipulations of polynucleotide structures.

Before the present invention is described, it is to be understood that this invention is not limited to particular embodiments described, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Where a range of values is provided, it is understood that each intervening value, to the tenth of the unit of the lower limit unless the context clearly dictates otherwise, between the upper and lower limits of that range is also specifically disclosed. Each smaller range between any stated value or intervening value in a stated range and any other stated or intervening value in that stated range is encompassed within the invention. The upper and lower limits of these smaller ranges may independently be included or excluded in the range, and each range where either, neither or both limits are included in the smaller ranges is also encompassed within the invention, subject to any specifically excluded limit in the stated range. Where the stated range includes one or both of the limits, ranges excluding either or both of those included limits are also included in the invention.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, some potential and preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in

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connection with which the publications are cited. It is understood that the present disclosure supersedes any disclosure of an incorporated publication to the extent there is a contradiction.

It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a nucleic acid" includes a plurality of such nucleic acids and reference to "the compound" includes reference to one or more compounds and equivalents thereof known to those skilled in the art, and so forth.

The practice of the present invention may employ, unless otherwise indicated, conventional techniques and descriptions of organic chemistry, polymer technology, molecular biology (including recombinant techniques), cell biology, biochemistry, and immunology, which are within the skill of the art. Such conventional techniques include polymer array synthesis, hybridization, ligation, and detection of hybridization using a label. Specific illustrations of suitable techniques can be had by reference to the example herein below. However, other equivalent conventional procedures can, of course, also be used. Such conventional techniques and descriptions can be found in standard laboratory manuals such as *Genome Analysis: A Laboratory Manual Series* (Vols. I-IV), *Using Antibodies: A Laboratory Manual, Cells: A Laboratory Manual, PCR Primer: A Laboratory Manual, and Molecular Cloning: A Laboratory Manual* (all from Cold Spring Harbor Laboratory Press), Stryer, L. (1995) *Biochemistry* (4th Ed.) Freeman, New York, Gait, "*Oligonucleotide Synthesis: A Practical Approach*" 1984, IRL Press, London, Nelson and Cox (2000), Lehninger, A., *Principles of Biochemistry* 3rd Ed., W. H. Freeman Pub., New York, N.Y. and Berg et al. (2002) *Biochemistry,* 5th Ed., W. H. Freeman Pub., New York, N.Y., all of which are herein incorporated in their entirety by reference for all purposes.

The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

As summarized above, aspects of the present invention are drawn to the use of a 'reflex' sequence present in a polynucleotide (e.g., in an adapter structure of the polynucleotide, in a genomic region of the polynucleotide, or a combination of both) to move a domain of the polynucleotide intra-molecularly from a first location to a second location. The reflex process described herein finds use in any number of applications, e.g.,

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placing functional elements of a polynucleotide (e.g., sequencing primer sites and/or MID tags) into proximity to a desired sub-region of interest.

Nucleic Acids

The reflex process (as described in detail below) can be employed for the manipulation and analysis of nucleic acid sequences of interest from virtually any nucleic acid source, including but not limited to genomic DNA, complementary DNA (cDNA), RNA (e.g., messenger RNA, ribosomal RNA, short interfering RNA, microRNA, etc.), plasmid DNA, mitochondrial DNA, synthetic DNA, etc. Furthermore, any organism, organic material or nucleic acid-containing substance can be used as a source of nucleic acids to be processed in accordance with the present invention including, but not limited to, plants, animals (e.g., reptiles, mammals, insects, worms, fish, etc.), tissue samples, bacteria, fungi (e.g., yeast), phage, viruses, cadaveric tissue, archaeological/ancient samples, etc. In certain embodiments, the nucleic acids in the nucleic acid sample are derived from a mammal, where in certain embodiments the mammal is a human.

In certain embodiments, the nucleic acid sequences are enriched prior to the reflex sequence process. By enriched is meant that the nucleic acid is subjected to a process that reduces the complexity of the nucleic acids, generally by increasing the relative concentration of particular nucleic acid species in the sample (e.g., having a specific locus of interest, including a specific nucleic acid sequence, lacking a locus or sequence, being within a specific size range, etc.). There are a wide variety of ways to enrich nucleic acids having a specific characteristic(s) or sequence, and as such any convenient method to accomplish this may be employed. The enrichment (or complexity reduction) can take place at any of a number of steps in the process, and will be determined by the desires of the user. For example, enrichment can take place in individual parental samples (e.g., untagged nucleic acids prior to adaptor ligation) or in multiplexed samples (e.g., nucleic acids tagged with primer sites, MID and/or reflex sequences and pooled; MID are described in further detail below).

In certain embodiments, nucleic acids in the nucleic acid sample are amplified prior to analysis. In certain of these embodiments, the amplification reaction also serves to enrich a starting nucleic acid sample for a sequence or locus of interest. For example, a starting nucleic acid sample can be subjected to a polymerase chain reaction (PCR) that amplifies one or more region of interest. In certain embodiments, the amplification reaction is an exponential amplification reaction, whereas in certain other embodiments, the amplification reaction is a linear amplification reaction. Any convenient method for performing

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amplification reactions on a starting nucleic acid sample can be used in practicing the subject invention. In certain embodiments, the nucleic acid polymerase employed in the amplification reaction is a polymerase that has proofreading capability (e.g., phi29 DNA Polymerase, Thermococcus litoralis DNA polymerase, Pyrococcus furiosus DNA polymerase, etc.).

In certain embodiments, the nucleic acid sample being analyzed is derived from a single source (e.g., a single organism, virus, tissue, cell, subject, etc.), whereas in other embodiments, the nucleic acid sample is a pool of nucleic acids extracted from a plurality of sources (e.g., a pool of nucleic acids from a plurality of organisms, tissues, cells, subjects, etc.), where by "plurality" is meant two or more. As such, in certain embodiments, a nucleic acid sample can contain nucleic acids from 2 or more sources, 3 or more sources, 5 or more sources, 10 or more sources, 50 or more sources, 100 or more sources, 500 or more sources, 1000 or more sources, 5000 or more sources, up to and including about 10,000 or more sources.

In certain embodiments, nucleic acid fragments that are to be pooled with nucleic acid fragments derived from a plurality of sources (e.g., a plurality of organisms, tissues, cells, subjects, etc.), where by "plurality" is meant two or more. In such embodiments, the nucleic acids derived from each source includes a multiplex identifier (MID) such that the source from which the each tagged nucleic acid fragment was derived can be determined. In such embodiments, each nucleic acid sample source is correlated with a unique MID, where by unique MID is meant that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID. Any type of MID can be used, including but not limited to those described in co-pending U.S. Patent Application Serial Number 11/656,746, filed on January 22, 2007, and titled "Nucleic Acid Analysis Using Sequence Tokens", as well as U.S. Patent 7,393,665, issued on July 1, 2008, and titled "Methods and Compositions for Tagging and Identifying Polynucleotides", both of which are incorporated herein by reference in their entirety for their description of nucleic acid tags and their use in identifying polynucleotides. In certain embodiments, a set of MIDs employed to tag a plurality of samples need not have any particular common property (e.g., T_m, length, base composition, etc.), as the asymmetric tagging methods (and many tag readout methods, including but not limited to sequencing of the tag or measuring the length of the tag) can accommodate a wide variety of unique MID sets.

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In certain embodiments, each individual polynucleotide (e.g., double-stranded or single-stranded, as appropriate to the methodological details employed) in a sample to be analyzed is tagged with a unique MID so that the fate of each polynucleotide can be tracked in subsequent processes (where, as noted above, unique MID is meant to indicate that each different MID employed can be differentiated from every other MID employed by virtue of at least one characteristic, e.g., the nucleic acid sequence of the MID). For example (and as described below), having each nucleic acid tagged with a unique MID allows analysis of the sequence of each individual nucleic acid using the reflex sequence methods described herein. This allows the linkage of sequence information for large nucleic acid fragments that cannot be sequenced in a single sequencing run.

Reflex Sequence Process

As summarized above, aspects of the present invention include methods and compositions for moving a domain in a polynucleotide from a first location to a second location in the polynucleotide. An exemplary embodiment is shown in Figure 1A.

Figure 1A shows a single stranded polynucleotide 100 comprising, in a 5' to 3' orientation, a first domain (102; the domain to be moved); a reflex sequence 104; a nucleic acid sequence 106 having a site distal to the first domain (Site A), and a complement of the reflex sequence 108 (positioned at the 3' terminus of the polynucleotide). The steps of the reflex method described below will move the first domain into closer proximity to Site A. It is noted here that the prime designation in Figure 1A denotes a complementary sequence of a domain. For example, First Domain' is the complement of the First Domain.

In Step 1, the reflex sequence and its complement in the polynucleotide are annealed intramolecularly to form polynucleotide structure 112, with the polynucleotide folding back on itself and hybridizing to form a region of complementarity (i.e., double stranded reflex/reflex' region). In this configuration, the 3' end of the complement of the reflex sequence can serve as a nucleic acid synthesis priming site. Nucleic acid synthesis from this site is then performed in extension Step 2 producing a complement of the first domain at the 3' end of the nucleic acid extension (shown in polynucleotide 114; extension is indicated with dotted arrow labeled "extend").

Denaturation of polynucleotide 114 (e.g., by heat) generates linear single stranded polynucleotide 116. As shown in Figure 1, resultant polynucleotide 116 contains a complement of the first domain at a position proximal to Site A (i.e., separated by only the complement of the reflex sequence). This resultant polynucleotide may be used for any

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subsequent analysis or processing steps as desired by the user (e.g., sequencing, as a template for amplification (linear, PCR, etc.), sequence specific extraction, etc.).

In alternative embodiments, the first domain and reflex sequence are removed from the 5' end of the double-stranded region of polynucleotide 114 (shown in polynucleotide 118; removal is shown in the dotted arrow labeled "remove"). Removal of this region may be accomplished by any convenient method, including, but not limited to, treatment (under appropriate incubation conditions) of polynucleotide structure 114 with T7 exonuclease or by treatment with Lambda exonuclease; the Lambda exonuclease can be employed so long as the 5' end of the polynucleotide is phosphorylated. If the region is removed enzymatically, resultant polynucleotide 118 is used in place of polynucleotide 116 in subsequent steps (e.g., copying to reverse polarity).

In certain embodiments, polynucleotide 116 or 118 is used as a template to produce a double stranded polynucleotide, for example by performing a nucleic acid synthesis reaction with a primer that primes in the complement of the first domain. This step is sometimes referred to as copying to reverse polarity of a single stranded polynucleotide, and in some instances, the double-stranded intermediate product of this copying is not shown (see, e.g., Figure 3). For example, copying to reverse the polarity of polynucleotide 116 results in single-stranded polynucleotide 120 having, in a 5' to 3' orientation, the first domain (122); the reflex sequence (124); the complement of polynucleotide 106 (oriented with the complement of Site A (Site A'; 126) proximal to the reflex sequence); the complement of the reflex sequence (128); and the complement of the first domain (130).

In certain embodiments, the first domain in the polynucleotide comprises one or more elements that find use in one or more subsequent processing or analysis steps. Such sequences include, but are not limited to, restriction enzyme sites, PCR primer sites, linear amplification primer sites, reverse transcription primer sites, RNA polymerase promoter sites (such as for T7, T3 or SP6 RNA polymerase), MID tags, sequencing primer sites, etc. Any convenient element can be included in the first domain and, in certain embodiments, is determined by the desires of the user of the methods described herein.

As an exemplary embodiment, suppose we want to sequence a specific polynucleotide region from multiple genomes in a pooled sample where the polynucleotide region is too long to sequence in a single reaction. For example, sequencing a polynucleotide region that is 2 kilobases or more in length using Roche 454 (Branford, CT) technology, in which the length of a single sequencing run is about 400 bases. In this scenario, we can design a set of left hand primers (A_n) and right hand primers (B_n) specific

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for the polynucleotide region that are positioned in such a way that we can obtain direct sequences of all parts of the insert, as shown in Figure 1B. Note that the polynucleotide shown in Figure 1B (140) has a domain (142) containing a primer site and an MID denoting from which original sample(s) the polynucleotide is derived. Site 142 thus represents an example of a First Domain site such identified as 122 in the Figure 1A. The polynucleotide also includes a reflex site (144), which can be part of the polynucleotide region itself (e.g., a genomic sequence), added in a ligated adapter domain along with the primer site and the MID (an artificial sequence), or a combination of both (a sequence spanning the adapter/polynucleotide junction).

It is noted here that polynucleotide 140 can be categorized as a precursor to polynucleotide 100 in Figure 1A, as it does not include a 3' reflex sequence complementary to the reflex site (domain 108 in Figure 1A). As detailed below, polynucleotide 140 can be converted to a polynucleotide having the structural configuration of polynucleotide 100, a polynucleotide suitable as a substrate for the reflex process described herein (e.g., by primer extension using a B_n primer and reversal of polarity).

In an exemplary embodiment, each A_n-B_n primer pair defines a nucleic acid region that is approximately 400 bases in length or less. This size range is within the single-sequencing run read length of the current Roche 454 sequencing platform; a different size range for the defined nucleic acid region may be utilized for a different sequencing platform. Thus, each product from each reflex process can be sequenced in a single run. It is noted here that primer pairs as shown in Figure 1B can be used to define regions 1 to 5 shown in Figure 3 (described in further detail below).

In certain embodiments, to obtain the first part of the sequence of the polynucleotide region (i.e., in the original structure, that part of the polynucleotide closest to the first domain), we only need a right hand primer (e.g., B_0) and we do not need to transfer the MID as it is within reach of this sequencing primer (i.e., the MID is within 400 bases of sequencing primer B_0). All other B_n primers have the reflex sequence added to their 5' ends ("R" element shown on B primers) so that they read 5' reflex-B_n. However, in certain embodiments, the B_0 primer does include the reflex sequence and is used in the reflex process (along with a corresponding A_0 primer) as detailed below.

As described above, we obtain a single stranded polynucleotide having, in the 5' to 3' orientation, a primer site (e.g., for Roche 454 sequencing), an MID, a reflex sequence and the polynucleotide to be sequenced. Numerous methods for obtaining single-stranded polynucleotides of interest have been described and are known in the art, including in U.S.

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Patent 7,217,522, issued on May 15, 2007; U.S. Patent Application 11/377,462, filed on March 16, 2006; and U.S. Patent Application 12/432,080, filed on April 29, 2009; each of which is incorporated by reference herein in their entirety. For example, a single stranded product can be produced using linear amplification with a primer specific for the primer site of the template. In certain embodiments, the primer includes a binding moiety to facilitate isolation of the single stranded nucleic acid of interest, e.g., to immobilize the top strand on a binding partner of the binding moiety immobilized on a solid support. Removal of a hybridized, non-biotinylated strand by denaturation using heat or high pH (or any other convenient method) serves to isolate the biotinylated strand. Binding moieties and their corresponding binding partners are sometimes referred to herein as binding partner pairs. Any convenient binding partner pairs may be used, including but not limited to biotin/avidin (or streptavidin), antigen/antibody pairs, etc.

It is noted here that while the figures and description of the reflex process provided herein depict manipulations with regard to a single stranded polynucleotide, it is not necessarily required that the single stranded polynucleotide described or depicted in the figures be present in the sample in an isolated form (i.e., isolated from its complementary strand). In other words, double stranded polynucleotides may be used where only one strand is described/depicted, which will generally be determined by the user.

The implementation of a single strand isolation step using the methods described above or variations thereof (or any other convenient single strand isolation step) will generally be based on the desires of the user. One example of isolating single stranded polynucleotides is shown in Figure 2. In this Figure, a starting double stranded template (with 5' to 3' orientation shown as an arrow) is denatured and primed with a biotinylated synthesis primer specific for the primer site. After extension of the primer (i.e., nucleic acid synthesis), the sample is contacted with a solid support having streptavidin bound to it. The biotin moiety (i.e., the binding partner of streptavidin) on the extended strands will bind to the solid-phase streptavidin. Denaturation and washing is then performed to remove all non-biotinylated polynucleotide strands. If desired, the bound polynucleotide, which can be used in subsequent reflex process steps (e.g., as a template for B_n primer extension reactions), may be eluted from the streptavidin support. Alternatively, the bound polynucleotide may be employed in subsequent steps of the desired process while still bound to the solid support (e.g., in solid phase extension reactions using B_n primers). This process, with minor variations depending on the template being used and the identity of the desired single stranded polynucleotide, may be employed at any of a number of steps in which a single

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stranded product is to be isolated. It is noted that in certain embodiments, substrate bound biotinylated polynucleotide can be used to produce and isolate non-biotinylated single stranded products (i.e., by eluting the non-biotinylated products while leaving the biotinylated templates bound to the streptavidin on the solid support). Thus, the specifics of how binding partners are used to isolate single stranded polynucleotides of interest will vary depending on experimental design parameters.

Additional single-stranded isolation/production methods include asymmetric PCR, strand-specific enzymatic degradation, and the use of in-vitro transcription followed by reverse transcriptase (IVT-RT) with subsequent destruction of the RNA strand. As noted above, any convenient single stranded production/isolation method may be employed.

To the single stranded polynucleotide shown in Figure 1B we anneal one of the B_n primers having the appended reflex sequence, denoted with a capital "R" (e.g., B_1) and extend the primer under nucleic acid synthesis conditions to produce a copy of the polynucleotide that has a reflex sequence at its 5' end. A single stranded copy of this polynucleotide is then produced to reverse polarity using a primer specific for the primer site in the first domain' (complement of the first domain 102). The resulting nucleic acid has structure 100 shown in Figure 1A, where the first domain 102 includes the primer site and the MID. Site A (110) in Figure 1 is determined by the specificity of the 5' reflex-B_n primer used.

The reflex process (e.g., as shown in Figure 1) is then performed to produce a product in which the primer site and the MID are now in close proximity to the desired site (or region of interest (ROI)) within the original polynucleotide (i.e., the site defined by the primer used, e.g., B_1). The resulting polynucleotide can be used in subsequent analyses as desired by the user (e.g., Roche 454 sequencing technology).

It is noted here that, while not shown in Figure 1A and 1B, any convenient method for adding adapters to a polynucleotide to be processed as described herein may be used in the practice of the reflex process (adapters containing, e.g., primer sites, polymerase sites, MIDs, restriction enzyme sites, and reflex sequences). For example, adapters can be added at a particular position by ligation. For double stranded polynucleotides, an adapter can be configured to be ligated to a particular restriction enzyme cut site. Where a single stranded polynucleotide is employed, a double stranded adapter construct that possesses an overhang configured to bind to the end of the single-stranded polynucleotide can be used. For example, in the latter case, the end of a single stranded polynucleotide can be modified to include specific nucleotide bases that are complementary to the overhang in the double

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stranded adaptor using terminal transferase and specific nucleotides. In other embodiments, PCR or linear amplification methods using adapter-conjugated primers is employed to add an adapter at a site of interest. Again, any convenient method for producing a starting polynucleotide may be employed in practicing the methods of the subject invention.

In certain embodiments, the nucleic acid may be sequenced directly using a sequencing primer specific for the primer site. This sequencing reaction will read through the MID and desired site in the insert.

In certain embodiments, the polynucleotide may be isolated (or fractionated) using an appropriate A_n primer (e.g., when using B_1 as the first primer, primer A_1 can be used). In certain embodiments, the A_n primed polynucleotide is subjected to nucleic acid synthesis conditions to produce a copy of the fragment produced in the reflex process. In certain of these embodiments, the A_n primer has appended on its 5' end a primer site that can be used in subsequent steps, including sequencing reactions. Providing a primer site in the A_n primer allows amplifying and/or sequencing from both ends of the resultant fragment: from the primer site in the first domain 102 and the primer site in the A_n primer (not shown in Figure 1B). Because of the position of the primer sites and their distance apart (i.e., less than one sequencing run apart), sequencing from both ends will usually capture the sequence of the desired site (or ROI) and the sequence of the MID, which can be used for subsequent bioinformatic analyses, e.g., to positively identify the sample of origin. It is noted here that while sequencing in both directions is possible, it is not necessary, as sequencing from either primer site alone will capture the sequence of the ROI as well as its corresponding MID sequence.

Note that in certain embodiments, the first fragment obtained by amplification/extension from primer B_0 directly, the polarity of the ROI in the resulting fragment is reversed as compared to the ROI in fragments obtained by primers B_1-B_n. This is because the B_0-generated fragment, unlike the B_1-B_n generated fragments, has not been subjected to a reflex process which reverses the orientation of the ROI sequence with respect to the first domain/reflex sequence (as described above). Therefore, the B_0 primer may have appended to it a primer site (e.g., at its 5' end) that can be used for subsequent amplification and/or sequencing reactions (e.g., in Roche 454 sequencing system) rather than a reflex sequence as with primers B_1-B_n. However, in certain embodiments, as noted above, the reflex process may be used with a corresponding B_0-A_0 primer pair as described above, i.e., using a B_0 primer having a 5' reflex sequence and a corresponding A_0 primer with its corresponding 5' adapter domain (e.g., a primer site).

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It is noted here that because the particular sections of sequence to be analyzed are defined by the A_n-B_n primer pairs (as shown and described above), a much higher sequence specificity is achieved as compared to using previous extraction methods that employ only a single oligo binding event (e.g., using probes on a microarray).

Figure 3 provides a detailed flow chart for an exemplary embodiment that employs reflex sequences for use in sequencing multiple specific regions in a polynucleotide (i.e., regions 1, 2, 3, 4 and 5 in an 11kb region of lambda DNA).

A single parent DNA fragment 202 is generated that includes adapter domains (i.e., a Roche 454 sequencing primer site, a single MID, and a reflex sequence) and the sequence of interest. In the example shown, the sequence of interest is from lambda DNA and the reflex sequence is present on the top strand (with its complement shown in the bottom strand). Any convenient method for producing this parent DNA fragment may be used, including amplification with a primer that includes the adapter domains (e.g., using PCR), cloning the fragment into a vector that includes the adapter domains (e.g., a vector with the adapter domains adjacent to a cloning site), or by attaching adapters to polynucleotide fragments (e.g., fragment made by random fragmentation, by sequence-specific restriction enzyme digestion, or combinations thereof). While only a single fragment with a single MID is shown, the steps in Figure 3 are applicable to samples having multiple different fragments each with a different MID, e.g., a sample having a population of homologous fragments from any number of different sources (e.g., different individuals). Figure 3 describes the subsequent enzymatic steps involved in creating the five daughter fragments in which regions 1, 2, 3, 4 and 5 (shown in polynucleotide 204) are rearranged to be placed within a functional distance of the adapter domains (i.e., close enough to the adapter domains to be sequenced in a single Roche 454 sequencing reaction). Note that certain steps are shown for region 4 only (206).

In step 1, the five regions of interest are defined within the parent fragment (labeled 1 to 5 in polynucleotide 204) and corresponding primer pairs are designed for each. The distance of each region of interest from the reflex sequence is shown below polynucleotide 204. The primer pairs are designed as described and shown in Figure 1B (i.e., the A_n-B_n primer pairs). For clarity, only primer sites for region 4 are shown in Figure 3 ("primer sites" surrounding region 4). In step 2, sequence specific primer extensions are performed (only region 4 is shown) with corresponding B_n primers to produce single stranded polynucleotides having structure 208 (i.e., having the reflex sequence on the 5' terminus). As shown, the B_n primer for region 4 will include a sequence specific primer site that primes

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at the 3'-most primer site noted for region 4 (where "3'-most" refers to the template strand, which in Figure 3 is the top strand). This polynucleotide is copied back to produce polynucleotide 210 having reversed polarity (e.g., copied using a primer that hybridizes to the 454A' domain). Polynucleotide 210 has structure similar to polynucleotide 100 shown at the top of Figure 1. Step 4 depicts the result of the intramolecular priming between the reflex sequence and its complement followed by extension to produce the MID' and 454A' structures at the 3' end (polynucleotide 212). In the embodiments shown in Figure 3, polynucleotide 212 is treated with T7 exonuclease to remove double stranded DNA from the 5' end (as indicated above, this step is optional). The polynucleotide formed for region 4 is shown as 216 with polynucleotides for the other regions also shown (214).

It is noted here that the formation of each of the polynucleotides 214 may be accomplished either in separate reactions (i.e., structure with region 1 in proximity to the adapter domains is in a first sample, the structure with region 2 in proximity to the adapter region is in a second sample, etc.) or in one or more combined sample.

In step 6 the polynucleotides 214 are copied to reverse polarity to form polynucleotides 218. In step 7, each of these products are then primed with the second primer of the specific primer pair (see A_n primers as shown in Figure 1B) each having a second Roche 454 primer site (454B) attached at the 5' end, and extended to form products 220. Steps 6 and 7 may be combined (e.g., in a single PCR or other amplification reaction).

In summary, Figure 3 shows how the reflex process can be employed to produce five daughter fragments 220 of similar length (e.g., ~500 bp) each of which contain DNA sequences that differ in their distance from the reflex sequence in the starting structure 202 while maintaining the original MID.

Figure 4 shows another exemplary use of the reflex process as described herein. In the embodiment shown in Figure 4, a target sequence (i.e., containing region of interest "E") is enriched from a pool of adapter-attached fragments. In certain embodiments, the fragments are randomly sheared, selected for a certain size range (e.g., DNA having a length from 100 to 5000 base pairs), and tagged with adapters (e.g., asymmetric adapters, e.g., as described in US Patent Application Ser. No. 12/432,080, filed on April 29, 2009). The asymmetric adaptor employed in Figure 4 contains a sequencing primer site (454A, as used in the Roche 454 sequencing platform), an MID, an X sequence, and an internal stem region (ISR), which denotes the region of complementarity for the asymmetric adapter that is adjacent to the adapter attachment site (see, e.g., the description in US Application Ser. No. 12/432,080, filed on April 29, 2009, incorporated herein by reference in its entirety). The X

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sequence can be any sequence that can serve as a binding site for a polynucleotide containing the complement of the X sequence (similar to a primer site). As described below, the X sequence allows for the annealing of an oligonucleotide having a 5' overhang that can serve as a template for extension of the 3' end of the adaptor oligonucleotide. The sequencing direction of the sequencing primer site (454A primer site in structure 401 of Figure 4) is oriented such that amplification of the adapter ligated fragment using the sequencing primer site proceeds away from the ligated genomic insert. This has the effect of making the initial asymmetric adapter ligated library 'inert' to amplification using this primer, e.g., in a PCR reaction.

To extract a region of interest (the "E" region), the library is mixed with an oligonucleotide (403) containing a 3' X' sequence and a target specific priming sequence (the 1' sequence) under hybridization/annealing conditions. The target specific sequence 1' is designed to flank one side of the region of interest (the 1' sequence adjacent to E in the genomic insert; note that only the E-containing polynucleotide fragment is shown in Figure 4), much like a PCR primer. After annealing primer 403, the hybridized complex is extended, whereby all of the adaptor tagged fragments will obtain the complement of the target specific sequence (i.e., the 1 sequence) on the 3' end (see structure 405; arrows denote the direction of extension).

Extended products 405 are then denatured and the 1/1' regions allowed to hybridize intramolecularly in a reflex process priming event, after which nucleic acid extension is performed to form structure 407 (extension is from the 1 priming site; shown with an arrow). This reflex reaction creates a product (407) that, unlike its parent structure (405), has a sequencing primer site (454A) that is oriented such the extension using this primer sequence proceeds towards the region of interest. Thus, in the absence of a priming and extension reflex reaction, extension with a sequencing primer will not generate a product containing the region of interest (the E region). In other words, only E-region containing target polynucleotides will have a 454A sequence that can amplify genomic material (structure 407).

After completing the reflex process (using 1/1' as the reflex sequences), a PCR amplification reaction is performed to amplify the region of interest (with associated adapter domains). However, before performing the PCR reaction, the fragment sample is "inactivated" from further extension using terminal transferase and ddNTPs. This inactivation prevents non-target adaptor tagged molecules from performing primer extension from the 3' primer 1 site. Once inactivated, a PCR reaction is performed using a sequencing

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primer (i.e., 454A primer 409) and a second primer that primes and extends from the opposite side of the region of interest (i.e., primer 411, which includes a 5' 454B sequencing primer site and a 3' "2" region that primes on the opposite end of E from the 1 region). Only fragments that have undergone the reflex process and contain the E region will be suitable templates for the PCR reaction and produce the desired product (413).

Thus, the process exemplified in Figure 4 allows for the movement of an adapter domain (e.g., containing functional elements and/or MID) into proximity to a desired region of interest.

The reflex process described herein can be used to perform powerful linkage analysis by combining it with nucleic acid counting methods. Any convenient method for tagging and /or counting individual nucleic acid molecules with unique tags may be employed (see, e.g., U.S. Patent 7,537,897, issued on May 26, 2009; U.S. Patent 7,217,522, issued on May 15, 2007; U.S. Patent Application 11/377,462, filed on March 16, 2006; and U.S. Patent Application 12/432,080, filed on April 29, 2009; each of which is incorporated by reference herein in their). All of this can be conducted in parallel thus saving on the cost of labor, time and materials.

In one exemplary embodiment, a large collection of sequences is tagged with MID such that each polynucleotide molecule in the sample has a unique MID. In other words, each polynucleotide in the sample (e.g., each individual double stranded or single stranded polynucleotide) is tagged with a MID that is different from every other MID on every other polynucleotide in the sample. In general, to accomplish such molecular tagging the number of distinct MID tags to be used should be many times greater than the actual number of molecules to be analyzed. This will result in the majority of individual nucleic acid molecules being labeled with a unique ID tag (see, e.g., Brenner et al., Proc. Natl. Acad. Sci. USA. 2000 97(4):1665-70). Any sequences that then result from the reflex process on that particular molecule (e.g., as described above) will thus be labeled with the same unique MID tag and thus inherently linked. Note that once all molecules in a sample are individually tagged, they can be manipulated and amplified as much as needed for processing so long as the MID tag is maintained in the products generated.

For example, we might want to sequence one thousand viral genomes (or a specific genomic region) or one thousand copies of a gene present in somatic cells. After tagging each polynucleotide in the sample with a sequencing primer site, MID and reflex sequence (as shown in the figures and described above), we use the reflex process to break each polynucleotide into lengths appropriate to the sequencing procedure being used, transferring

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the sequencing primer site and MID to each fragment (as described above). Obtaining sequence information from all of the reflex-processed samples can be used to determine the sequence of each individual polynucleotide in the starting sample, using the MID sequence to defining linkage relationships between sequences from different regions in the polynucleotide being sequenced. Using a sequencing platform with longer read lengths can minimize the number of primers to be used (and reflex fragments generated).

The advantages noted above are shown in Figure 5. This figure shows a comparison of methods for identifying nucleic acid polymorphisms in homologous nucleic acids in a sample (e.g., the same region derived from a chromosomal pair of a diploid cell or viral genomes/transcripts). The top schematic shows two nucleic acid molecules in a sample (1 and 2) having a different assortment of polymorphisms in polymorphic sites A, B and C (A1, B1, C1 and C2). Standard sequencing methods using fragmentation (left side) can identify the polymorphisms in these nucleic acids but do not retain linkage information. Employing the reflex process described herein to identify polymorphisms (right side) maintains linkage information. It is noted that not all domain structures and steps are shown in the reflex process for simplicity.

Kits and Systems

Also provided by the subject invention are kits and systems for practicing the subject methods, as described above, such vectors configured to add reflex sequences to nucleic acid inserts of interest and regents for performing any steps in the cloning or reflex process described herein (e.g., restriction enzymes, nucleotides, polymerases, primers, exonucleases, etc.). The various components of the kits may be present in separate containers or certain compatible components may be precombined into a single container, as desired.

The subject systems and kits may also include one or more other reagents for preparing or processing a nucleic acid sample according to the subject methods. The reagents may include one or more matrices, solvents, sample preparation reagents, buffers, desalting reagents, enzymatic reagents, denaturing reagents, where calibration standards such as positive and negative controls may be provided as well. As such, the kits may include one or more containers such as vials or bottles, with each container containing a separate component for carrying out a sample processing or preparing step and/or for carrying out one or more steps of a nucleic acid variant isolation assay according to the present invention.

In addition to above-mentioned components, the subject kits typically further include instructions for using the components of the kit to practice the subject methods, e.g., to prepare nucleic acid samples for perform the reflex process according to aspects of the

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subject methods. The instructions for practicing the subject methods are generally recorded on a suitable recording medium. For example, the instructions may be printed on a substrate, such as paper or plastic, etc. As such, the instructions may be present in the kits as a package insert, in the labeling of the container of the kit or components thereof (i.e., associated with the packaging or sub-packaging) etc. In other embodiments, the instructions are present as an electronic storage data file present on a suitable computer readable storage medium, e.g. CD-ROM, diskette, etc. In yet other embodiments, the actual instructions are not present in the kit, but means for obtaining the instructions from a remote source, e.g. via the internet, are provided. An example of this embodiment is a kit that includes a web address where the instructions can be viewed and/or from which the instructions can be downloaded. As with the instructions, this means for obtaining the instructions is recorded on a suitable substrate.

In addition to the subject database, programming and instructions, the kits may also include one or more control samples and reagents, e.g., two or more control samples for use in testing the kit.

Utility

The reflex process described herein provides significant advantages in numerous applications, a few of which are noted below (as well as described above).

For example, as described above, certain aspects of the reflex process define the particular sections of sequence to be analyzed by a primer pair, as in PCR (e.g., the two oligos shown as A_n-B_n in Figure 1B). This results in higher sequence specificity as compared to other extraction methods (e.g., using probes on a microarray) that only use a single oligo sequence. The separation of the probes defines a length that can be relatively uniform (hence making subsequent handling including amplification more uniform) and can also be tailored to the particular sequencing platform being employed.

Further, as described above, aspects of the present invention can be used to analyze homologous genomic locations in a multiplexed sample (i.e., a sample having polynucleotides from different genomic samples) in which the polynucleotides are tagged with the MID. This is possible because the reflex process, which operates intramolecularly, maintains the MID thus linking any particular fragment to the sample from which it originates.

Finally, as the reflex processes described herein function intramolecularly, one can determine the genetic linkage between different regions on the same large fragment that are too far apart to be sequenced in one sequence read. Such a determination of linkage may be of great value in plant or animal genetics (e.g., to decide if a particular set of variations are

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linked together on the same stretch of chromosome) or in viral studies (e.g., to determine if particular variations are linked together on the same stretch of a viral genome/transcripts, e.g., HIV, hepatitis virus, etc.).

EXAMPLES

Example I

Figures 6 and 7 provide experimental data and validation of the reflex process described herein using synthetic polynucleotide substrates.

METHODS

Substrate:

The 100 base oligonucleotide substrate (as shown diagrammatically in Figure 6A) was synthesized with internal fluorescein-dT positioned between the REFLEX and REFLEX' sequences. This label provides convenient and sensitive method of detection of oligonucleotide species using polyacrylamide gel electrophoresis.

Extension reactions:

Reactions were prepared which contained 1 μM of the 100 base oligonucleotide substrate, 200 μM dNTPs, presence or absence of 1 μM competitor oligonucleotide, 0.5 μl of each DNA polymerase ("DNAP"): Vent (NEB, 2 units/μl), Taq (Qiagen HotStarTaq 5 units/μl) and Herculase (Stratagene), and made up to 50 μl with the appropriate commercial buffers for each polymerase and dH_20. For Taq titrations 0.5 μl, 1 μl, 2 μl, and 3 μl enzyme was used in the same 50 μl volume. Reactions were heated in a Biometra thermocycler to 95 °C for 15 minutes (Taq) or 5 minutes (Herculase, Vent), followed by 55 °C or 50 °C for 30 seconds, and a final incubation at 72 °C for 10 minutes.

T7 exonuclease digestions:

Reactions were prepared with 10 μl extension reactions above, 0.5 μl T7 exonuclease (NEB, 10 units/μl), and made up to 50 μl using NEB Buffer 4 and dH_20. Reactions were incubated at 25 °C for 30 minutes.

Gel Electrophoresis analysis:

An 8% denaturing polyacrylamide gel was used to analyze reaction species. 0.4 μl of extension reactions, and 2 μl of digestion reactions were loaded and ran at 800V for ~1.5 hours. Gels were analyzed for fluorescein using an Amersham/General Electric Typhoon imager.

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RESULTS

Figure 6A shows the structure of each stage of reflex sequence processing with the expected nucleic acid size shown on the left. The initial single stranded nucleic acid having a sequencing primer site (the Roche 454 sequencing primer A site; listed as 454A); an MID; a reflex sequence; the insert; and a complement of the reflex sequence is 100 nucleotides in length. After self-annealing and extension, the product is expected to be 130 nucleotides in length. After removal of the double stranded region from the 5' end, the nucleic acid is expected to be 82 bases in length.

Figure 6B shows the results of three experiments using three different nucleic acid polymerases (Vent, Herculase and Taq, indicated at the top of the lanes). The temperature at which the annealing was carried out is shown at the top of each lane (either 50°C or 55°C). The sizes of the three nucleic acids as noted above are indicated on the left and right side of the gel.

As shown in figure 6B, extension appears to be most efficient under the conditions used with Herculase (Herculase is a mixture of two enzymes: modified Pfu DNAP and Archaemax (dUTPase)). Most (or all) of the initial 100 base pair nucleic acid are converted to the 130 base pair product (see lanes 6 and 7). However, after T7 exonuclease digestion the 3'-5' exonuclease activity of Herculase results in partial digestion of the desired 82 base product (note bands at and below the 82 base pairs in lanes 8 and 9).

Taq, which lacks 3'-5' exonuclease activity, shows a stronger band at the expected size of the final product after T7 exonuclease digestion (see lane 13).

Figure 7 shows the effect on the reflex process of increasing amounts of Taq polymerase as well as the use of a reflex sequence competitor (schematically shown in Figure 7A).

As shown in lanes 2 to 5, increased Taq concentration improves extension to ~90% conversion of the starting nucleic acid (see lane 5). Lanes 7 to 8 show that T7 exonuclease digestion does not leave a perfect 82 base product. This may be due to collapse of dsDNA when T7 exonuclease has nearly completed its digestion from the 5' end in the double stranded region of the fold-back structure. It is noted that in many embodiments, the removal of a few additional bases from the 5' end of the polynucleotide will not interfere with subsequent analyses, as nucleotide bases at the 5' end are often removed during subsequent steps.

As shown in Lanes 11-14, addition of a competitor (which can interfere with annealing of the reflex sequences to form the fold-back structure) results in only a small

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decrease (~5-10%) of fully extended product. Thus, as expected, the intramolecular reaction is heavily favored. Although not shown, we have observed that the competitor oligonucleotide also gets extended by the same amount (~5-10%).

The concentration of the competitor, the concentration of the reflex substrate, and the overall genetic complexity, will all likely affect specific results. The experiments shown in Figures 6 and 7 demonstrate that the core parts of the reflex processes as described herein is functional and can be implemented.

Example II

Figure 8 shows the reflex workflow (diagram at left) and exemplary results of the workflow (gel at right) for a specific region of interest (ROI). The starting material is a double stranded nucleic acid molecule (700) that contains a 454A primer site, an MID, a reflex site, and a polynucleotide of interest having three ROIs (2, 3 and 4) at different locations therein. This starting material was subjected to reflex processes (as described in above) specific for ROI 2 as shown in the diagram at the left of the figure, both with and without the use of a T7 exonuclease step (the T7 exonuclease step is shown in the diagram is indicated as "Optional").

Completion of all steps shown in the reflex process should result in a double stranded polynucleotide of 488 base pairs (702) with or without the T7 exonuclease step.

As shown in the gel on the right of Figure 8, the 488 base pair product was produced in reflex processes with and without the T7 exonuclease step.

Figure 9 shows an exemplary protocol for a reflex process based on the results discussed above. The diagram shows specific reflex process steps with indications on the right as to where purification of reaction products is employed (e.g., using Agencourt SPRI beads to remove primer oligos). One reason for performing such purification steps is to reduce the potential for generating side products in a reaction (e.g., undesirable amplicons). While Figure 9 indicates three purification steps, fewer or additional purification steps may be employed depending on the desires of the user. It is noted that the steps of reversing polarity, reflex priming and extension, and "stretch out" (or denaturation) / second reversing polarity step can be performed without intervening purification steps.

The protocol shown in Figure 9 includes the following steps:

annealing a first primer containing a 5' reflex sequence (or reflex tail, as noted in the figure) specific for the 3' primer site for the R' region to the starting polynucleotide and extending (the primer anneals to the top strand at the primer site at the right of R in

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polynucleotide 902, indicated with a *; this step represents the first denature, anneal and extend process indicated on the right);

after purification, adding a 454A primer and performing three cycles of denaturing, annealing and extending: the first cycle results in the copy-back from the 454A primer to reverse the polarity of the strand just synthesized; the second cycle breaks apart the double stranded structure produced, allows the reflex structure to form and then extend; the third cycle results in another copy-back using the same 454A primer originally added;

after purification, adding a second primer specific for the second primer site for the R' region having a 5' 454B tail (this primer anneals to the primer site 3' of the R' region in polynucleotide 904, indicated with a *) and denaturing, annealing and extending resulting in a polynucleotide product having 454A and 454B sites surrounding the MID, the reflex sequence, and R'. Note that the first primer specific for the R' region and the second primer specific for the R' region define its boundaries, as described above and depicted in Figure 1B);

after another purification, adding 454A and 454B primers and performing a PCR amplification reaction.

Example III

As described above, a reflex sequence can be an "artificial" sequence added to a polynucleotide as part of an adapter or can be based on a sequence present in the polynucleotide of interest being analyzed, e.g., a genomic sequence (or "non-artificial").

The data shown in prior Examples used "artificial" reflex sites. In this Example, the reflex site is a genomic sequence present in the polynucleotide being analyzed.

The starting material is a double stranded DNA containing a 454A site, an MID and a polynucleotide to be analyzed. The 454A and MID were added by adapter ligation to parent polynucleotide fragments followed by enrichment of the polynucleotide to be analyzed by a hybridization-based pull-out reaction and subsequent secondary PCR amplification (see Route 1 in Figure 13). Thus, the reflex site employed in this example is a sequence normally present at the 5' end of the subject polynucleotide (a genomic sequence). The polynucleotide being analyzed includes a region of interest distal to the 454A and MID sequences that is 354 base pairs in length.

This starting double stranded nucleic acid is 755 base pairs in length. Based on the length of each of the relevant domains in this starting nucleic acid, the reflex process should result in a product of 461 base pairs.

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Figure 10 shows the starting material for the reflex process (left panel) and the resultant product generated using the reflex process (right panel; reflex process was performed as described in Example II, without using a T7 exonuclease step). A size ladder is included in the left hand lane of each gel to allow estimation of the size of the test material. This figure shows that the 755 base pair starting nucleic acid was processed to the expected 461 base pair product, thus confirming that a "non-artificial" reflex site is effective in moving an adapter domain from one location to another in a polynucleotide of interest in a sequence specific manner.

Example IV

Figure 11 shows a schematic of an experiment in which the reflex process is performed on a single large initial template (a "parent" fragment) to generate 5 different products ("daughter" products) each having a different region of interest (i.e., daughter products are produced having either region 1, 2, 3, 4 or 5). The schematic in Figure 11 shows the starting fragment (11,060 base pairs) and resulting products (each 488 base pairs) generated from each of the different region of interest-specific reflex reactions (reflex reactions are performed as described above). The panel (gel) on the bottom of Figure 11 shows the larger starting fragment (Lane 1) and the resulting daughter products for each region-specific reflex reaction (lanes 2 to 6, with the region of interest noted in each in the box), where the starting and daughter fragments have the expected lengths. Sequencing of the products confirmed the identity of the region of interest in each of the reflex products shown in the gel. These results demonstrate that multiple different reflex products can be generated from a single, asymmetrically tagged parent fragment while maintaining the adapter domains (e.g., the primer sites and MID).

Example V

Figure 12 details experiments performed to determine the prevalence of intramolecular rearrangement (as desired in the reflex process) vs. intermolecular rearrangement. Intermolecular rearrangement is undesirable because it can lead to the transfer of an MID from one fragment to another (also called MID switching). MID switching can occur if a reflex sequence in a first fragment hybridizes to its complement in a second fragment during the reflex process, leading to appending the MID from the second fragment to the first fragment. Thus, intermolecular rearrangement, or MID switching, should be minimized to prevent the transfer of an MID from one fragment in the sample to another, which could lead to a misrepresentation of the source of a fragment.

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To measure the prevalence of MID switching under different reflex conditions, fragments having different sizes were generated that included two different MIDs, as shown in the top panel of Figure 12. The common sequence on these fragments serves as the priming site for the first extension reaction to add the second reflex sequence (see, e.g., step 2 of Figure 3). Three exemplary fragments are shown in Figure 12 for each different fragment size (i.e., 800 base pairs with an MIDB and MIDA combination; 1900 base pairs with MIDC and MIDA combination; and 3000 base pairs with MIDD and MIDA combination). For each MID family (A, B, C and D), there are 10 different members (i.e., MIDA had 10 different members, MIDB has 10 different members, etc.). A set of 10 dual MID fragments for each different size fragment (i.e., 800, 1900 and 3000 base pairs) were generated, where the MID pairs (i.e., MIDA/MIDB, MIDA/MIDC, and MIDA/MIDD) were designated as 1/1, 2/2, 3/3, 4/4, 5/5, 6/6, 7/7, 8/8, 9/9, and 10/10. All 10 fragments of the same size were then mixed together and a reflex protocol was performed.

Due to the domain structure of the fragments, a successful reflex process results in the two MIDs for each fragment being moved to within close enough proximity to be sequenced in a single read using the Roche 454 sequencing platform (see the reflex products shown in the schematic of Figure 12). The reflex reactions for each fragment size were performed at four different fragment concentrations to determine the effect of this parameter, as well as fragment length, in the prevalence of MID switching. The reflex products from each reaction performed were subjected to 454 sequencing to determine the identity of both MIDs on each fragment, and thereby the proportion of MID switching that occurred.

The panel on the bottom left of Figure 12 shows the rate of MID switching (Y axis, shown in % incorrect (or switched) MID pair) for each different length fragment at each different concentration (X axis; 300, 30, 3 and 0.3 nM). As shown in this panel, the MID switch rate decreases with lower concentrations, as would be expected, because intermolecular, as opposed to intramolecular, binding events are concentration dependent (i.e., lower concentrations lead to reduced intermolecular hybridization/binding). In addition, the MID switch rate decreases slightly with length. This is somewhat unexpected as the ends of longer DNA fragments are effectively at a lower concentration with respect to one another. The reasons for why we do not see this is probably because the production of reflex priming intermediates continues during the final PCR, which means that reflex priming reactions are happening continuously which contributes to MID switching. It is probably the case that the shorter reflex products are able to undergo a higher rate of 'background' reflexing, and therefore increase the overall MID switch rate a little.

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These results demonstrate that MID switching can be minimized (e.g., to below 2%, below 1% or even to nearly undetectable levels) by altering certain parameters of the reaction, e.g., by reducing fragment concentration and/or fragment length.

The panel on the bottom right of Figure 12 shows the frequency of MID switching in the reflex process for the 800 base pair fragments (i.e., MIDA/MIDB containing fragments). In this figure, the area of each circle is proportional to the number of reads containing the corresponding MIDA and MIDB species (e.g., MIDA1/MIDB1; MIDA1/MIDB2; etc.). Thus, a circle representing 200 reads will be 40 times larger in terms of area than a circle representing 5 reads.

As noted above, the MIDA/MIDB combinations having the same number (shown on the X and Y axis, respectively) represent the MIDA/MIDB combinations present in the sample prior to the reflex process being performed (i.e., MIDA/MIDB combinations 1/1, 2/2, 3/3, 4/4, 5/5, 6/6, 7/7, 8/8, 9/9, and 10/10 were present in the starting sample). All other MIDA/MIDB combinations identified by Roche 454 sequencing were the result of MID switching.

This figure shows that the MID switching that occurs during the reflex process is random, i.e., that MID switching is not skewed based on the identity of the MIDs in the reaction).

Exemplary Reflex Protocols

Figure 13 shows a diagram of exemplary protocols for performing the reflex process on pools of nucleic acids, for example, pools of nucleic acids from different individuals, each of which are labeled with a unique MID. In Route 3, a pooled and tagged extended library is subjected directly to a reflex process. In Route 2, the pooled library is enriched by target-specific hybridization followed by performing the reflex process. In Route 1 employs enrichment by PCR amplification. As shown in Figure 13, PCR enrichment can be performed directly on the pooled tagged extended library or in a secondary PCR reaction after a hybridization-based enrichment step has been performed (as in Route 2) to generate an amplicon substrate that is suitable for the reflex process. Additional routes for preparing a polynucleotide sample for performing a reflex process can be implemented (e.g., having additional amplification, purification, and/or enrichment steps), which will generally be dependent on the desires of the user.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it is readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes

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and modifications may be made thereto without departing from the spirit or scope of the appended claims.

Accordingly, the preceding merely illustrates the principles of the invention. It will be appreciated that those skilled in the art will be able to devise various arrangements which, although not explicitly described or shown herein, embody the principles of the invention and are included within its spirit and scope. Furthermore, all examples and conditional language recited herein are principally intended to aid the reader in understanding the principles of the invention and the concepts contributed by the inventors to furthering the art, and are to be construed as being without limitation to such specifically recited examples and conditions. Moreover, all statements herein reciting principles, aspects, and embodiments of the invention as well as specific examples thereof, are intended to encompass both structural and functional equivalents thereof. Additionally, it is intended that such equivalents include both currently known equivalents and equivalents developed in the future, i.e., any elements developed that perform the same function, regardless of structure. The scope of the present invention, therefore, is not intended to be limited to the exemplary embodiments shown and described herein. Rather, the scope and spirit of present invention is embodied by the appended claims.

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CLAIMS

That which is claimed is:

1. A method of moving a domain in a nucleic acid, the method comprising:

a) annealing a reflex sequence in a polynucleotide strand in a sample with a complement of the reflex sequence present in the polynucleotide strand, wherein the polynucleotide strand comprises the following in a 5' to 3' orientation:

a first domain;

the reflex sequence;

a polynucleotide of interest; and

the complement of the reflex sequence, wherein the complement of the reflex sequence is present at the 3' end of the polynucleotide strand; and

b) extending from the 3' end of the complement of the reflex sequence through the first domain to produce a double stranded region;

whereby a complement of the first domain is present at the 3' end of the extended polynucleotide strand, thereby moving the first domain in the polynucleotide strand.

2. The method of claim 1, wherein the first domain comprises a multiplex identifier (MID).

3. The method of claim 1, wherein the first domain comprises a primer site.

4. The method of claim 1, wherein the reflex sequence is from 10 to 50 nucleotides in length.

5. The method of claim 1, wherein the reflex sequence comprises an RNA polymerase site.

6. The method of claim 1, the method further comprising removing the first domain and the reflex sequence from the 5' end of the double stranded region.

7. The method of claim 6, wherein the removing step comprises treating the nucleic acid of step b with T7 exonuclease.

8. The method of claim 1, wherein the first domain is present in an adapter region attached to the polynucleotide of interest.

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9. The method of claim 8, wherein the reflex sequence is present in the adapter region.

10. The method of claim 8, wherein the reflex sequence is a sequence present within the 5' region of the polynucleotide of interest.

11. The method of claim 1, wherein the sample is a multiplexed sample, wherein the first domain in each of the polynucleotide strands in the multiplexed sample comprises a MID corresponding to its parental sample.

12. The method of claim 1, wherein the sample comprises multiple polynucleotide strands, and wherein each polynucleotide strand in the sample comprises a unique MID in the first domain.

13. The method of claim 1, wherein the polynucleotide strand is produced by:

annealing a nucleic acid synthesis primer to a parent polynucleotide strand, wherein the parent polynucleotide strand comprises the following in a 5' to 3' orientation:

the first domain;

the reflex sequence; and

a second domain comprising the polynucleotide of interest;

wherein the nucleic acid synthesis primer comprises:

a 3' priming domain that is complementary to a site adjacent to and 3' of the polynucleotide of interest in the second domain; and

a 5' reflex sequence;

extending the nucleic acid synthesis primer to produce an extension product; and

replicating the resultant extension product with a second nucleic acid synthesis primer that anneals at the 3' end of the complement of the first domain, thereby producing the polynucleotide strand.

14. The method of claim 13, wherein the length of the second domain is from 30 bases to 30 kilobases.

15. The method of claim 13, wherein the parent polynucleotide strand is enriched prior to the annealing step based on its sequence.

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16. The method of claim 1, further comprising the steps of:

c) replicating the polynucleotide strand of step b with a first nucleic acid synthesis primer that anneals at the 3' end of the complement of the first domain to produce a first extension product;

d) annealing a second nucleic acid synthesis primer to the first extension product, wherein the second nucleic acid synthesis primer comprises a 3' priming domain that is complementary to a site within the polynucleotide of interest in the first extension product; and

e) extending the second synthesis primer to produce a second extension product.

17. The method of claim 16, wherein the second synthesis primer comprises a 5' domain that is not complementary to the polynucleotide of interest in the first extension product.

18. The method of claim 17, wherein the first domain comprises a first primer site and the 5' domain of the second synthesis primer comprises a second primer site.

19. The method of claim 18, wherein the length of the polynucleotide of interest in the second extension product is from 50 to 10,000 nucleotides.

20. A polynucleotide strand comprising the following in a 5' to 3' orientation:

a first domain;

a reflex sequence;

a polynucleotide of interest; and

a complement of the reflex sequence, wherein the complement of the reflex sequence is present at the 3' end of the polynucleotide strand.

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ABSTRACT OF THE DISCLOSURE

Aspects of the present invention are drawn to processes for moving a region of interest in a polynucleotide from a first position to a second position with regard to a domain within the polynucleotide, also referred to as a "reflex method". In certain embodiments, the reflex method results in moving a region of interest into functional proximity to specific domain elements present in the polynucleotide (e.g., primer sites and/or MID). Compositions, kits and systems that find use in carrying out the reflex processes described herein are also provided.

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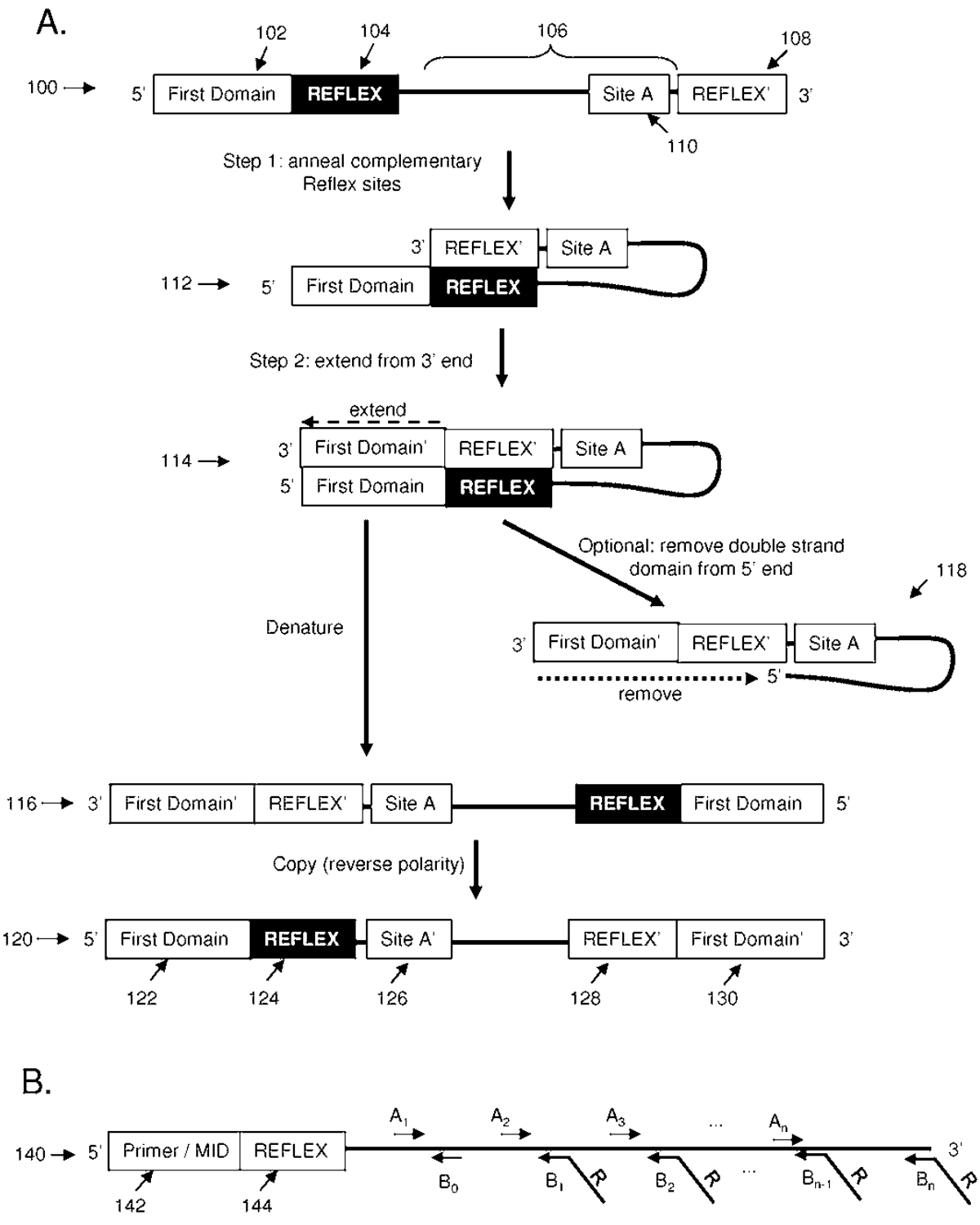

A.
100
5'
First Domain
REFLEX
102
104
106
108
Site A
REFLEX'
3'
110
Step 1: anneal complementary Reflex sites
112
3'
REFLEX'
Site A
5'
First Domain
REFLEX
Step 2: extend from 3' end
extend
114
3'
First Domain'
REFLEX'
Site A
5'
First Domain
REFLEX
Optional: remove double strand domain from 5' end
118
Denature
3'
First Domain'
REFLEX'
Site A
5'
remove
116
3'
First Domain'
REFLEX'
Site A
REFLEX
First Domain
5'
Copy (reverse polarity)
120
5'
First Domain
REFLEX
Site A'
REFLEX'
First Domain'
3'
122
124
126
128
130
B.
140
5'
Primer / MID
REFLEX
142
144
A1
A2
A3
...
An
B0
B1
B2
Bn-1
Bn
R
3'

Fig. 1

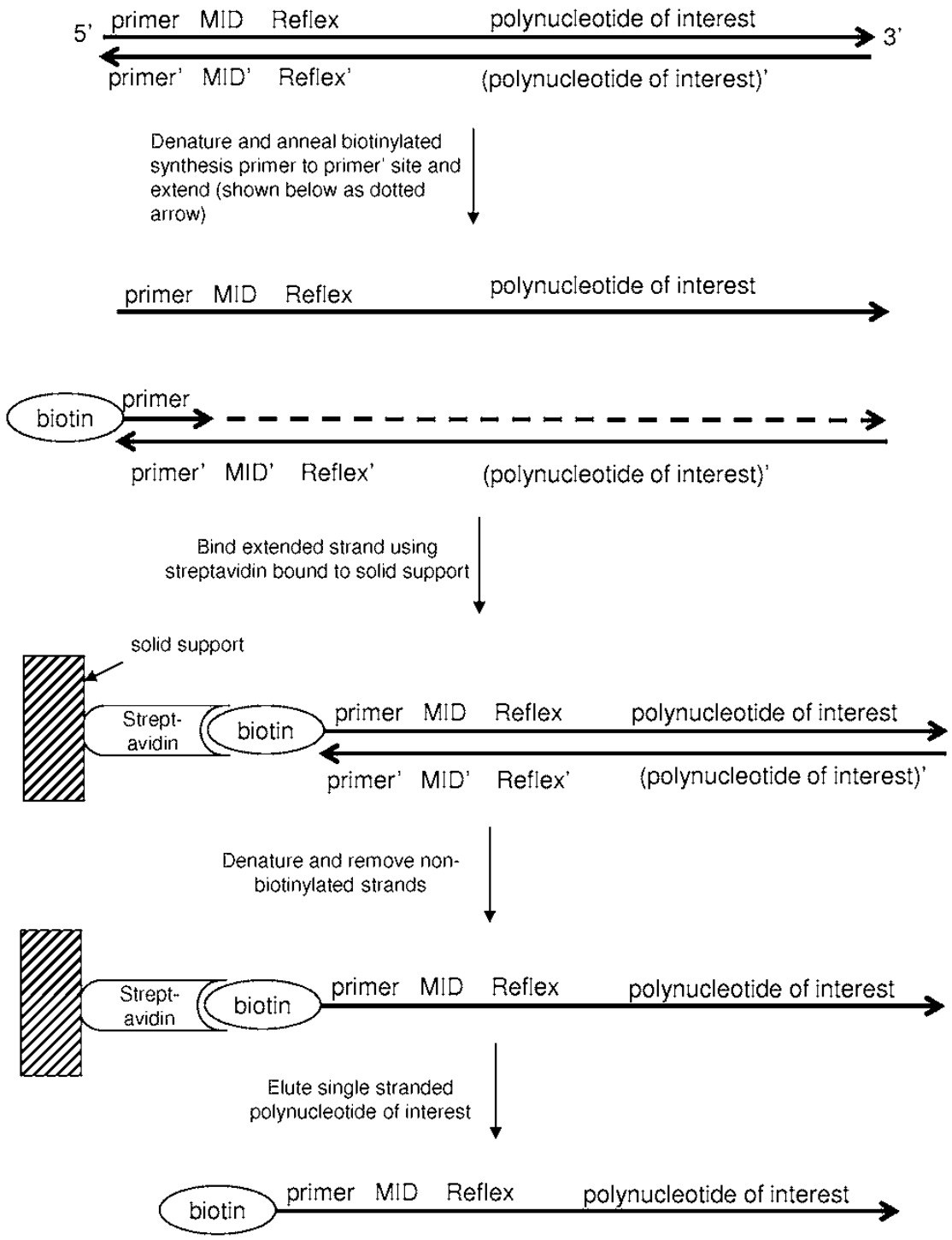
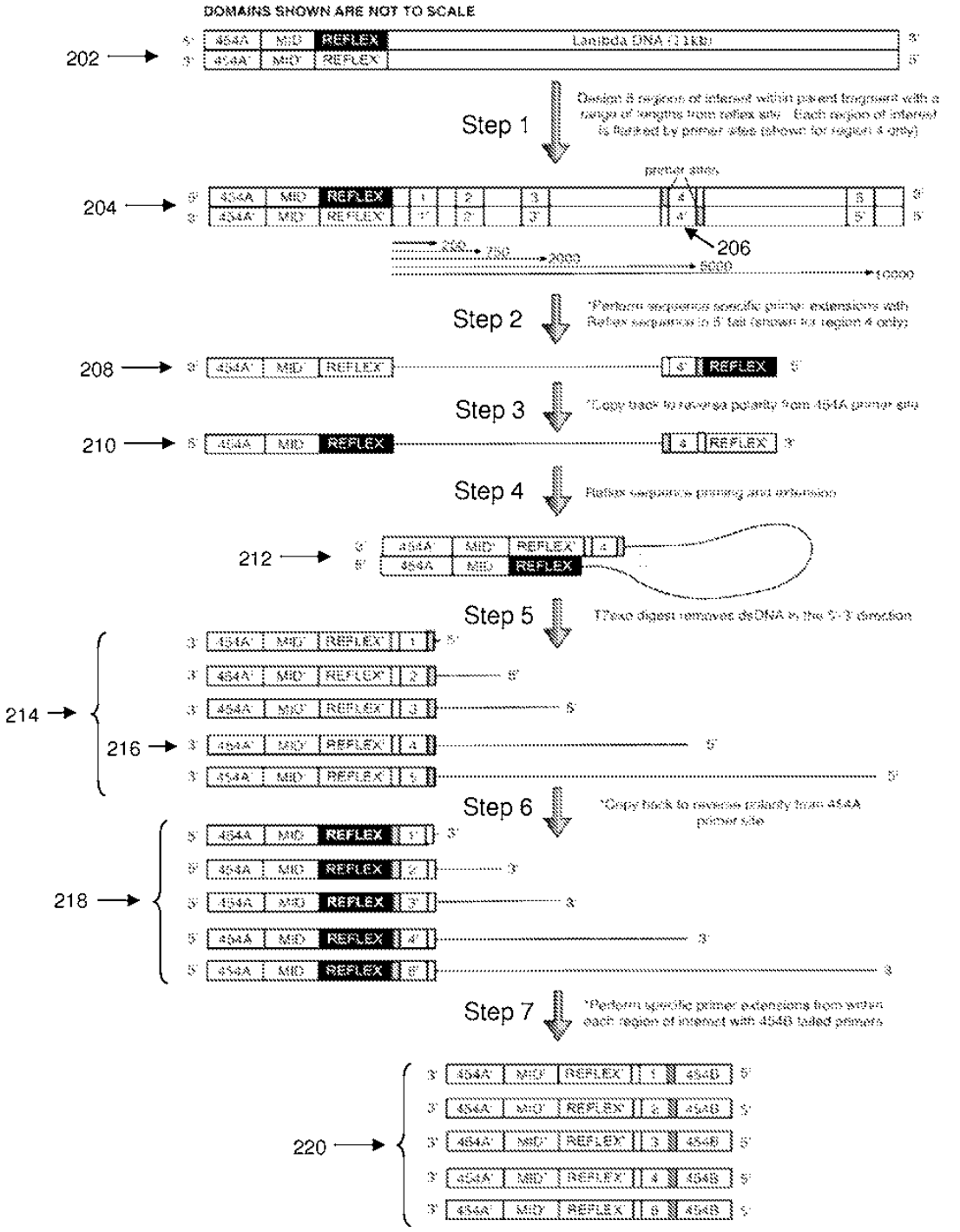

5'
primer MID Reflex
polynucleotide of interest
3'
primer' MID' Reflex'
(polynucleotide of interest)'
Denature and anneal biotinylated synthesis primer to primer' site and extend (shown below as dotted arrow)
primer MID Reflex
polynucleotide of interest
biotin
primer
primer' MID' Reflex'
(polynucleotide of interest)'
Bind extended strand using streptavidin bound to solid support
solid support
Strept-avidin
biotin
primer MID Reflex
polynucleotide of interest
primer' MID' Reflex'
(polynucleotide of interest)'
Denature and remove non-biotinylated strands
Strept-avidin
biotin
primer MID Reflex
polynucleotide of interest
Elute single stranded polynucleotide of interest
biotin
primer MID Reflex
polynucleotide of interest

Fig. 2



Primer extension reactions with * may be performed such that isolation of single strand species is facilitated (e.g., using primers with binding moieties and/or multiple cycles of extension)

Fig. 3

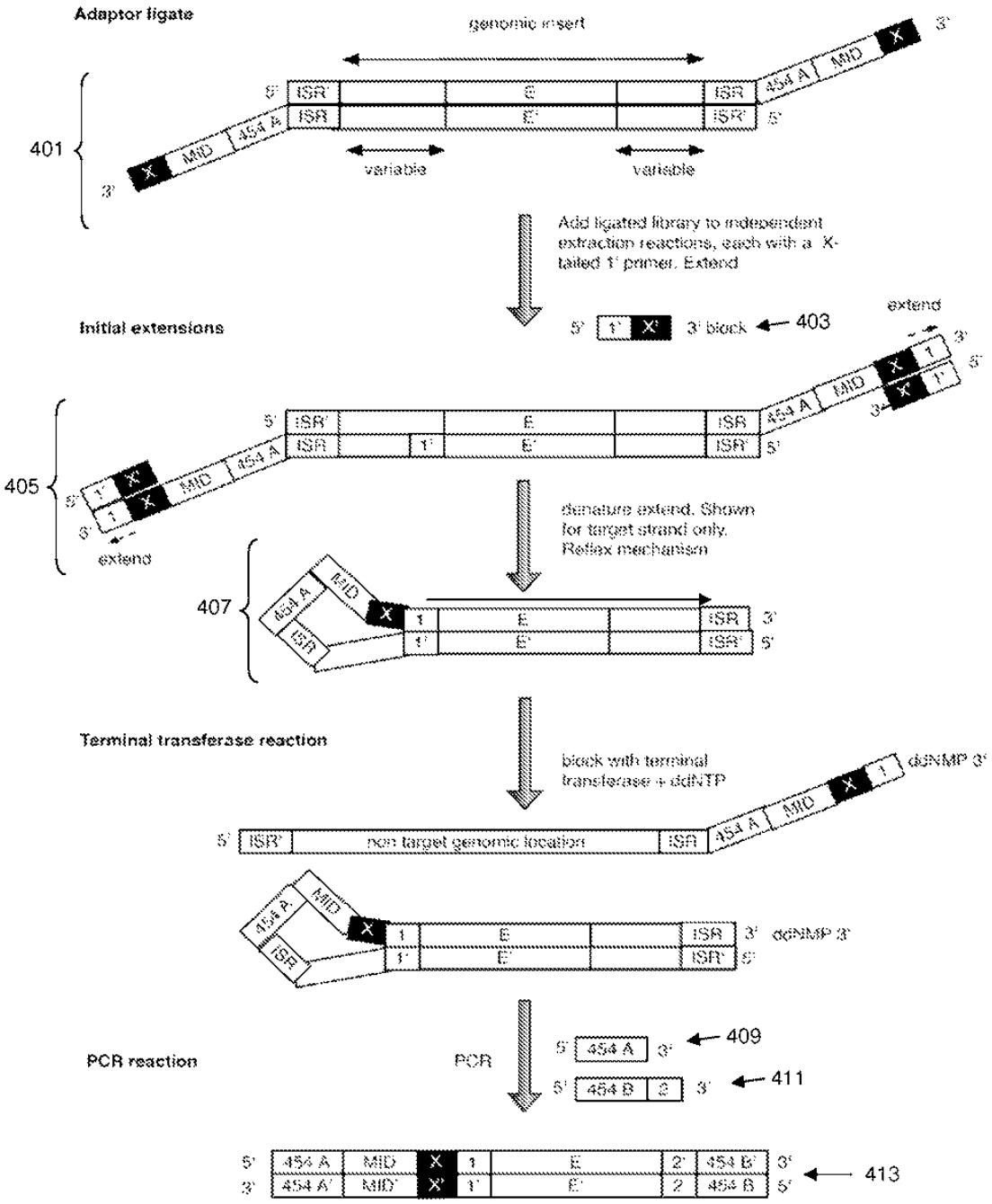

Adaptor ligate
genomic insert
401
454 A
MID
X
ISR
E
variable
Add ligated library to independent extraction reactions, each with a X-tailed 1' primer. Extend
Initial extensions
403
3' block
extend
405
407
Denature extend. Shown for target strand only. Reflex mechanism
Terminal transferase reaction
block with terminal transferase + ddNTP
ddNMP 3'
non target genomic location
PCR reaction
PCR
409
411
413

Fig. 4

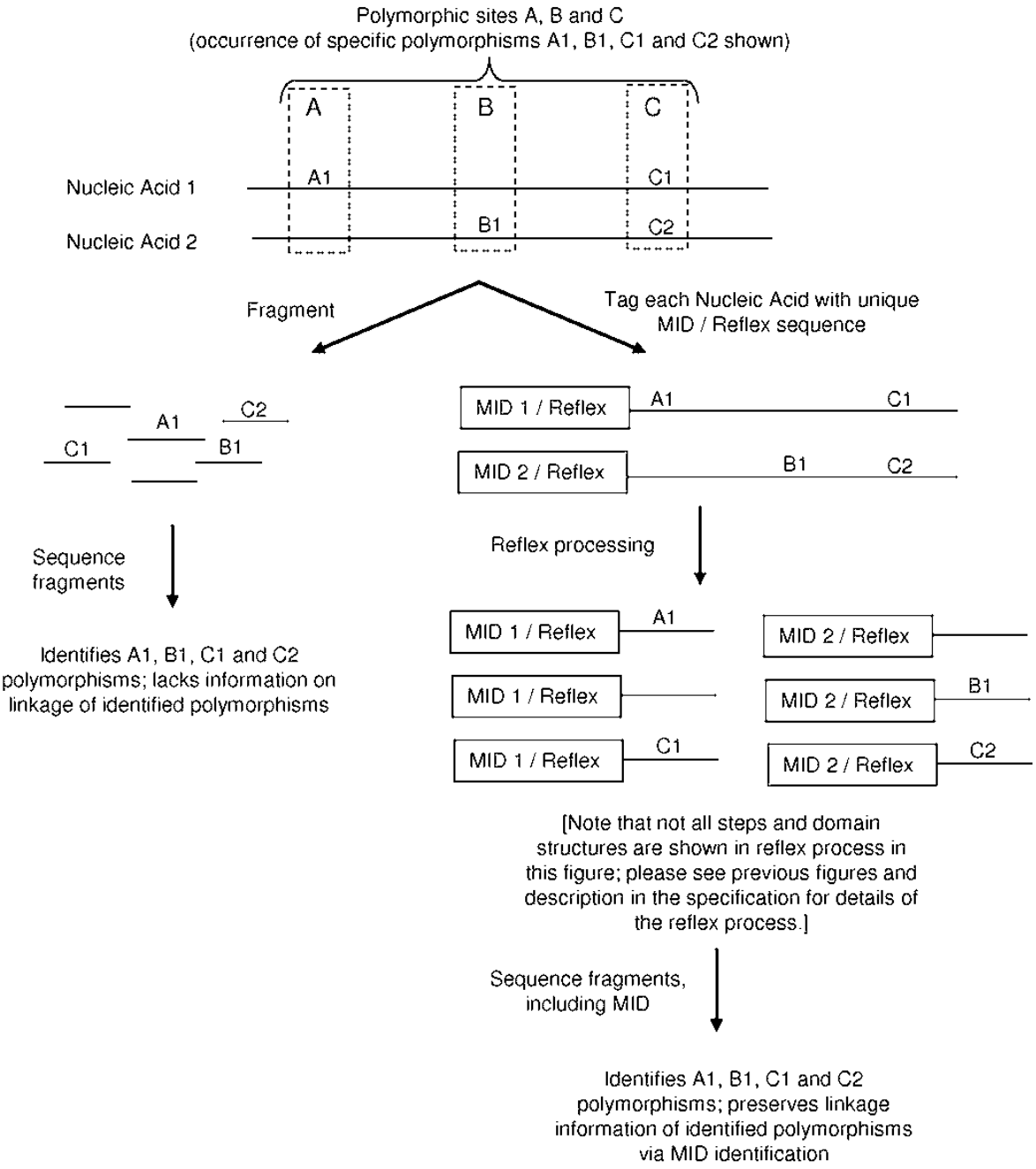
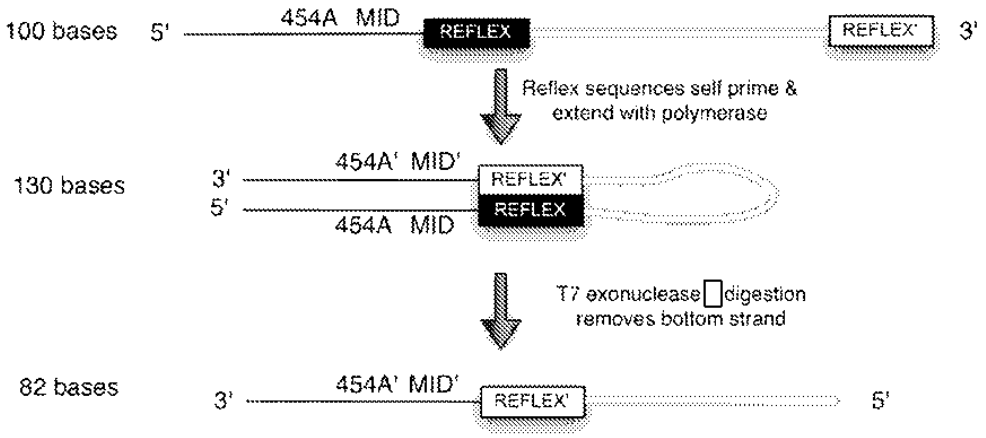
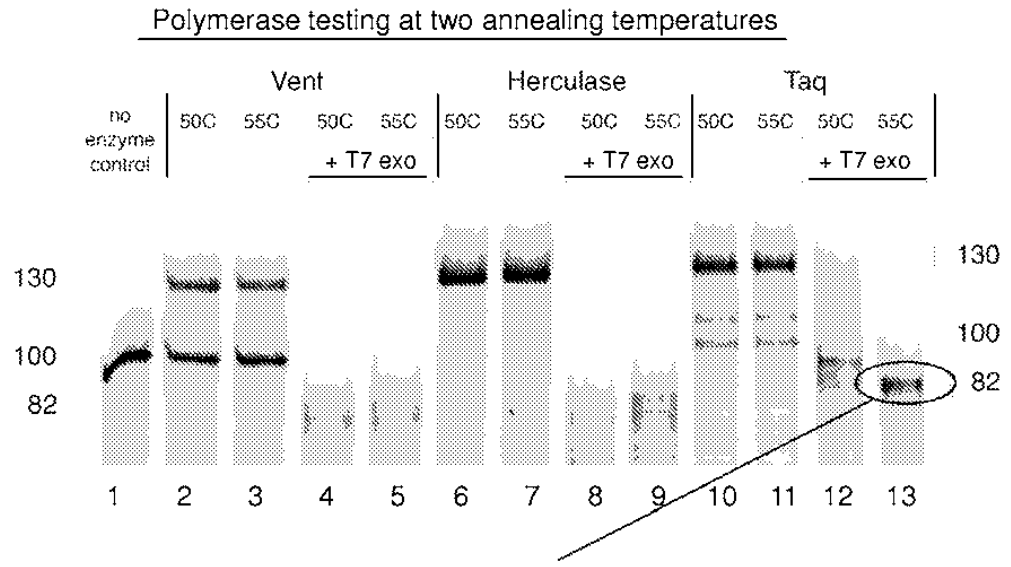

Polymorphic sites A, B and C
(occurrence of specific polymorphisms A1, B1, C1 and C2 shown)
A
B
C
Nucleic Acid 1
A1
C1
Nucleic Acid 2
B1
C2
Fragment
Tag each Nucleic Acid with unique MID / Reflex sequence
A1
C2
C1
B1
Sequence fragments
Identifies A1, B1, C1 and C2 polymorphisms; lacks information on linkage of identified polymorphisms
MID 1 / Reflex
A1
C1
MID 2 / Reflex
B1
C2
Reflex processing
MID 1 / Reflex
A1
MID 2 / Reflex
MID 1 / Reflex
MID 2 / Reflex
B1
MID 1 / Reflex
C1
MID 2 / Reflex
C2
[Note that not all steps and domain structures are shown in reflex process in this figure; please see previous figures and description in the specification for details of the reflex process.]
Sequence fragments, including MID
Identifies A1, B1, C1 and C2 polymorphisms; preserves linkage information of identified polymorphisms via MID identification

Fig. 5

A.



B.



Extension is best with Herculase, but 3'-5' exonuclease activity results in partial digestion of the desired 82 base product. Taq, which lacks 3'-5' exonuclease activity, shows a stronger band at the expected size of the final product.

Fig. 6

A.

5'
454A MID
REFLEX
REFLEX'
3'
+ Competitor
5'
REFLEX'
3'

B.

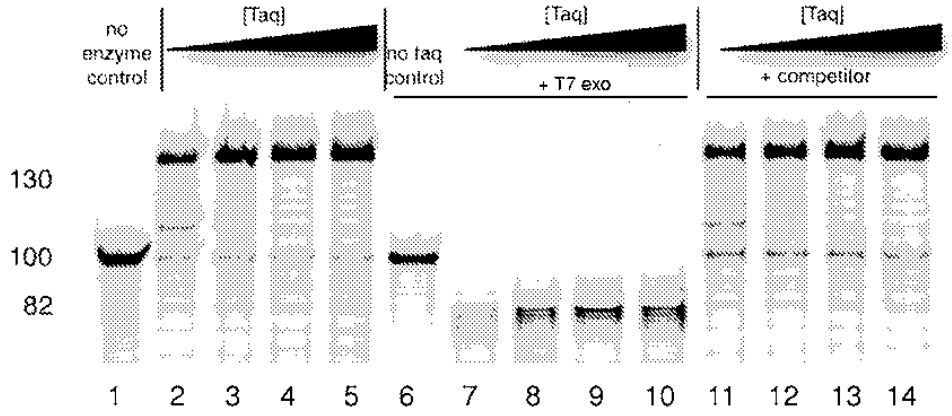
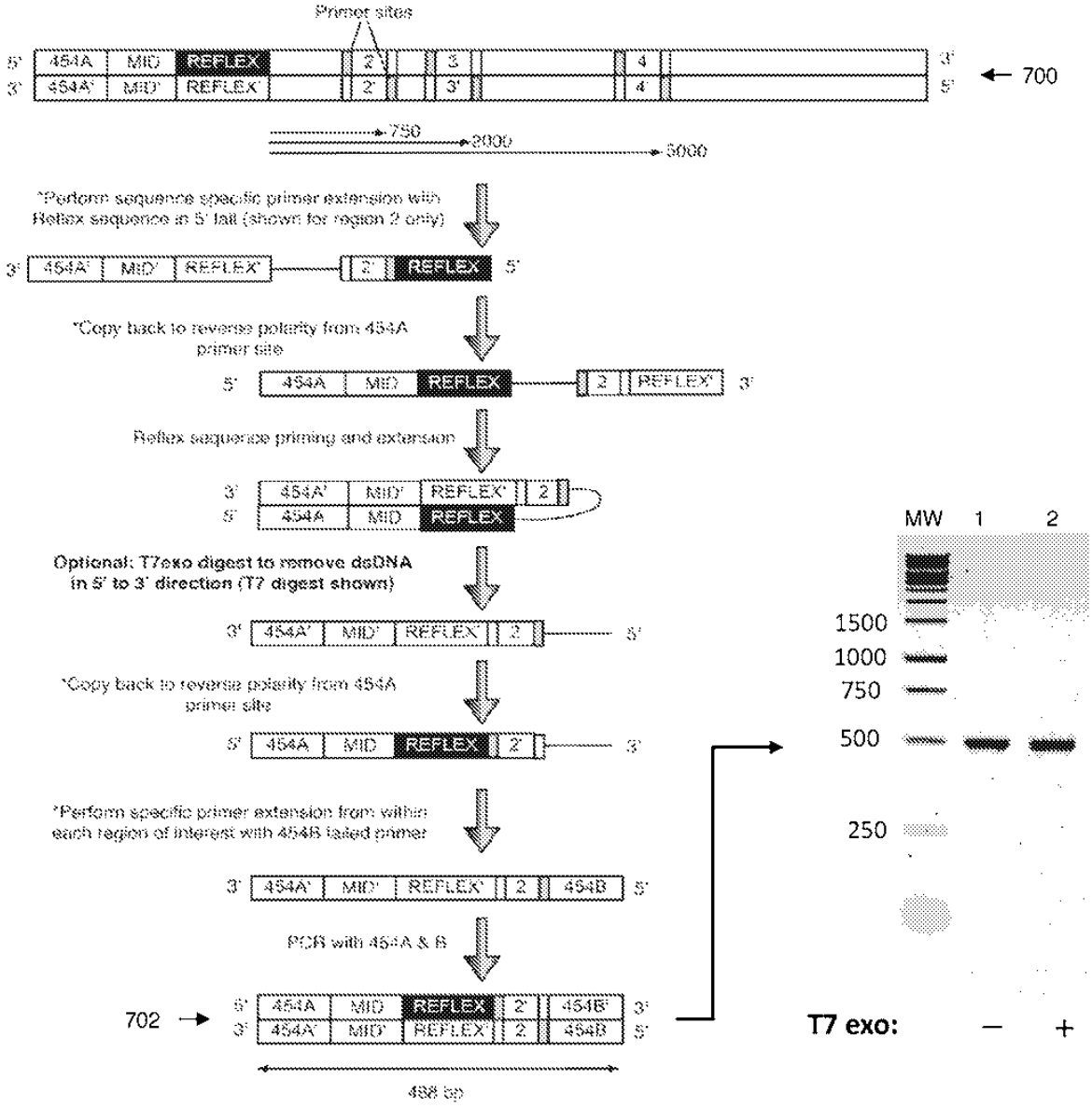

no enzyme control
[Taq]
no taq control
[Taq]
+ T7 exo
[Taq]
+ competitor
130
100
82
1
2
3
4
5
6
7
8
9
10
11
12
13
14

Fig. 7



Primer extension reactions with * may be performed such that isolation of single strand species is facilitated (e.g., using primers with binding moieties and/or multiple cycles of extension)

Fig. 8

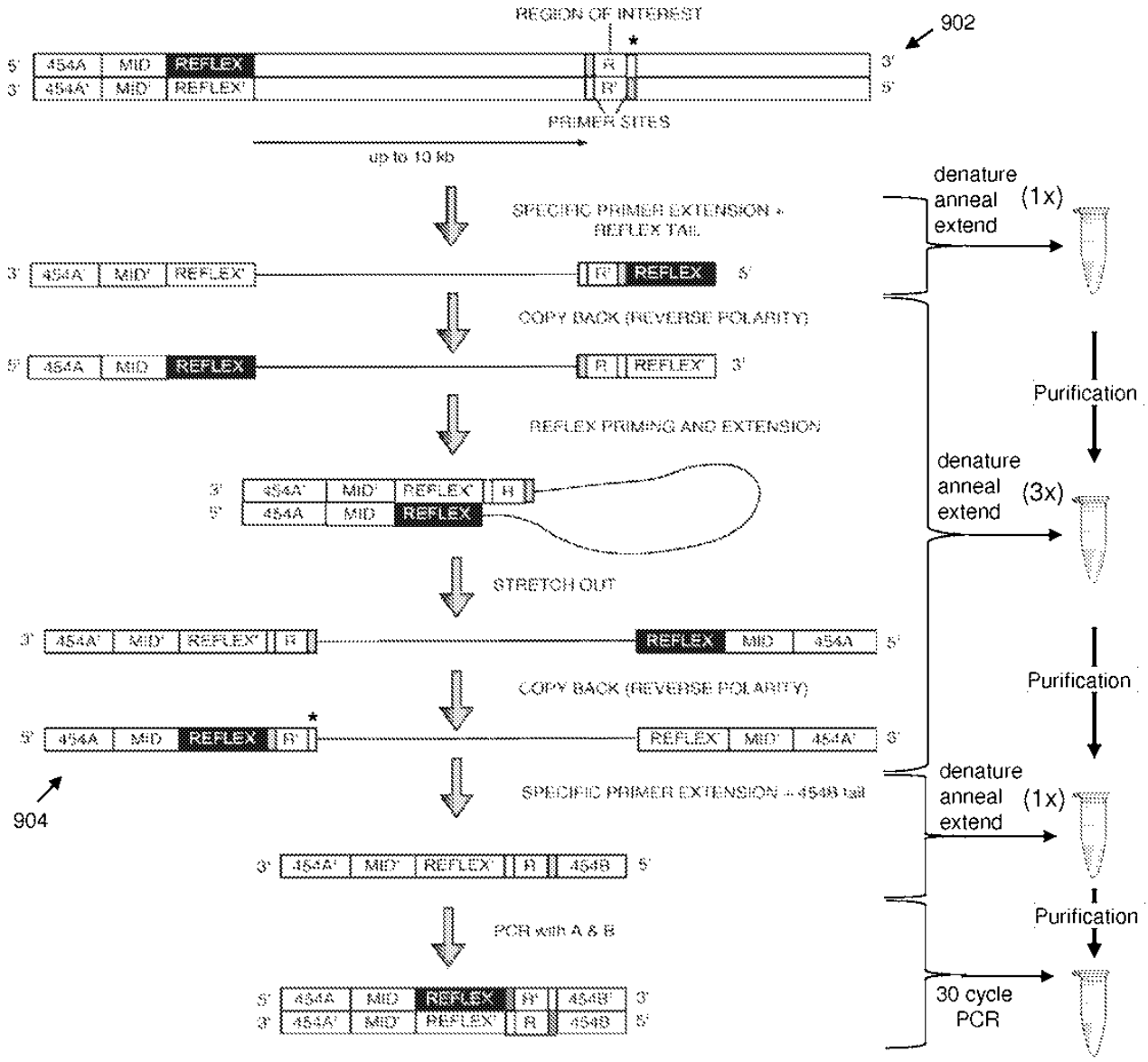

REGION OF INTEREST
902
5' 454A MID REFLEX R 3'
3' 454A' MID' REFLEX' R' 5'
PRIMER SITES
up to 10 kb
SPECIFIC PRIMER EXTENSION + REFLEX TAIL
3' 454A' MID' REFLEX' R' REFLEX 5'
COPY BACK (REVERSE POLARITY)
5' 454A MID REFLEX R REFLEX' 3'
REFLEX PRIMING AND EXTENSION
3' 454A' MID' REFLEX' R
5' 454A MID REFLEX
STRETCH OUT
3' 454A' MID' REFLEX' R REFLEX MID 454A 5'
COPY BACK (REVERSE POLARITY)
5' 454A MID REFLEX R' REFLEX' MID' 454A' 3'
SPECIFIC PRIMER EXTENSION + 454B tail
904
3' 454A' MID' REFLEX' R 454B 5'
PCR with A & B
5' 454A MID REFLEX R' 454B' 3'
3' 454A' MID' REFLEX' R 454B 5'
denature
anneal (1x)
extend
Purification
denature
anneal (3x)
extend
Purification
denature
anneal (1x)
extend
Purification
30 cycle
PCR

Fig. 9

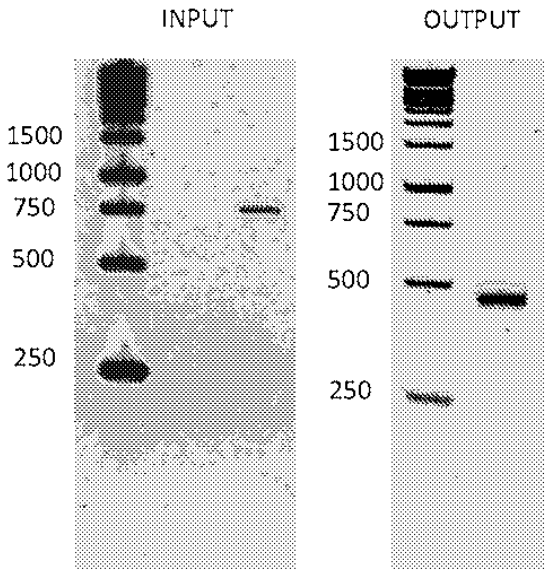
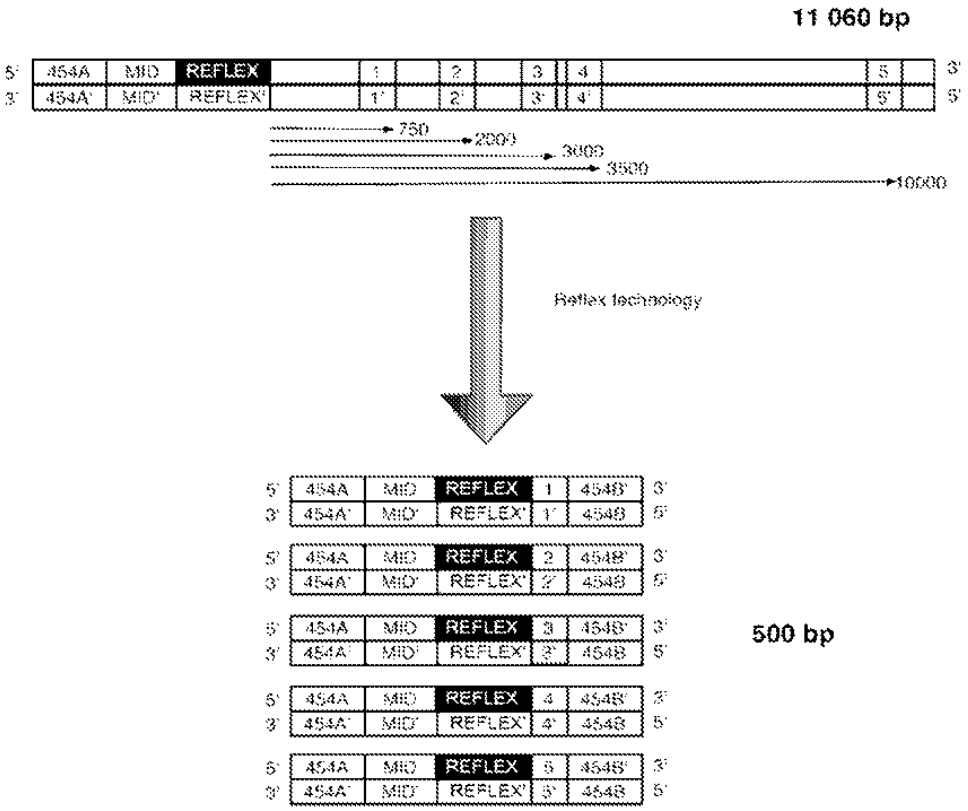


Fig. 10


11 060 bp
454A
MID
REFLEX
454A'
MID'
REFLEX'
750
2000
3000
3500
10000
Reflex technology
454B
454B'
500 bp

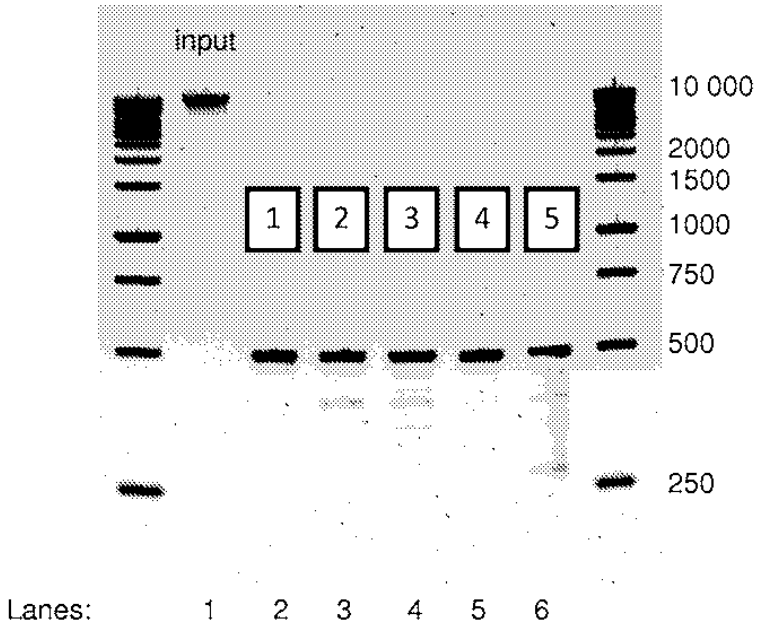
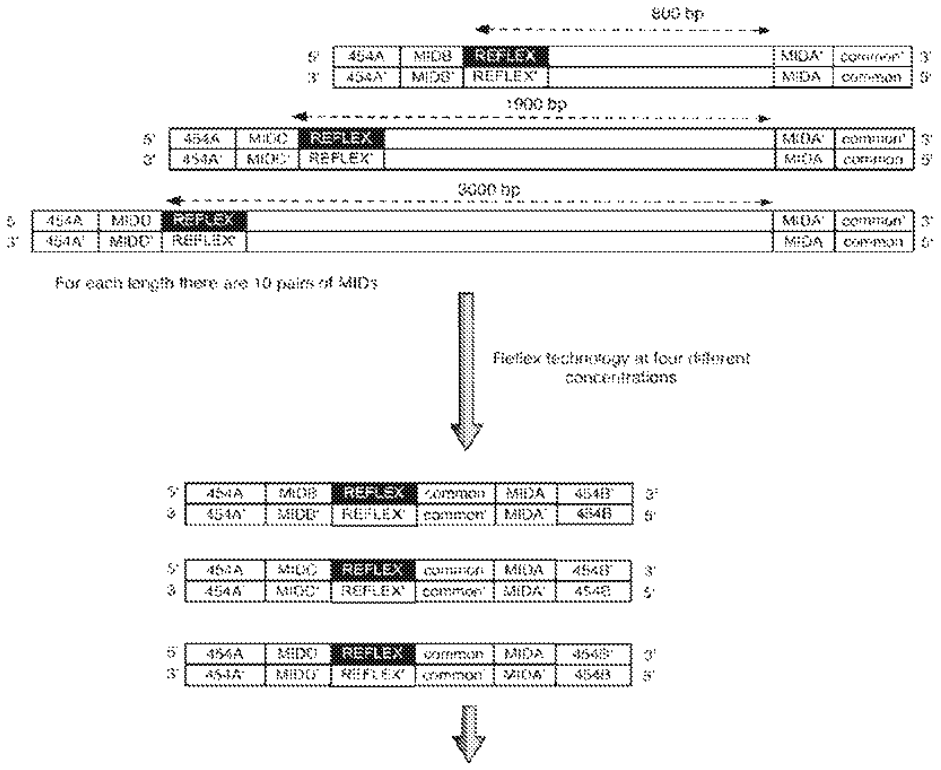
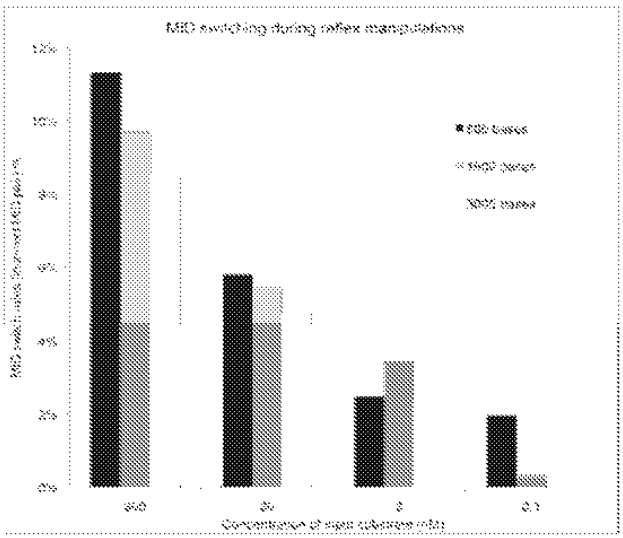

input
10 000
2000
1500
1000
750
500
250
1
2
3
4
5
Lanes: 1 2 3 4 5 6

Fig. 11


800 bp
454A
MID8
REFLEX
MIDA
common
>900 bp
3000 bp
For each length there are 10 pairs of MIDs
Reflex technology at four different concentrations
454B
Roche 454 Sequencing


MID switching during reflex manipulations
800 bases
>900 bases
3000 bases

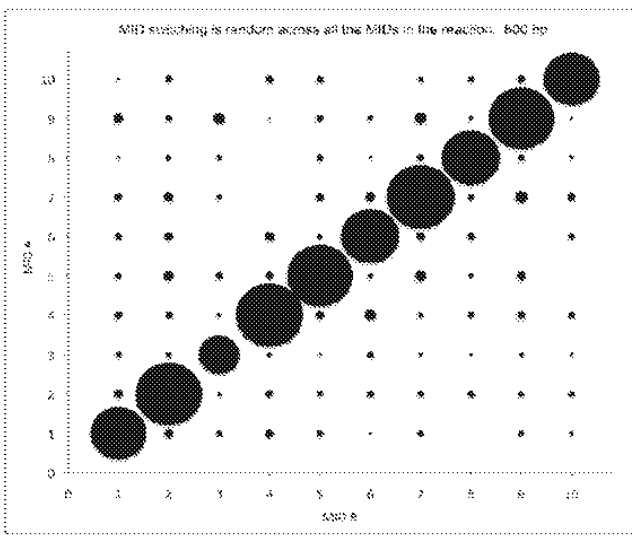

MID switching is random across all the MIDs in the reaction. 800 bp

Fig. 12

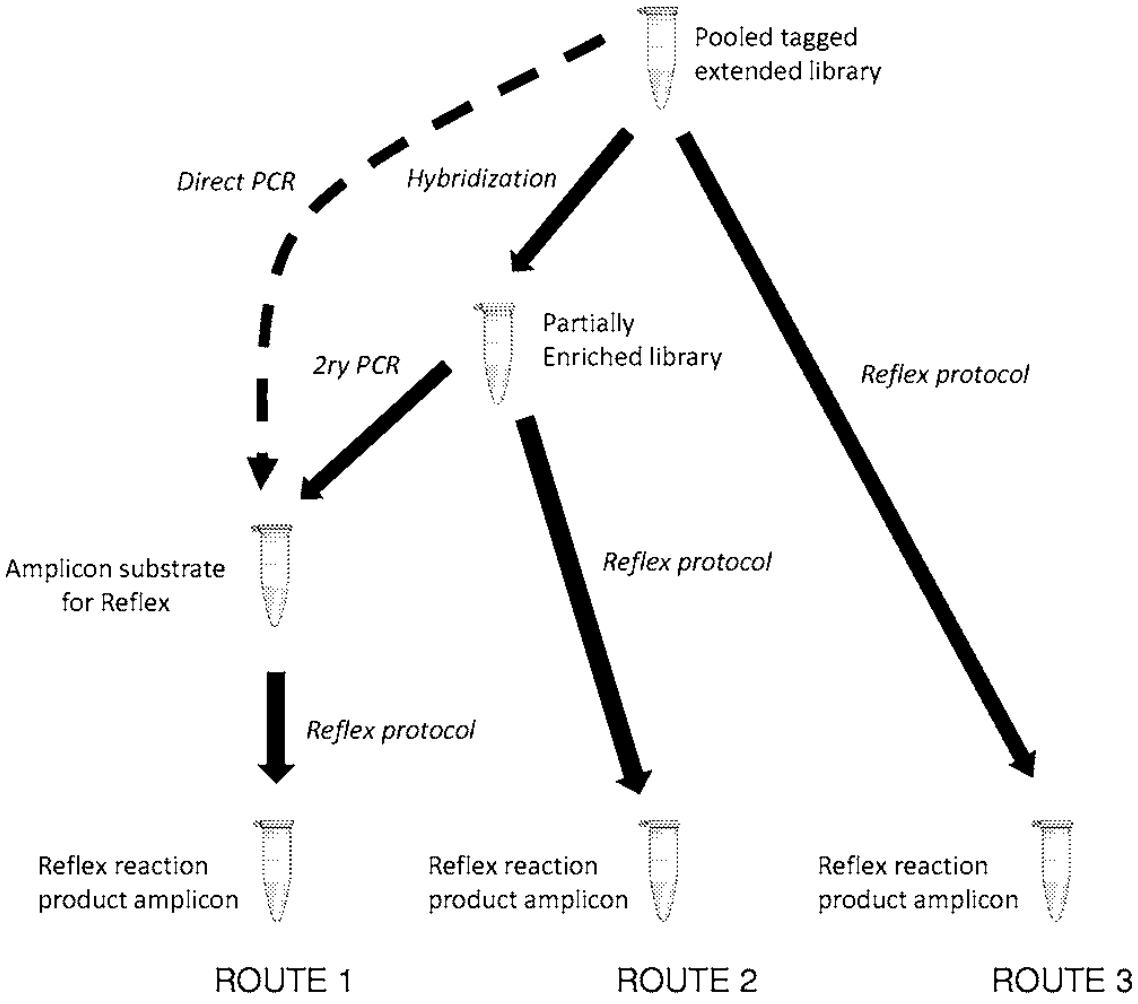

Pooled tagged
extended library
Direct PCR
Hybridization
Partially
Enriched library
2ry PCR
Reflex protocol
Amplicon substrate
for Reflex
Reflex protocol
Reflex protocol
Reflex reaction
product amplicon
Reflex reaction
product amplicon
Reflex reaction
product amplicon
ROUTE 1
ROUTE 2
ROUTE 3

Fig. 13

Doc code : PET.OP.AGE
Description : Petition to make special based on Age/Health

PTO/SB/130 (07-09)
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PETITION TO MAKE SPECIAL BASED ON AGE FOR ADVANCEMENT OF EXAMINATION UNDER 37 CFR 1.102(c)(1)

Application Information

Application Number		Confirmation Number		Filing Date	
Attorney Docket Number (optional)	CGLC-020CON2	Art Unit		Examiner	
First Named Inventor	SYDNEY BRENNER				
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement				

Attention: Office of Petitions

An application may be made special for advancement of examination upon filing of a petition showing that the applicant is 65 years of age, or more. No fee is required with such a petition. See 37 CFR 1.102(c)(1) and MPEP 708.02 (IV).

APPLICANT HEREBY PETITIONS TO MAKE SPECIAL FOR ADVANCEMENT OF EXAMINATION IN THIS APPLICATION UNDER 37 CFR 1.102(c)(1) and MPEP 708.02 (IV) ON THE BASIS OF THE APPLICANT'S AGE.

A grantable petition requires one of the following items:
(1) Statement by one named inventor in the application that he/she is 65 years of age, or more; or
(2) Certification by a registered attorney/agent having evidence such as a birth certificate, passport, driver's license, etc. showing one named inventor in the application is 65 years of age, or more.

Name of Inventor who is 65 years of age, or older

Given Name	Middle Name	Family Name	Suffix
SYDNEY		BRENNER	

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18.
Please see 37 CFR 1.4(d) for the format of the signature.

Select (1) or (2) :

○ (1) I am an inventor in this application and I am 65 years of age, or more.

◉ (2) I am an attorney or agent registered to practice before the Patent and Trademark Office, and I certify that I am in possession of evidence, and will retain such in the application file record, showing that the inventor listed above is 65 years of age, or more.

Signature	/James S. Keddie, Reg. No. 48920/	Date (YYYY-MM-DD)	2013-04-09
Name	James S. Keddie	Registration Number	48920

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Fr eedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about indivi duals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	SYDNEY		BRENNER	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	ELy	Country of Residence	GB

Mailing Address of Inventor:

Address 1	3 Barton Square		
Address 2			
City	Ely	**State/Province**	
Postal Code	CB7 4PJ	**Country**	GB

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	GI		MIKAWA	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Cambridge	Country of Residence	GB

Mailing Address of Inventor:

Address 1	104 High Street		
Address 2	GT Abington		
City	Cambridge	**State/Province**	
Postal Code	CB1 6A3	**Country**	GB

Inventor 3 Remove

Legal Name

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Prefix	Given Name	Middle Name	Family Name	Suffix
	ROBERT		OSBORNE	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Essex	Country of Residence	GB

Mailing Address of Inventor:

Address 1	38 Pilgrim Close		
Address 2	Great Chesterfiord		
City	Essex	**State/Province**	
Postal Code	CB10 1QG	**Country**	GB

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	ANDREW		SLATTER	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	London	Country of Residence	GB

Mailing Address of Inventor:

Address 1	65a Huddleston Road		
Address 2			
City	London	**State/Province**	GB
Postal Code	N7 0AE	**Country**	GB

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	93726		
Email Address	docket@bozpat.com	Add Email	Remove Email

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Application Information:

Title of the Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement		
Attorney Docket Number	CGLC-020CON2	**Small Entity Status Claimed** ☒	
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	13	**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for thr Representative Information during processing.

Please Select One:	◉ Customer Number	◯ US Patent Practitioner	◯ Limited Recognition (37 CFR 11.9)
Customer Number	93726		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13622872	2012-09-19
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13622872	Continuation of	13387343	2012-02-15
Prior Application Status	Pending		Remove

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13387343	a 371 of international	PCT/IB2010/002243	2010-08-13
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
IB2010002243	non provisional of	61288792	2009-12-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
IB2010002243	non provisional of	61235595	2009-08-20

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country i	Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

PTO/AIA/14 (08-12)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Remove

(•) Assignee	( ) Legal Representative under 35 U.S.C. 117
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Assignee is an Organization check here. [X]

Organization Name	Population Genetics Technologies Ltd		
Mailing Address Information:			
Address 1	Babraham Research Campus		
Address 2			
City	Cambridge	**State/Province**	
Country [i]	GB	Postal Code	CB22 3AT
Phone Number		Fax Number	
Email Address	docket@bozpat.com		

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/James S. Keddie, Ph.D., Reg. No. 48,920/			Date (YYYY-MM-DD)	2013-04-09
First Name	James S.	Last Name	Keddie	Registration Number	48920

Additional Signature may be generated within this form by selecting the Add button. Add

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00073

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 13622872

filed on September 19, 2012.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Sydney Brenner Date (Optional): _____

Signature: Sydney Brenner

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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LEGAL NAME OF INVENTOR

Inventor: Gi Mikawa Date (Optional): 5 Nov 2012

Signature: Gi Mikawa

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LEGAL NAME OF INVENTOR

Inventor: Robert Osborne Date (Optional): 5/11/12

Signature: Robert Osborne

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LEGAL NAME OF INVENTOR

Inventor: Andrew Slatter Date (Optional): 5th November 2012

Signature: Andrew Slatter

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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PRELIMINARY AMENDMENT Under CFR 1.115	Attorney Docket No.	CGLC-020CON2
	Confirmation No.	TBD
	First Named Inventor	Sydney Brenner
	Application Number	TBD
	Filing Date	TBD
	Group Art Unit	TBD
	Examiner Name	TBD
Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"	

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

AMENDMENTS TO THE SPECIFICATION

Please insert the paragraph on page 1, line 3, as follows:

This application is a continuation of U.S. Patent Application Serial Number 13/622,872, filed on September 19, 2012, which is a continuation of U.S. Patent Application Serial Number 13/387,343, filed on February 15, 2012, which is a 371 National Phase of International Application Number PCT/IB2010/00224, filed on August 13, 2010, which claims the priority benefit of U.S. Provisional Patent Application Serial Number 61/235,595, filed on August 20, 2009 and also claims the priority benefit of U.S. Provisional Patent Application Serial Number 61/288,792, filed on December 21, 2009, all of which are incorporated herein their entirety.

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AMENDMENTS TO THE CLAIMS

Please amend the claims as shown below. A complete listing of the claims, including their current status identifiers, is set forth below.

1-20 (Canceled)

21. (New) A composition comprising a mixture of:

a) a first plurality of fragments that have been amplified from different parts of a single nucleic acid molecule of a locus in genomic DNA, wherein each of said first plurality of fragments is appended to a first multiplex identifier (MID) sequence; and

b) a second plurality of fragments that have been amplified from different parts of another nucleic acid molecule of said locus, wherein each of said second plurality of fragments is appended to a second MID sequence and said first MID sequence and said second MID are different.

22. (New) The composition of claim 21, wherein said genomic DNA is mammalian genomic DNA.

23. (New) The composition of claim 22, wherein said mammalian genomic DNA is human genomic DNA.

24. (New) The composition of claim 21, wherein said fragments are in the range of 100 to 5,000 bp in length.

25. (New) The composition of claim 21, wherein said fragments are 400 bp or less in length.

26. (New) The composition of claim 21, wherein:

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the different parts of said single nucleic acid molecule are distributed along said single nucleic acid molecule; and

the different parts of said another nucleic acid molecule are distributed along said another nucleic acid molecule.

27. (New) The composition of claim 26, wherein:

the different parts of said single nucleic acid molecule are distributed along said single nucleic acid molecule at intervals in the range of 250 bp to 5kb; and

the different parts of said another nucleic acid molecule are distributed along said another nucleic acid molecule at intervals in the range of 250 bp to 5kb.

28. (New) The composition of claim 21, wherein:

substantially all parts of said single nucleic acid molecule of said locus are represented in said first plurality of fragments; and

substantially all parts of said another nucleic acid molecule of said locus are represented in said first plurality of fragments.

29. (New) The composition of claim 21, wherein said locus is up to 30kb in length.

30. (New) The composition of claim 21, wherein said genomic DNA is genomic DNA from a virus or bacteria.

31. (New) The composition of claim 21, further pluralities of fragments that have each been amplified from different parts of a further molecule of said locus, wherein each of said further plurality of fragments is appended to a unique MID sequence that identifies the molecule from which they were amplified.

32. (New) A method comprising:

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sequencing said first plurality of fragments and said a second plurality of fragments of a composition of claim 21 to provide a plurality of sequences;

wherein each sequence comprises: (i) the nucleotide sequence of at least a portion of said locus and (ii) an associated MID sequence.

33. (New) The method of claim 32, further comprising defining a linkage relationship between said sequences using the MID sequence that is associated with each of the sequences, wherein sequences that comprise the first MID sequence are linked and sequences that comprise the second MID sequence are linked.

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REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 1-20 are canceled without prejudice. New claims 21-33 are new. New claims 21-22 are fully supported within the originally filed application, particularly at the positions indicated in the table shown below.

Claim	Support
21	Fig. 5, where "nucleic acid 1" and "nucleic acid 2" in Fig. 5 correspond to the "single nucleic acid molecule" and "another nucleic acid molecule" in the claims, the fragments (e.g., A, B and C) are shown on the right of the figure, and the first and second MIDs in the claims correspond to MID1 and MID2 in the figure.
22	Page 18, lines 13-14, i.e., "the nucleic acids in the nucleic acid sample are derived from a mammal"
23	Page 18, line 14, i.e., "in certain embodiments the mammal is a human"
24	Page 27, lines 27-28, i.e., "DNA having a length from 100 to 5000 base pairs"
25	Page 22, lines 16-17, i.e., "approximately 400 bases in length or less"
26	Fig. 1B and Fig 3, where sequences 1, 2, 3, 4, and 5 correspond to the amplified parts of the molecule.
27	Fig 3, where the lengths of the arrows beneath element 204 provide support for the range of 250 bp to 5kb.
28	Page 22, lines 1-2, i.e., "we can obtain direct sequences of all parts of the insert"
29	Original claim 14, i.e., "wherein the length of the second domain is from 30 bases to 30 kilobases"
30	Page 18, line 12, i.e., "bacteria, fungi (e.g., yeast), phage, viruses"
31	Page 19, line 11, i.e., , "a nucleic acid sample can contain nucleic acids from 2 or more sources, 3 or more sources"
32	Page 30, lines 1-4, i.e., "Obtaining sequence information from all of the reflex-processed samples can be used to determine the sequence of each individual polynucleotide in the starting sample, using the MID sequence"

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33	Page 30, lines 3-5, i.e., "using the MID sequence to defining linkage relationships between sequences from different regions in the polynucleotide being sequenced" and page 30 lines 12-15, i.e., "Employing the reflex process described herein to identify polymorphisms (right side) maintains linkage information."

The specification has been amended to insert the continuity data on page one.

No new matter has been added.

Consideration of this application is requested.

If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone James Keddie at (650) 833 7723.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CGLC-020CON2.

Respectfully submitted,

Date: April 9, 2013

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie, Ph.D.
Registration No. 48,920

BOZICEVIC FIELD & FRANCIS LLP
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Electronically Filed

INFORMATION DISCLOSURE STATEMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	CGLC-020CON2
	First Named	Brenner, Sydney
	Application Number	
	Confirmation No.	
	Filing Date	
	Group Art Unit	
	Examiner Name	
	Title: *"Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"*	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO-SB/08A and a copy of each document is also enclosed.

The Examiner is requested to make the documents listed on the enclosed PTO-SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO-SB/08A, indicating the document cited therein have been considered and made of record herein.

All of the references identified herein were disclosed in parent application serial number 13/622,872, filed 9/19/2012 and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number CGLC-020CON2.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS, LLP

Date: April 9, 2013

By: /James S. Keddie, Reg. No.48,920/
James S. Keddie, Ph.D., Reg. No.48,920

BOZICEVIC, FIELD & FRANCIS, LLP
1900 University Avenue, Suite 200
East Palo Alto, California 94303
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

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❿ Holder's signature/ Llofnod y deiliad/ Ainm sgrìobhte an neach-seilbhe/ Handtekening van de houder/ Signature du titulaire/ Unterschrift der Inhaberin (des Inhabers)/ Firma del titolare/ Indehaverens underskrift/ Síniú an tsealbhóra/ Υπογραφή του κατόχου/ Assinatura do titular/ Firma del titular/ Haltijan nimikirjoitus/ Passinnehavarens namnteckning/ Podpis držitele/ Omaniku allkiri/ Pilsoņa paraksts/ Savininko parašas/ Firma ta' min inħariġlu l-passaport/ Podpis posiadacza/ Podpis imetnika/ Podpis držiteľa/ A tulajdonos aláírása

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Surname/Nom (1): BRENNER
Given names/Prénoms (2): SYDNEY
Nationality/Nationalité (3): BRITISH CITIZEN
Date of birth/Date de naissance (4): 13 JAN /JAN 27
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Place of birth/Lieu de naissance (6): GERMISTON
Date of issue/Date de délivrance (7): 23 AUG /AOUT 06
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Date of expiry/Date d'expiration (9): 23 AUG /AOUT 16
Holder's signature/Signature du titulaire (10): Sydney Brenner

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SCORE Placeholder Sheet for IFW Content

Application Number: 13859450 Document Date: 04/09/2013

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/859,450	Filing Date 04/09/2013	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 = *		X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 = *		X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/09/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 13	Minus	** 20	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
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* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

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Application Number	13859450
Filing Date	2013-04-09
First Named Inventor	Brenner, Sydney
Art Unit	
Examiner Name	
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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	6723513		2004-04-20	LEXOW	
	2	7700325		2010-04-20	CANTOR, et al.	
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	1	20040224331		2004-11-11	CANTOR, et al	
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	Attorney Docket Number	CGLC-020CON2

	3	20090155780		2009-06-18	XIAO, et al	
	4	20100120098		2010-05-13	GRUNENWALD, et al	
	5	20110287435		2011-11-24	GRUNENWALD, et al	
	6	20120208724		2012-08-16	STEEMERS, et al	
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	3	WO2013036929	WO		2013-03-14	UNIVERSITY LELAND STANFORD JUNIOR		☐

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	Art Unit	
	Examiner Name	
	Attorney Docket Number	CGLC-020CON2

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T5
	1	BOULANGER, et al. Massively parallel haplotyping on microscopic beads for the high-throughput phase analysis of single molecules. PLoS One. 2012 7:e36064.	☐
	2	CASBON, et al. Reflex: intramolecular barcoding of long-range PCR products for sequencing multiple pooled DNAs. Nucleic Acids Res. 2013.	☐
	3	FAN, et al. Whole-genome molecular haplotyping of single cells, Nat Biotechnol. 2011, 29: 51-7	☐
	4	HIATT, et al. Parallel, tag-directed assembly of locally derived short sequence reads. Nat Methods. 2010, 7:119-122.	☐
	5	KAPER, et al. Whole-genome haplotyping by dilution, amplification, and sequencing. Proc Natl Acad Sci U. S. A. 2013 110: 5552-7.	☐
	6	KIRKNESS, et al. Sequencing of isolated sperm cells for direct haplotyping of a human genome. Genome Res. 2013 23: 826-32.	☐
	7	KITZMAN, et al. Haplotype-resolved genome sequencing of a Gujarati Indian individual. Nat Biotechnol. 2011 29:59-63.	☐
	8	KOZAREWA, et al. Amplification-free Illumina sequencing-library preparation facilitates improved mapping and assembly of GC-biased genomes. Nat Methods. 2009 6: 291-5.	☐
	9	KONAREWA, et al, 96-plex molecular barcoding for the Illumina Genome Analyzer. Methods Mol Biol. 2011, 733: 279-98.	☐
	10	KWOK. Single-molecule analysis for molecular haplotyping. Hum Mutat. 2004, 23:442-6.	☐

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	Application Number	13859450
	Filing Date	2013-04-09
	First Named Inventor	Brenner, Sydney
	Art Unit	
	Examiner Name	
	Attorney Docket Number	CGLC-020CON2

	11	LUNDIN, et al. Hierarchical molecular tagging to resolve long continuous sequences by massively parallel sequencing, Sci Rep. 2013, 3:1186.	☐
	12	OYOLA, et al. Optimizing Illumina next-generation sequencing library preparation for extremely AT-biased genomes. BMC Genomics. 2012, 13:1	☐
	13	REISNER, et al. Single-molecule denaturation mapping of DNA in nanofluidic channels. Proc Natl Acad Sci U S A. 2010, 107: 13294-9.	☐
	14	TURNER, et al. Assaying chromosomal inversions by single molecule haplotyping. Nat Methods. 2006, 3: 439-445.	☐
	15	TURNER, et al. High-throughput haplotype determination over long distances by haplotype fusion PCR and ligation haplotyping. Nat Protoc. 2009, 4: 1771-83.	☐
	16	VAN NIEUWERBURGH, et al. Illumina mate-paired DNA sequencing-library preparation using Cre-Lox recombination. Nucleic Acids Res. 2012, 40:1-8.	☐
	17	XAIO, et al, Determination of haplotypes from single DNA molecules: a method for single-molecule barcoding. Hum Mutat. 2007, 28: 913-21.	☐

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	Application Number	13859450
	Filing Date	2013-04-09
	First Named Inventor	Brenner, Sydney
	Art Unit	
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie, Reg. No. 48,920/	Date (YYYY-MM-DD)	2013-05-15
Name/Print	James S. Keddie	Registration Number	48920

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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Page 00097

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 November 2001 (29.11.2001)

PCT

(10) International Publication Number
WO 01/90418 A1

(51) International Patent Classification[7]: C12Q 1/68, C07H 21/04

(21) International Application Number: PCT/US01/16394

(22) International Filing Date: 22 May 2001 (22.05.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/206,512 22 May 2000 (22.05.2000) US

(71) Applicant: **THE REGENTS OF THE UNIVERSITY OF CALIFORNIA** [US/US]; Los Alamos National Laboratory, LC/BPL, MS D412, Los Alamos, NM 87545 (US).

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(74) Agents: **WILSON, Ray, G.** et al.; Los Alamos National Laboratory, LC/BPL, MS D412, Los Alamos, NM 87545 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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WO 01/90418 A1

(54) Title: RAPID HAPLOTYPING BY SINGLE MOLECULE DETECTION

(57) Abstract: The present invention includes a method for rapid haplotyping a DNA or RNA segment. Two or more target sites on a segment of DNA or RNA are labeled with separate distinguishable luminescent hybridization probes, where the targets are selected genetic markers. A dilute solution is formed containing the labeled DNA or RNA segments. Each DNA or RNA segment is illuminated with light beams effective to excite each luminescent hybridization probe, when present. The presence or absence of each luminescent hybridization probe on each DNA or RNA segment is detected to determine the haplotype of each DNA or RNA segment.

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RAPID HAPLOTYPING BY SINGLE MOLECULE DETECTION

RELATED CASES

This case claims the benefit of U.S. Provisional Application 60/206,512, filed May 22, 2000.

STATEMENT REGARDING FEDERAL RIGHTS

This invention was made with government support under Contract No. W-7405-ENG-36 awarded by the U.S. Department of Energy. The government has certain rights in the invention.

SEQUENCE LISTING

The DNA sequences listed herein are submitted on the single compact disk submitted herewith.

FIELD OF THE INVENTION

The present invention relates generally to haplotyping, and, more particularly, to rapid haplotyping using single molecule fluorescence detection.

BACKGROUND OF THE INVENTION

As the Human Genome Project progresses rapidly toward completion of the human DNA sequence, it is recognized that natural sequence variation (i.e., polymorphisms) is a fundamental property of all genomes. Any two human chromosomes (haploids) show multiple sites and types of polymorphisms. Some polymorphisms have functional implications and cause or implicate disease, whereas many do not.

Polymorphisms exist in different forms such as single nucleotide variations [nucleotide repeats, multibase deletion (more than one nucleotide deleted from the consensus sequence), multibase insertion (more than one nucleotide inserted from the consensus sequence)], microsatellite repeats (small numbers of nucleotide repeats with a typical 5-1000 repeat units), di-nucleotide repeats, tri-nucleotide repeats, sequence rearrangements (including translocation and duplication), chimeric sequence (two sequences from different gene origins are fused together), and the like. Among all these sequence polymorphisms, the most frequent polymorphisms in the human genome are single-base variations, also called single-nucleotide polymorphisms (SNPs). SNPs are abundant, stable and widely distributed across the genome. SNPs are important for the following reasons:

(1) SNPs serve as ideal genetic markers for complex disease association studies (linkage analysis), in which particular alleles (one of two or more genes that occur at the same locus of homologous chromosomes) of genetic markers (haplotype) in close proximity to a disease mutation are consistently associated with the disease. Recently, a collaborative effort between public and private sectors has been undertaken to produce a large library of ~ 300,000 SNPs in the human genome. It is expected that the Human Genome Project, coupled with high throughput SNP screening and genotyping systems, will permit the rapid establishment of this database. The availability of the SNP library as well as other genetic polymorphisms will allow the elucidation of complex genetic components of human disease and thereby accelerate the drug discovery process (Brookes 1999; Kowk 1999).

(2) SNPs are good markers for population, evolution and forensic studies.

(3) Polymorphism profiles offer the potential to assess a disease risk or predict a drug response based on an individual's genetic profile.

(4) SNP profiles may be used to tailor drug treatments to individual patients, to improve the efficacy and safety of the treatment.

As the first step toward linking SNP profiles for diagnostic and medical treatment, the linkage between a disease and a response to a particular set of polymorphism (or SNPs) has to be established. In such linkage or association studies, a group of patients with a particular disease is compared to a control group to find genetic factors that occur significantly more (or less) frequently in the affected individuals than in the control. The study is typically done with the help of well-mapped polymorphism markers. It is possible to map disease genes to particular regions on chromosomes by studying the transmission of genetic markers along with a disease since the markers in a close physical proximity to a disease mutation co-segregate with the disease at a higher frequency than the more distant markers. Due to the abundance (estimated to be one of every one thousand bases) and stability of SNPs, they serve as good genetic markers for association studies. The effort to build a large SNP library is mainly motivated by the prospect of using SNPs as genetic markers for disease association studies. It has been proposed that an average of 5 SNPs be used for each candidate disease gene in association studies. About 40,000 genes in a human cell, or about 200,000 SNPs, will be needed for such association studies.

The haplotype is a set of genetic determinants located on a single chromosome and it typically contains a particular combination of alleles (all the alternative sequences of a gene) in a region of a chromosome. In other words, the haplotype is a phased sequence information on individual chromosomes. Very often, phased SNPs on a chromosome define a haplotype. The combination of two haplotypes on two human chromosomes ultimately determines the genetic profiles of a human cell. It is the haplotype that determines a linkage between a specific genetic marker and a disease mutation (Kowk 1999; Davidson 2000). Current methods of scoring SNPs (such as hybridization microarray or direct gel sequencing reviewed by Landgren 1998) can accurately type individual SNPs, but can not determine which chromosome of a diploid pair is associated with each polymorphism. Without the phased information of haplotypes, it might be

impossible to detect the association due to numerous possibilities of different haplotypes (Hodge 1999; Kowk 1999; Drysdale 2000).

The haplotype deduced from a genotype is typically done in bulk as follows (inferred haplotypes). The region of interest is PCR amplified, the genotype is determined, and the haplotype is deduced from homozygous individuals. Since the genotype is based on a bulk measurement on a mixture of both chromosomes, this genotyping approach has serious limitations for large numbers of SNP markers. Consider the following example:

----------A1---------B2---------C1---------M---------D1----------E2

----------A2 --------B1---------C2----------D2----------E1

For a given five SNP genotype results, A1/A2-B1/B2-C1/C2-D1/D2-E1/E2, there are 16 possible haplotypes (Kowk 1999), as shown in Table 1.

TABLE 1

1	A1/B1/C1/D1/E1 and A2/B2/C2/D2/E2	2	A1/B1/C1/D1/E2 and A2/B2/C2/D2/E1
3	A1/B1/C1/D2/E1 and A2/B2/C2/D1/E2	4	A1/B1/C2/D1/E1 and A2/B2/C1/D2/E2
5	A1/B2/C1/D1/E1 and A2/B1/C2/D2/E2	6	A2/B1/C1/D1/E1 and A1/B2/C2/D2/E2
7	A1/B2/C2/D1/E1 and A2/B1/C1/D2/E2	8	A1/B2/C1/D2/E1 and A2/B1/C2/D1/E2
9	A1/B2/C1/D1/E2 and A2/B1/C2/D2/E1	10	A1/B1/C2/D1/E2 and A2/B2/C1/D2/E1
11	A1/B1/C2/D2/E1 and A2/B2/C1/D1/E2	12	A1/B1/C1/D2/E2 and A2/B2/C2/D1/E1
13	A1/B1/C2/D2/E2 and A2/B2/C1/D1/E1	14	A1/B2/C2/D2/E1 and A2/B1/C1/D1/E2
15	A1/B2/C2/D1/E2 and A2/B1/C1/D2/E1	16	A1/B2/C1/D2/E2 and A2/B1/C2/D1/E1

For a 5-SNP mapping on a gene, there are 528 possible haploidtypes, and for a given genotype, there may be as many as 16 different haploidtypes. As the number of SNP markers grows larger, the identification of the haploidtype from the genotype is increasingly difficult since the number of possible haploidtypes increases rapidly, and the probability of finding a homozygous individual decreases. Without knowing the particular haplotypes, the mutation (M) association to the nearby C1 or D1 might be missed.

Traditionally, association studies have been successful only for simple, monogenic diseases involving a small number of markers, where the possible

combinations of different haplotypes are limited. Therefore, the haplotypes can be typically deduced from genotypes by typing many individuals and by the availability of homozygotes and parental information. However, most diseases are complex and involve multiple genes. For polygenic association studies, many more markers are needed and, therefore, the number of possible haplotypes is large. In these cases, it is extremely difficult to infer the haplotype from the genotype. Many sophisticated algorithms have been developed for haplotype prediction and they are typically 70-90% accurate. Such accuracy is not useful when typing a large numbers of SNPs and also is not acceptable for clinical diagnostic purposes. In addition, it is often impossible or impractical to obtain parental genomic DNA. This raises a serious challenge: there is no easy way to directly determine a haplotype except when it is on the sex chromosomes where X and Y chromosome are sufficiently different to be distinguished in bulk methods.

As shown in Figure 1, a genetic profile based on a genotype can be incomplete, because it fails to provide the locations of SNPs on two chromosomes. For example, consider two genetic markers (or SNPs), A and B, on the same gene. For a genotype of aA/bB (A and B presents the wild type or dominant genotype that naturally occurs; a and b represent two mutations.), there are two possible combinations of haplotypes, ab/AB and Ab/aB. The disease phenotype for the individual with ab/AB may be less severe compared to the individual with Ab/aB. This is because the individual with ab/AB has one intact copy of the gene, whereas the individual with Ab/aB has no intact copy on either chromosome. For cases like this, the ability to find out whether two mutations are on the same chromosome or on different chromosomes (haplotypes) in a routine clinical setting is particularly useful for future risk assessment and disease diagnostics.

Another conventional alternative for haplotyping is allele-specific polymerase chain reaction (allele-specific PCR (Ruano 1990)), which is the most commonly used method for direct haplotyping. In these reactions, SNP-specific PCR primers are designed to distinguish and amplify a specific haplotype from two chromosomes. Such reactions require stringent reaction conditions and individual

optimization for each target. Therefore, this approach is not suitable for a large scale and high throughput haplotyping. More importantly, such assays are subject to the length limitations of PCR amplification and are not capable of typing SNPs that are more than several kilobases (kb) apart. In addition, such an amplification-based typing is often complicated by the contamination of a small amount of genomic DNA other than the sample DNA during sample handling process

Other haplotyping methods include single sperm or single chromosome measurements (Ruano 1990; Zhang 1992; Vogelstein 1999). In a single sperm sorting assay, PCR amplified DNA from individual sorted sperm cells is genotyped. Multiple sperm cells (at least 3-5) from an individual are typed in order to have enough statistical confidence to reveal the two haplotypes. In principle, this sorting approach could be applied to chromosomes. However, this technique is complicated, and, so far, has been successful in only a few research labs.

The molecular cloning method clones a target region of an individual's DNA (or cDNA) into a vector, and genotypes the DNA obtained from single colonies. For each individual, multiple colonies are needed to obtain two haplotypes. This method has been used by many laboratories, but is very labor-intensive, time-consuming and can be difficult to perform in some cases. Researchers are forced to use it because there is no easy alternatives.

Finally, haplotyping by AFM (Atomic Force Microscopy) imaging (Woolley et al. 2000, Taton 2000) is a new approach to directly visualize the polymorphic sites on individual DNA molecules. This method utilizes AFM with high resolution single walled carbon nanotube probes to read directly multiple polymorphic sites in DNA fragments containing from 100-10,000 bases. This approach involves specific hybridization of labeled oligonucleotide probes to target sequences in DNA fragments followed by direct reading of the presence and spatial localization of the labels by AFM. However, the throughput and sensitivity of such systems remain to be demonstrated; currently 200 samples per day, each with 10 images, can be processed.

In summary, there is no easy way to determine a haplotype currently except by using the sex chromosomes. All of the conventional methods require DNA amplification by PCR or cloning and extensive optimization. They are slow, labor intensive and expensive to perform, and not suited for a large-scale association studies, or routine clinical diagnostics (Kowk 1999).

Various objects, advantages and novel features of the invention will be set forth in part in the description which follows, and in part will become apparent to those skilled in the art upon examination of the following or may be learned by practice of the invention. The objects and advantages of the invention may be realized and attained by means of the instrumentalities and combinations particularly pointed out in the appended claims.

SUMMARY OF THE INVENTION

The present invention includes a method for rapid haplotyping a DNA or RNA segment. Two target sites on a segment of DNA or RNA are labeled with separate distinguishable luminescent hybridization probes, where the target sites are selected genetic markers. The presence or absence of each luminescent hybridization probe on each DNA or RNA segment is detected to determine the haplotype of each DNA or RNA segment.

In one embodiment, a dilute solution is formed containing the labeled DNA or RNA segments. Each labeled DNA or RNA segment is illuminated with light beams effective to excite each luminescent hybridization probe, when present.

BRIEF DESCRIPTION OF THE DRAWINGS

The accompanying drawings, which are incorporated in and form a part of the specification, illustrate embodiments of the present invention and, together with the description, serve to explain the principles of the invention. In the drawings:

FIGURE 1 illustrates haplotyping in accordance with one aspect of the present invention.

FIGURE 2 schematically depicts an exemplary apparatus for rapid haplotyping by two color single molecule fluorescence detection.

FIGURES 3A, B, and C depict the detection by fluorescence correlation spectroscopy of two color labels on a single DNA target.

DETAILED DESCRIPTION

The present invention for rapid haplotyping uses a single molecule approach based on the simultaneous detection of two luminescent labels that are specific to neighboring genetic markers, such as SNPs, from single chromosomes. Suitable techniques for distinguishing luminescence include color differentiation, luminescence lifetime, and luminescence intensity. By using single molecule detection and identification, the co-location of two markers on a given haploid can be rapidly determined.

The present invention encompasses the following types of targets, distinguishable luminescent hybridization probes, and labeling strategies, each of which is individually well known, but not previously applied to haplotyping:

(a) Targets of haplotyping are all sorts of DNA and RNA variations that are necessary to define a haplotype. They include any DNA or mRNA (cDNA) targets such as single nucleotide polymorphisms, single nucleotide variations [nucleotide repeats, multibase deletion (more than one nucleotide deleted from the consensus sequence), multibase insertion (more than one nucleotide inserted from the consensus sequence)], microsatellite repeats (small numbers of nucleotide repeats with a typical 5-1000 repeat units), di-nucleotide repeats, tri-nucleotide repeats, sequence rearrangements (including translocation and

duplication), chimeric sequence (two sequences from different gene origins are fused together), and the like. Samples that contain the targets can be unamplified genomic DNA or RNA samples or amplified DNA (or cDNA).

(b) Target labels are two sets of distinguishable luminescent hybridization probes that may be identified by difference in color, luminescence lifetime, luminescence intensity, luminescence burst duration, and luminescence polarization anisotropy. Such luminescent labels can be single dye molecules, energy transfer dye pairs, nano-particles, luminescent nano-crystals (e.g., quantum dots), intercalating dyes or molecular beacon that only fluoresce upon binding to a target. The forms of the hybridization probes can be any of DNA, cDNA, RNA, PNA (peptide nucleic acid) or LNA (locked nucleic acid) in either natural or synthetic or mixed use of any above forms.

(c) The design strategies for target-specific hybridization probes can be generalized into a one probe approach and multiple probes such as a two-probe approach (Landegren 1998). (1) One probe labeling strategy with probes that are specific for the targets, especially for SNP targets: one hybridization oligo DNA, cDNA, RNA, beacon, PNA, LNA or artificial mismatched oligo or other chemically modified and chimeric oligos (nondenaturation approaches, too). (2) Two or more oligo probes that act together to identify a target: hybridization pair, invader oligo pair, ligation oligo pair, mismatch extension, 5'-exonuclease oligo pair, 3'-exonuclease pair. Oligos can be DNA, cDNA, RNA, PNA, LNA, beacon or other modified and chimeric oligos.

(d) The specificity of probes will be evaluated on a commercial flow cytometer using the known protocols (Cai 1998; Cai 2000).

(e) The concentration range of samples for measurement can range from 100 nanomolar (nM) to the sub femtomolar (fM) range. Therefore, samples can be measured over a wide concentration range. This is especially useful for a very dilute sample in a routine clinical practice. A concentrated sample can be diluted to a proper range for detection.

Conventional fluorescence/luminescence characteristics and single molecule detection apparatus are used to provide the ultrasensitive fluorescence detection methods used in the present invention. The ability to detect and identify single luminescent molecules as they cross a focused excitation laser beam is now an available research tool. See, e.g., U.S. Patents 6,049,380, issued April 11, 2000; 5,834,204, issued November 10, 1998; 5,827,663, issued October 27, 1998; 5,799,682, issued September 1, 1998, all incorporated herein by reference. Work at Los Alamos National Laboratory has led to many of the advances in this field, which are reviewed in a number of recent papers (Goodwin, Ambrose et al. 1996; Keller, Ambrose et al. 1996; Ambrose, Goodwin et al. 1999), incorporated herein by reference.

The following fluorescence/luminescence parameters can be measured at the single molecule level (Ambrose et al. 1999):

- Luminescence emission spectral distribution (color).
- Luminescence emission decay rate (lifetime).
- Luminescence burst intensity (burst size).
- Luminescence burst duration.
- Luminescence polarization anisotropy.

All of these can be used individually or in combination to distinguish between labeled hybridization probes and to determine the presence of one or more labeled hybridization probes on a target fragment.

Measurements may be made on individual single molecule luminescence bursts to determine the presence of one or more labeled hybridization probes on a target fragment. Such measurements require that the luminescent molecules be interrogated one-at-a-time, that is, the average occupancy of the probe volume is much less than one luminescent molecule. Alternatively, fluorescence correlation spectroscopy (FCS) can be used to characterize fluctuations in the time history of the fluorescence (Rigler et al. 1993). For example, fluorescence from a single detection channel can be auto-correlated to measure the average fluorescence burst shape and duration for fluorescent molecules diffusing across the interrogation

volume. The cross-correlation between two spectrally separate and spatially overlapping fluorescence detection channels can be used to detect the co-hybridization of two different hybridization probes labeled with spectrally-distinct fluorophores to target fragments. In contrast to single molecule fluorescence burst measurements, FCS can be used at higher concentrations of the fluorescent analyte (average probe volume occupancy > 1) as long as the fluorescence fluctuations due to single fluorescent molecules are detectable.

Confocal microscopy in combination with laser epi-illumination may be used to attain femtoliter or smaller fluorescence/luminescence detection volumes. The small interrogation (probe) volume allows the detection of single molecule fluorescence excited with inexpensive, low-power, continuous-wave lasers. For 0.1 nM and higher sample concentrations, diffusion is sufficient for transport of analyte molecules into and out of the probe volume. For lower analyte concentrations, the sample throughput rate through the probe volume can be increased by scanning the probe volume through the stationary sample or by scanning or flowing the sample through a stationary probe volume.

Pulsed laser excitation and time-correlated single-photon counting methods may be used to discriminate against background photons due to solvent Raman and Rayleigh scattering of the excitation laser. This allows the use of roughly 1000x larger, ~picoliter size, interrogation volumes for single molecule luminescence detection. Analyte molecules are carried through the probe volume in a flowing sample stream.

With reference to Figure 1, the first step in this assay is to label the two genetic marker target sites, e.g., SNPs, with distinguishable, luminescent hybridization probes for the genetic targets. Suitable types of probes include single dye molecules, energy transfer dye pairs, nano-particles, luminescent nano-crystals, and intercalating dyes that fluorescence only after binding to a target. An ultra-sensitive, luminescence confocal microscope (exemplary detection apparatus), shown in Figure 2, may be used to examine a dilute solution of the labeled DNA. Luminescence emission from two luminescent probes that are hybridized to single

DNA fragments are recorded in two separate detection channels. The co-localization of the two hybridization probes on the same DNA haploid is signaled by the simultaneous detection of luminescence in both channels. By performing a cross-correlation between the detectors, one determines whether the DNA illuminated by the light beams contains one or both hybridization probes.

While Figure 2 illustrates only the use of two luminescent probes with two corresponding detectors, it will be appreciated that more distinct probes might be used to simultaneously detect more genetic marker sites by inserting additional spectral filters and concomitant detectors for the wavelengths of interest. It is not intended to limit the present invention to only two probe types.

Haplotyping according to the present invention is applicable to a whole chromosome by sequentially and repeatedly typing pairs of neighboring genetic markers. For example, typing ten SNPs on a chromosome can be accomplished by typing two (or more) nearby SNPs (say SNP1 and SNP2) in the first experiment, SNP2 and SNP3 in the second experiment, SNP3 and SNP4 in the third experiment, and so forth.

In the example shown in Figure 1 to determine the four haplotype combinations that characterize a genetic profile, two sets of polymorphism-specific probes that specifically bind to either the wild-type (A or B) or mutant (a or b) forms of two polymorphic sites of a gene are constructed. For example, one color probe may bind to (A and a) and a second color probe may bind to (B and b). As shown in Figure 1, all four of the possible haplotypes can be identified by using both sets of probes in a pair of two-color, single molecule assays.

A typical protocol using well-known procedures would form four probes: two "red" probes to specifically hybridize with (A and a) sequences and two "green" probes to specifically hybridize with (B and b) sequences. The terms "red" and "green" as used herein are not limited to colors, but conveniently distinguish two distinct probe characteristics that are being detected. A two stranded DNA segment is denatured to provide two single stranded segments and a set of probes is then hybridized to the single stranded segments. For example, (A and B) probes are first

specifically hybridized to the segments and the results analyzed. In a parallel reaction, the (a and b) probes are specifically hybridized to the segments and the results analyzed. As used herein, the term "specifically hybridize" means that the probe will hybridize only to the exact complementary nucleotide sequence on the fragment being tested.

If only wild type sequences are on a single stranded segment, then only the first set of probes will produce an output to illustrate that A and B sequences are on all of the chromosomes. If a wild type and a mutant sequence are present on each chromosome, then there will be no two-color output since each segment will hybridize with only one probe for each probe set. If one chromosome contains only wild type sequences and another chromosome contains only a mutant sequence, then both sets of probes will produce two-color outputs. Finally, if both chromosomes contain only mutant type sequences, then only the (a and b) probe set will provide a two-color output. Thus, the four probes generate a complete haplotype of the chromosome.

It should be noted that a single haplotype requires only the identification of two polymorphisms in a region of a chromosome. In the above example, only two probes might be used if a specific pair of polymorphisms, e.g., A and b, a and B, A and B, or a and b, is being screened.

The proposed single molecule haplotyping approach has a number of advantages over current haplotyping methods. These are:

(1) Easy interpretation. The single molecule approach is a direct haplotyping method. No inferred analysis is needed.

(2) Ability to type large regions (~200 kb or more) in a single assay. Since the typing is performed directly on the chromosome, the length of the chromosome fragment that be can be typed is limited only by mechanical shearing of the genomic DNA during handling. In principle, the whole chromosome can be haplotyped by sequentially typing every two neighboring SNP markers with one common overlapping SNP. This will be significantly simpler than PCR-based typing, which is limited to a few kilobases between targets.

(3) High sensitivity. The assay will require only 20 ng or less of genomic DNA, about the same amount needed for a typical PCR reaction. No amplification of sample DNA is required prior to analysis.

(4) High throughput. The confocal microscope arrangement used for fluorescence detection can easily be adapted to a sample droplet array format for high throughput analysis.

(5) Less likely to have a false positive as a result of contaminant amplification. In a typical haplotyping, target amplification is required, such as PCR, which is very sensitive to sample contamination. For instance, a sample contaminated with a few copies of human DNA can be amplified and typed. As a result, a false positive or wrong haplotype may be obtained. Direct typing on human genomic DNA avoid the amplification of contamination, thus the typing result is less likely to be affected by a small amount of contamination.

Detection Schemes:

A schematic of exemplary apparatus capable of two-color single molecule lumisence detection is shown in Figure 2. Laser epi-illumination is used in combination with confocal fluorescence detection to probe an extremely small volume of the solvent. Two excitation lasers 10, 12 are focused through microscope objective 14 to simultaneously excite DNA sample 24 that has been labeled with one or two distinguishable fluorophores. For a very dilute DNA solution, no DNA fragments will be inside the focused laser beam most of the time. When an individual DNA strand diffuses into the excitation region, the fluorophore labels on the DNA will fluoresce. The fluorescence is collected with microscope objective 14, passes through polychroic beam splitter 13, and spectrally split with dichroic beam splitter 15 between two sensitive photon counting detectors 16, 18. DNA strands that contain both fluorophores will be registered in both detectors. DNA with only one label will be seen by a single detector 16 or 18. The intensity recorded by each detector 16, 18 is cross-correlated to detect the presence of DNA fragments containing both labels.

An exemplary apparatus is based on a known laser epi-illuminated and confocal fluorescence emission collection design. The linear dimensions of the probe volume for the sample 24 are on the order of a micron or less resulting in a probe volume on the order of 1 femtoliter (fL) (Rigler, et al. 1993). Laser 10 is an Ar^+ laser operating at 496 nm to excite a fluorescein fluorophore. Laser 12 is a helium neon laser operating at 633 nm to excite the fluorophore N,N'-biscarboxypentyl-5,5'-disulfonatoindodicarbocyanine (Cy5). Detectors 16 and 18 are single photon counting avalanche photodiodes. The detection channel from detector 16 is band pass filtered (filter not shown) to detect, e.g., green fluorescein emission. The detection channel from detector 18 is band pass filtered (filters not shown) to detect, e.g., red Cy5 emission. A pinhole 17 in the image plane of microscope objective 14 limits the field of view of two detectors 16, 18 to the immediate vicinity of the overlapping, focused laser beams. Sample 24, a microliter drop (e.g., 5 microliters) of a dilute solution of fluorescently labeled DNA in this exemplary apparatus, is suspended on the underside of a microscope coverslip. The coverslip is mounted on a scanning stage to allow the fluorescence detection probe volume to be raster scanned through the volume of the sample droplet. A personal computer (PC) 22 houses a commerically available digital correlator card (ALV 5000/E) that computes the cross-correlation between the two detection channels in real-time.

When an individual DNA fragment in sample 24 diffuses into the excitation region defined by microscope objective 14, the fluorescently-labeled probes on the DNA fragment will fluoresce. The fluorescence is collected and spectrally split between two sensitive detectors 16, 18. Signals from DNA fragments that contain both probes will be registered in both detectors. A signal from a DNA fragment with only one hybridization probe will be registered by only a single detector.

The intensity recorded by each detector is cross-correlated by computer 22 to look for instances where both probes were present on the same DNA fragment. In cross-correlation analysis, the time history of the fluorescence intensity recorded by one of the detectors (e.g., a red detector), $F_r(t)$, is multiplied with that recorded by the second detector

(e.g., a green detector), $F_g(t)$, at some later time, τ. This multiplication is averaged over all of the measurement time and the result is normalized and displayed as a function of the delay time, τ, between the two detectors. (See Equation 1):

$$G_{rg}(\tau) \propto \langle \delta F_r(t) \delta F_g(t+\tau) \rangle \qquad \text{Eq (1)}$$

In the above expression, the brackets denote a time average, δ the deviation from the average value (i.e. $\delta F(t)=F(t)-\langle F \rangle$), and $G_{rg}(\tau)$ is the cross-correlation between, e.g., the green and red fluorescence signals.

When individual DNA fragments labeled with both "red" and "green" fluorophores cross the excitation laser beam, fluorescence is recorded by both detectors and a non-zero cross-correlation between the detectors results. In this situation, the cross-correlation function should peak at $\tau = 0$ (i.e., zero delay time) and decay with a time constant that is roughly equal to the diffusion time of the DNA through the laser beam. Fluorescence from DNA fragments labeled with only a single color are detected in only one of the two channels and do not contribute to the cross correlation.

In practice, the sensitivity of the above analysis is limited by cross-talk between the green and red detection channels due to fluorescence from the red tail of the green fluorophore that overlaps the detection bandpass of the red detector. With currently available fluorophore pairs the cross-talk of the green emission into the red detector is ~1% of that detected in the green channel. This limits the detection sensitivity of the doubly-labeled adduct to ~1% of the green labeled species (Schwille et al. 1997). To avoid this problem, the data from the two detectors can be searched for photon bursts and the burst detection times from the red and green detectors can be cross correlated (Castro et al. 1997). The threshold for burst detection in the red channel can be adjusted to eliminate cross-talk between the green and red detection channels. This analysis requires that the average occupancy of fluorescent species in the probe volume be $<<1$, that is, the sample must be extremely dilute.

Another issue is that of unbound fluorescent probe. In the two-color FCS analysis described above, the amplitude of the cross-correlation, $G_{rg}(\tau)$, is proportional to the concentration of the double-labeled target DNA and inversely proportional to the product of the concentrations of the 'green' and 'red' probes. Therefore, excessively high concentrations of unbound probes will give small cross-correlation amplitudes and will reduce the accuracy of the measurement. If necessary, excess unbound probe can be removed from the sample prior to analysis using standard separation techniques such as, column chromatography (e.g., size exclusion and ion exchange) and electrophoresis.

The technique, described above, illustrates a detection capability for two hybridization probes located on the same or different DNA strands. However, the method as outlined suffers from the drawback that it can take a few milliseconds for the DNA in solution to diffuse into and out of the laser beam. For dilute DNA solutions, the excitation laser beams will be probing empty solvent most of the time. Consequently, with extremely dilute (<1 pM) DNA solutions, excessively long interrogation times would be necessary to determine whether or not two hybridization probes were on the same or different DNA strands.

This problem has been circumvented (Castro et al. 1997) by flowing the sample through the excitation laser beam at rates approaching ~100 microns/sec and by probing a relatively large volume of solvent. The combination of these techniques allowed a rapid (~800 seconds) determination of whether or not two fluorescent hybridization probes were co-hybridized to single DNA fragments with excellent signal to noise at DNA fragment concentrations below 10 fM. The signal to noise demonstrated in this technique could be sacrificed to allow shorter analysis times.

Alternate solutions are to move the sample through a stationary probe volume or to move the prove volume through a stationary sample. By using scanning speeds of ~ 5 mm/second and ~50 femtomolar concentration of labeled DNA, analysis times on the order of ~1000 seconds can determine whether or not two fluorecent hybridization probes are on the same or separate DNA strands.

This approach can be used for single molecule haplotyping. However, the apparatus is equipment intensive and is not suitable for clinical research. In order to detect single fluorescent molecules in relatively large (1 pL) probe volumes, a pulsed excitation laser and time gated single photon detection have been used (Ambrose et al. 1999). In time gated detection, photons that arrive coincident with the laser pulse are ignored, as these are mainly due to Raman and Rayleigh scatter of the solvent. Scattered light background can be suppressed by approximately two orders of magnitude using pulsed excitation and time-gated detection. Time-gating has been successfully employed for many single molecule studies.

Proof of Principle Protocol

A two-color, single molecule fluorescence detection apparatus based on a previous design (Schwille 1997) was used to detect the simultaneous presence of two different, single fluorophore labels on DNA fragments. To demonstrate that two different fluorophore labels can be detected on a single DNA strand, M13mp18, a single-stranded, circular DNA 7249 bases in length was used as target DNA for the preliminary experiments described here. M13mp18 DNA contains single EcoR I and Hind III restriction sites at base positions 6230 and 6281, respectively. Two fluorescently labeled DNA oligonucleotide hybridization probes were purchased from a commercial oligonucleotide synthesis service. These were further purified by polyacrylamide gel electrophoresis.

The first probe was a 20-mer complementary to a 20 base region of the M13mp18 target containing the EcoR I restriction site. This oligonucleotide was labeled at its 5' end with a single carboxyfluorescein (FAM) fluorophore. The sequence of this oligonucleotide is 5'FAM-gctc**gaattc**gtaatcatcg-3' [SEQ ID NO: 1]. The base sequence comprising the EcoR I restriction site in the FAM-labeled probe is shown in bold type.

The second hybridization probe was an 18-mer complementary to an 18 base region of the M13mp18 target containing the Hind III restriction site and had the sequence 5'Cy5-cagtgcc**aagctt**cgatg-3' [SEQ ID NO: 2]. This oligonucleotide was labeled at its 5' end with a single N,N'-biscarboxypentyl-5,5'-

disulfonatoindodicarbocyanine (Cy5) fluorophore. The base sequence comprising the Hind III restriction site contained in the Cy5-labeled probe is shown in bold type.

The hybridization reaction between the fluorescently labeled probes and the M13mp18 target DNA is shown schematically in Figure 3A. The fluorescent products resulting from this reaction are also shown in Figure 3A. The doubly-labeled probe/target adducts generate correlated fluorescence signals in the red and green detection channels and are detected by cross-correlation analysis. The singly-labeled fluorescent products do not produce correlated fluorescence signals in the red and green detection channels.

The samples consisted of 5 nM each of the fluorescently tagged oligonucleotide probes in a buffer containing 100 mM NaCl, 50 mM Tris pH 7.9, 10 mM MgCl2, 1 mM dithiothreitol and either 1 mg/ml or 0.1 mg/ml sheared salmon sperm DNA. Salmon sperm DNA was added to minimize non-specific binding of the target DNA and hybridization probes to surfaces during preparation and analysis of the samples. Target DNA concentrations were in the range of 2.5 nM to 25 nM. Negative controls included the probes without the M13mp18 template DNA as well as probes and template DNA digested with 10-20 units of EcoR I restriction enzyme to cut the hybridized FAM-probe/M13mp18 template adduct at the EcoR I restriction site in order to separate the FAM probe from the template. Hybridization reactions were carried out as follows. Samples were heated in a thermal cycler to 92 °C for a few minutes to denature double-stranded to single-stranded DNA and then cooled 50 °C and held at that temperature overnight to allow the complementary sequences (i.e., probes and template) to specifically hybridize to one another. When applicable, the samples were cooled to 37 °C at which point the EcoR I restriction enzyme was added. The restriction enzyme digestion was carried out for 2 hours at 37 °C.

Samples were analyzed by two-color fluorescence cross-correlation using the apparatus shown in Figure 2. A small amount (~5 μL) of sample was pipetted onto a #1 borosilicate glass coverslip. The coverslip with the hanging sample

droplet was placed under the microscope objective of the two-color fluorescence detection apparatus and the fluorescence excitation volume was positioned within the sample droplet ~10 micrometers below the coverslip. Unless otherwise noted, cross-correlations were calculated from 600s of fluorescence data collected from each sample. The samples were analysed at room temperature.

Figure 3B shows cross-correlations obtained from samples containing different concentrations of the M13mp18 target DNA ranging from 0 nM to 25 nM. Each of these samples contained 1 mg/ml of sheared salmon sperm DNA. The cross-correlation from the sample containing no target DNA (dotted line) was calculated from 1800s of fluorescence data. Under these experimental conditions, good cross-correlation was obtained from the sample containing 2 nM M13mp18 target and two hybridization probes.

Figure 3C shows cross-correlations obtained from samples containing 25 nM M13mp18 target DNA (solid line), and 25 nM M13mp18 target DNA digested with EcoR I (dashed line). Each of these samples additionally contained 0.1 mg/ml of sheared salmon sperm DNA. The cross-correlation obtained from the sample that contained doubly labeled M13 shows substantial amplitude out to a delay of 100 ms. In contrast, the cross-correlation obtained from the EcoR I restricted sample (dashed line) shows very little amplitude. The EcoR I restriction enzyme specifically cuts at the six-base recognition site located within the duplex region formed by the hybridization of the FAM-labeled probe to its target sequence on the M13mp18 DNA. Once cut, the short FAM-labeled probe fragment dissociates from the M13mp18 DNA to effectively eliminate doubly-labeled target DNA adducts from the sample.

In the present invention, selected genetic marker sites would correspond to the Hind III and EcoR I restriction sites in the above experiment.

Target-specific probe design.

A single probe approach refers to one probe that is targeted to one SNP. Compared with a multiple probe approach such as two-probe approach, where two

probes are used to define one SNP, a single probe is economical and straightforward. Since most human SNPs are bi-allelic (only two alternative bases for each probe), SNP typing only needs to discriminate two bases at a given SNP site. DNA, PNA, molecular beacons, and LNA are possible probes for SNP analysis.

(1) Exemplary DNA and PNA probes:

Example 1: Leukemia Chimera Detection

In abnormal circumstances (such as some cancers), segments of genes may be recombined together, forming a so called chimera gene that is composed of incomplete parts of two genes. Traditionally, these hybrid genes are detected in a three step process using reverse transcriptase polymerase chain reaction (RT-PCR) amplification of mRNA; PCR amplification and DNA sequencing; and northern/southern blots or minisequencing. In accordance with the present invention, the amplification steps are eliminated and the two halves of the chimera gene messenger RNA are simultaneously detected using differently labeled fluorescent hybridization probes and fluorescence correlation spectroscopy (FCS). Since single molecule haplotyping can distinguish between a double and a single label, this method can distinguish between the chimera, which will be doubly labeled, and the singly labeled wild type transcripts present on separate messenger RNA molecules.

One example of a chimera, which is diagnostic of an acute lymphoblastic leukemia, is the *MLL* (*HRX, Htrx*) and *AF4* (*FEL*) gene fusion. It is planned to use this system to develop methods to detect such chimera genes using FCS. Preliminary experiments will be conducted on a synthetic chimera template with sequence derived from both genes:

MLL-AF4/98(+)

Biotin-TEG 5'-

gaagttcccaaaaccactcctagtgagcccaagaaaaagcagcctccaccaccaaaacaatatgatacat cttcaaaaactcactcaaattctcagc-3' [SEQ ID NO: 3].

Bold type indicates the sequence derived from the MLL gene; plain type indicates the sequence derived from the AF4 gene. A 5' biotin is added to aid in troubleshooting, if necessary (see below). There is also a synthetic oligonucleotide complementary to the chimera synthetic template sequence above, designated MLL-AF4/98(-).

Fluorescently labeled DNA, peptide nucleic acid (PNA), and locked nucleic acid (LNA) oligonucleotides complementary to the sequences above are used as potential hybridization probes.

1. DNA probes sequences, including a linker of five extra dATPs follow:

MLL 3968L20

5'[Cy5]aaaaatttcttgggcttcactagggag-3' [SEQ ID NO: 4]

AF4 4025L24

5'[FAM or Rhodamine Green X]aaaaaaatttgagtgagtttttgaagatg-3' [SEQ ID NO: 5]

2. PNA probe sequences. O stands for a linker sequence required between label and base.

MLLCy5P

(N)5'-[Cy5]-OOtttcttgggctcO-3'(C) [SEQ ID NO: 6]

AF4FAMP

(N)5'-[FLU]-OOtttgagtgagttOlys-3'(C) [SEQ ID NO: 7]

3. LNA probe sequences, locked nucleic acids bolded.

MLLCy5L

5'[Cy5]-**ttt**cttg**gg**gctc-3' [SEQ ID NO: 8]

AF4RGXL

5'[Rhodamine Green X]-**tttgagtg**agtt-3' [SEQ ID NO: 9]

(Look 1997; VanDongen (1999))

The probes are labeled with biotin to allow binding to microspheres for fluorescence detection by a commercial flow cytometer (FACS Calibur, BD). Since the exemplary flow cytometer (FACS Calibur, BD) is optimized for detection of

fluorescence in the mid-visible, fluorescein labels are used for all these evaluation studies. As shown in Figure 1, two sets of the probes are needed, one that is wild type specific and another one that is mutant specific.

The probes (including DNA, PNA and LNA forms) will be tested for specificity to chimeric templates that are immobilized on the microspheres (Cai, Kommander et al. 1998; Nolan, Cai et al. 1998; Cai et al. 2000, Genomics.)

Example 2: HLA haplotying

One example of a region where haplotyping is critical for successful organ transplants is the human leukocyte antigen (HLA) gene. The method of the present invention is used pairwise on a set of variant alleles in this case. Preliminary work will be conducted on a set of synthetic oligonucleotide templates (haplotypes) containing a subset of the relevant sequence variants, where the variant alleles are underlined and the space represents a sequence of bases , e.g., a kb in length, separating variant alleles in the templates, where the missing sequence is not needed to construct a probe:

A*02011/A/TT/GT

5'tggcagctcagaccaccaagc**a**caagtgggag [SEQ ID NO: 10]

...gcggcccatgtggcggagcag**tt**gagagcctacctggagggcacgtgcgtgga**gt**ggctccgcagatacctg gaga-3' [SEQ ID NO: 11]

A*0212/A/CA/GT

5'tggcagctcagaccaccaagc**a**caagtgggag [SEQ ID NO: 12]

...gcggcccatgtggcggagcag**ca**gagagcctacctggagggcacgtgcgtgga**gt**ggctccgcagatacct ggaga-3' [SEQ ID NO: 13]

A*0236/A/TT/CG

5'tggcagctcagaccacccaaga**c**aagtgggag [SEQ ID NO: 14]

...gcggcccatgtggcggagcag**tt**gagagcctacctggagggcacgtgcgtgga**cg**ggctccgcagatacctg gaga-3' [SEQ ID NO: 15]

A*2402101/G/CA/CG

5'tggcagctcagaccacccaag**g**caagtgggag [SEQ ID NO: 16]
...gcggcccatgtggcggagcag**ca**gagagcctacctggagggcacgtgcgtgga**cg**ggctccgcagatacct ggaga-3' [SEQ ID NO: 17]
A*24031/G/CA/GT
5'tggcagctcagaccacccaag**g**caagtgggag [SEQ ID NO: 18]
...gcggcccatgtggcggagcag**ca**gagagcctacctggagggcacgtgcgtgga**gt**ggctccgcagatacct ggaga-3' [SEQ ID NO: 19]
A*2413/G/TT/GT
5'tggcagctcagaccacccaag**g**caagtgggag [SEQ ID NO: 20]
...gcggcccatgtggcggagcag**tt**gagagcctacctggagggcacgtgcgtgga**cg**ggctccgcagatacctg gaga-3' [SEQ ID NO: 21]

Target-specific fluorescent probes of DNA, PNA and LNA are designed to interrogate the sites of interest underlined above. The specificity of fluorescent probes will be tested on the above synthetic haplotype templates using flow methods described above.

(2) Molecular Beacon: Molecular beacons are oligonucleotide probes that fluoresce when they hybridize to their target. The hairpin shape of the molecular beacon causes mismatched probe/target hybrids to easily dissociate at significantly lower temperature than exactly complementary hybrids. This thermal instability of mismatched hybrids increases the specificity of molecular beacons. The presence or absence of a particular SNP sequence in DNA can be determined using a molecular beacon with a loop sequence complementary to a SNP target (Kostrikis et al., 1998; Tyagi et al., 1998). Exploiting the option to employ different dyes, molecular beacon assays can be multiplexed and have been used for real-time fluorescent genotyping (Kostrikis et al., 1998; Tyagi et al., 1998) and in the simultaneous detection of four different pathogenic retroviruses in clinical samples (Vet et al., 1999).

In single molecule haplotyping, two SNP specific molecular beacon probes are designed and labeled with two distinguishable fluorescent labels such as FAM and Cy5 using a standard protocol (Kostrikis et al., 1998; Tyagi et al., 1998). Upon simultaneous binding of the two beacon probes to a specific haplotype, the hairpins of two beacons will open up to release quenching of the fluorescence and a positive cross correlation of FAM and Cy5 will be detected and measured indicating the presence of that particular haplotype.

The main advantage of molecular beacons is that they remain nonfluorescent unless bound to a target. The fluorescence signal of a bound beacon compared to a free beacon can be as high as 500 fold (Tyagi 1998). The use of a beacon may enable single molecule haplotyping on unamplified genomic DNA without the separation of free probes. Furthermore, it was also reported that a beacon discriminates better than a DNA probe due to its rigid stem structure (Kostrikis et al. 1998).

(2) One probe labeling protocol using Peptide Nucleic Acid (PNA)

PNA is a unique class of informational molecule containing nucleobases attached to a neutral 'peptide-like' backbone (Egholm, M., 1993). PNA hybridizes to complementary RNA or DNA with higher affinity and specificity than conventional oligonucleotides and oligonucleotide analogues (Egholm, M., 1993, Wittung, P., 1994). The special properties of PNA allow novel molecular biology and biochemistry applications unachievable with traditional oligonucleotides and peptides (Buchardt, O.,1993).

The backbone of the PNA molecule consists of repeating N-(2-aminoethyl) glycine units linked by amide bonds. The bases are attached to the backbone by methylene carbonyl linkages. Unlike DNA or other DNA analogs, PNA does not contain any pentose sugar moieties or phosphate groups. By convention, PNA is depicted like peptides, with the N-terminus at the first (left) position and the C-terminus at the right.

In single molecule haplotyping, two PNA probes labeled with two distingushable fluorophores (e.g., fluorophores available from Applied Biosystems)

are designed to be specific for two SNPs of a particular haplotype. The presence of a specific haplotype is identified by the positive cross correlation of two fluorophores on the same chormosome. The protocol of PNA design, synthesis and the hybridization is known (Orum, et al. 1993; Castro, A. 1997).

It is expected that all the single probe biochemistry will work for this two SNP model system. However, PNA and molecular beacons are expected to be better choices, compared to a DNA probe, because of their greater discrimination capability between matched and mismatched bases. The replacement of a phosphodiester bond with a peptide bond makes PNA binding when paired with a matched DNA, but more unstable when bound to a mismatch. These properties of PNA have enabled PNA to be used in single point mutation detection through PCR clamping, a PCR amplification method of PNA-based single base discrimination assay (see, e.g., Orum et al. 1993). In addition, the single molecule detection of specific nucleic acid sequences in unamplified genomic DNA has been demonstrated using PNA probes(Castro 1997). All these results indicate that PNA-based sequence discrimination is highly specific. Therefore, the PNA probes are expected to be a good choice for single molecule haplotyping on genomic DNA.

(3). One probe approach-LNA

LNA (Locked Nucleic Acid) is a novel class of nucleic acid analogues. LNA monomers are bicyclic compounds structurally similar to RNA nucleosides (Koshkin 1998). The term "Locked Nucleic Acid" has been coined to emphasize that the furanose ring conformation is restricted in LNA by a methylene linker that connects the 2'-O position to the 4'-C position. For convenience, all nucleic acids containing one or more LNA modifications are called LNA. LNA oligomers obey Watson-Crick base pairing rules and hybridize to complementary oligonucleotides. LNA provides vastly improved hybridization performance when compared to DNA and other nucleic acid derivatives in a number of situations. LNA/DNA or LNA/RNA duplexes have increased thermal stability compared with similar duplexes formed by DNA or RNA. LNA has the highest affinity towards complementary DNA and RNA ever reported. In general, the thermal stability of a LNA/DNA duplex is increased 3°C to

8°C per modified base in the oligonucleotide. The design, synthesis and hybridization of LNA probes are known (Koshkin, 1998, Wahlestedt, 2000).

For single molecule haplotyping, LNA probes are designed, synthesized, and hybridized to SNPs according to the standard protocol in the references (Orum 1993; Orum 1999).

(4) FRET-two probe approaches

Two hybridization probes, a probe bearing the fluorescence energy donor and an immediate adjacent probe bearing the energy transfer acceptor, i.e., energy transfer oligo pairs, are used for typing. The fluorophore of the donor may be the same for both SNPs, so a single excitation laser is used for both SNP targets. The acceptor fluorophores of two SNPs are distinguishable so that two color FCS analysis can be conducted. The presence of the particular haplotype is determined by a positive correlation of two color fluorescence as described above.

The synthesis and hybridization of fluorescent FRET probes is described in (Rasmussen et al. 1998). The fluorescence labels can be at 3' or 5' of an oligo depending on the numbers of nucleotides for the hybridization primers.

(5). Enzymatic approach of specific labeling of SNPs.

Besides standard hybridization approaches (Landgren 1998), there have been numerous enzymatic labeling approaches that can be generally divided into polymerase-based (1-2), 3'-exonuclease-based (3), 5'-exonuclease-based (4), ligase-based (5) and endonuclease-based approaches (6-7). They can be a one primer approach or a two primer approache, or may be even combined. The respective protocols are known. (Syvanen 1990; Syvanen 1997; Davis et al. 1995; Lee. et al. 1993; Landegren et al. 1998; Lyamichev et al. 1999).

Other modified forms of enzyme-mediated approaches such as polymerase-mediated (Chen et al. 1999), ligase-mediated genotyping (Landegren et al. 1988; Landegren 1998), 5'-exonuclease (e.g. Taqman approach, Lee 1993) and Invader assay (Lyamichevet al. 1999) can also be labeled with FRET fluorophores and adapted for single molecule haplotyping purpose.

The potential limitation of a single probe can be one of the following:

(a) Optimization needed for each SNP. Since all above approaches are based on hybridization differences between a mismatched and matched base pairs, the thermal dynamic difference is small, especially for a T:G mismatch versus T:A match. To design a probe that is highly specific, experimental optimization may be needed even with the help of design guidelines and oligo analysis software.

(b) Routine experimentation may be needed to find a hybridization condition that would work for all probes in a large scale SNP analysis. There is a recent report showing multiplexed analysis of four targets in one reaction using four different molecular beacons (Vet et al. 1999). Adjusting the sequences of stems to make the beacon work at the desired temperature range is possible, but there may be some cases where the base discrimination only happens at a narrow range of temperature, and the hybridization condition for one SNP may not be the best for the second SNP. If this problem occurs, then the two probe designs such as oligo ligation and 5' exonuclease may be used. Because multiple probes are required to define one SNP target, it generally has greater discrimination of the target over other genomic DNA than the one probe approach where only a single probe is required for each target as described in the two probe section.

The two-color, single molecule fluorescence detection laboratory apparatus can be optimized using the synthetic fluorescently-labeled oligo system and model hybridization probe systems derived from biochemistry research discussed above. Specific optimization parameters include the size of the excitation/detection volume, the excitation laser powers, and sample stage scanning rate for single molecule haplotyping. A synthetic fluorescently labeled oligo system may be used to explore the sensitivity of the apparatus to two-color labeled DNA fragments in the presence of a background of one-color labeled DNA. Data acquisition times and cross-correlation analysis routines can be optimized to give acceptably low assay error rates.

A number of hybridization probe schemes for haplotyping can be evaluated using conventional flow cytometry methods (Cai 1998; Cai et al. 2000.). The most promising of these can be tested with the single molecule fluorescence detection

apparatus. Given the sensitivity of this apparatus, fluorescent hybridization probe schemes will likely have to be modified to minimize the introduction or retainment of fluorescent impurities that will degrade the single molecule fluorescence assay. Moreover, problems associated with non-specific binding of hybridization probes to genomic DNA, which become apparent only at the single molecule level, may arise.

Compared with the single probe approach, one advantage of multiple probes, such as a two-probe method, is the higher specificity of SNP targeting, because it requires the simultaneous hybridization of two probes to one SNP site. Unlike the conventional genotyping, where target sequences are amplified before typing, the high specificity of targeting may be needed for typing a specific target on the unamplified genomic DNA. As a matter of fact, the detection of a specific sequence on unamplified maize genomic DNA by two color single molecule technique has been done by using two PNA probes (Castro et al.1997). Another advantage of a two-probe method is that very little optimization is needed for the probes because the discrimination of matched and mismatched base pairs is dependent upon the intrinsic discrimination properties of enzymes such as ligase or 5' exonuclease, not the hybridization of probes (e.g., reviewed by Landegren et al. 1998), i.e., all the target probing procedures can be done under one universal enzyme reaction condition. Therefore, the optimization of probes may be minimized and a universal hybridization reaction condition may be used for multiple SNP typing. This universal typing reaction condition allows the usage of robots to simultaneously process many samples.

(1) Modified Oligo ligation assay: A conventional ligase-based oligo ligation assay by flow cytometry for bulk genotyping purpose has been demonstrated (Landgren et al. 1998). However, the assay can not be directly used for the single molecule approach. The conventional ligation assay has a denaturation step to separate ligation product from bound (but not ligated) probes, and to capture the ligation product for fluorescence detection. The denaturation, however, is not compatible with two-color haplotyping because two signals from one chromosome

are detected and the denaturation would cause the dissociation of the probe from the target.

To adapt the oligo ligation assay to single molecule haplotyping, a modified ligation assay may be performed for two-color haplotyping. Two types of probes may be generated: one is an universal fluorescent reporter probe that binds to the 5' end of a target, the other one is a blocker probe that has a specific base at the 5' end (opposite to the SNP site) and a modified 3' end (such as a carbon spacer). Upon the hybridization of two probes to a target, a ligase will join the matched blocker probe to the fluorescent reporter. Since the ligated fragment has a modified 3' end that is resistant to Exonuclease III digestion, the fluorescence reporter will remain bound on the target. In contrast, if a blocker has a wrong base opposite a SNP target, a mismatch will be formed. Consequently, the ligation of the reporter and the blocker is prohibited, and Exonuclease III will invade from the nick and digest the fluorescent reporter. Therefore no fluorescence signal will be preserved on the DNA for two-color detection.

(2) Modified 5' exonuclease assay (Taqman Assay): This is also an example of a two-probe approach that takes advantage of the 5' exonuclease activity of Taq DNA polymerase to digest a DNA probe annealed at a SNP site. Typically, one primer binds to the upstream of the SNP target, and the other primer binds to the target with its 5'-terminus opposite to the SNP site. If the 5' base of downstream primer B is perfectly matched with the SNP target, the polymerization continues. If the downstream primer is mis-paired with the SNP, then the polymerization is aborted at the SNP site. The 5' exonuclease-based Taqman assay has been very successful for SNP genotyping (Holland et al. 1991; Landegren et al. 1998; Luthra 1998) and is adaptable to the single molecule haplotyping.

Two probes are prepared for each SNP target: upstream primer and a 3'-fluorescent downstream primer. Taq polymerase starts the polymerization from the 3' end of upstream primer. When it encounters the matched downstream primer, the 5' exonuclease digests away the downstream primer and the polymerization continues. Consequently there are no labels attached to the target. Note the 3'-end

of the downstream primers is blocked with a fluorescein modification, and there is no polymerization on the downstream primer. On the other hand, if polymerase encounters a mismatched downstream primer, the 5' exonucelase reaction is highly inhibited. As a result, the downstream fluorescent primer remains bound to a target. The typing of a SNP is based on the intrinsic discrimination against mismatch of 5' exonucelase of Taq polymerase.

(3) Polymerase-associated proofreading exonuclease/ligation assay:

Two primers are used for each SNP target: a 5'-labeled fluorescent upstream primer that binds to a SNP target and a 3'-amino-labeled (as a blocker of the exonclease which degrades DNA from a nick site) downstream primer that binds adjacent to 3' of the target. If the upstream primer bears a correct 3' base opposite target SNP, two primers will be joint by DNA ligase in the presence of DNA polymerase-associated proofreading exonucelase (a 3'-5' exonucelase associated with a polymerase) and a additional exonuclease that degrades DNA from a nick. On the other hand, if the upstream primer bears a wrong base at the target site, polymerase-associated exonucelase will remove the wrong base and create a nick that is subjected to exonucelase degradation. As a result, fluorescent primer will be digested, and no fluorescence signal is given at the target site.

A potential limitation of the two probe approach is that a low signal-to-noise ratio originates from inefficient discrimination against the wrong bases. This can be intrinsic to ligase polymerase or exonuclease. However, data from available reports indicated that it should not be a big problem for most sequences (Holland et al. 1991; Lee et al. 1993; Luthra et al. 1998). If the target of leukemia and HLA do not permit a significant discrimination by a typical T4 phage ligase or Vent polymerase-associated 5'-exonuclease or other 3' exonucleases, the design of the SNP specific primer can be improved to make the hybridization more specific to the mismatch, so the mismached primer will not bind to the target. Another alternative is to use ligases and 5'-exonucelases with higher discrimination ability from other species. For example, instead of T4 phage ligase, a thermalphile ligase can be used at

higher temperatures, or *E.Coli* ligase, instead of Taq polymerase/exonuclease, or other polyemrases can be used.

In a typical pairing practice, the following parameters are evaluated and optimized for the single molecule haplotyping approach. The signal-to-noise level is obtained by comparing the positive signal of two-color correlation with a control experiment, where a restriction enzyme is added for cleavage between the two SNPs before the hybridization. Because the two SNPs are no longer physically linked, there should be no correlation between two SNPs.

Second, the amount of starting material needed for each assay is evaluated. This is important for future large-scale disease association analysis, because the ability for typing thousands of markers on the genomic DNA from each individual is crucial to find the link between markers and disease. In principle, the amount of DNA needed for the detection is less than one microliter at < 10 fM. However, there is a practical concern for the loss of the DNA at each step of the assay. To evaluate the actual amount of DNA needed for each typing experiment, different amounts of starting blood or tissue samples are tested for each step of the assay, such as genomic DNA extraction and purification, probe hybridization, SNP typing reaction, separation of unbound probes from the bound probes and detection.

Third, the time needed for efficient binding to a target is evaluated. Based on the two color, single molecule hybridization study results from Castro et al. 1997, 14 hours of hybridization are needed at 100 pM of PNA probe concentration. This indicates an inefficient hybridization between the probes and an unamplified target at low concentrations. A time course study for the probe hybridization to the unamplified genomic DNA at different probe concentrations will determine the minimum time for the hybridization step. The efficient hybridization between probes and the target is optimized by exploring parameters such as salt concentrations, pH, temperature and addition of molecular crowding reagents. The time needed for single molecule detection also is optimized to increase the throughput of an assay. The data collection time is varied to determine the shortest collection time needed for a accurate typing.

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The foregoing description of the invention has been presented for purposes of illustration and description and is not intended to be exhaustive or to limit the invention to the precise form disclosed, and obviously many modifications and variations are possible in light of the above teaching. The embodiments were chosen and described in order to best explain the principles of the invention and its practical application to thereby enable others skilled in the art to best utilize the invention in various embodiments and with various modifications as are suited to the particular use contemplated. It is intended that the scope of the invention be defined by the claims appended hereto.

WHAT IS CLAIMED IS:

1. A method for rapid haplotyping comprising the steps of:

labeling at least two target sites on a segment of DNA or RNA with separate distinguishable luminescent hybridization probes, where the targets are selected genetic markers; and

detecting the presence or absence of each luminescent hybridization probe on each DNA segment to determine the haplotype of each DNA or RNA segment.

2. A method for rapid haplotyping comprising the steps of:

labeling at least two target sites on a segment of DNA or RNA with separate distinguishable luminescent hybridization probes, where the targets are selected genetic markers;

forming a dilute solution containing the labeled DNA or RNA segments;

illuminating each labeled DNA or RNA segment with light beams; and

detecting the presence or absence of each luminescent hybridization probe on each DNA segment to determine the haplotype of each DNA or RNA segment.

3. The method of Claim 1, further including the step of sequentially and repeatedly haplotyping pairs of neighboring genetic makers on DNA segments forming a chromosome.

4. The method of Claim 1, wherein the step of detecting the presence or absence of each luminescent hybridization probe includes the step of detecting a luminescence characteristic emitted from each hybridization probe and cross-correlating the detected luminescence characteristic to indicate the presence or absence of both hybridization probes on a single DNA or RNA segment.

5. The method of Claim 2, wherein the step of detecting the presence or absence of each luminescent hybridization probe includes flowing the dilute solution of the DNA or RNA through a flow cytometer.

6. The method of Claim 2, wherein the step of detecting the presence or absence of each luminescent hybridization probe includes examining individual drops of the solution containing DNA or RNA with a confocal microscope.

7. The method of Claim 6, wherein the step of examining individual drops of the solution with a confocal microscope includes scanning each drop through a stationary probe volume or scanning the probe volume through a stationary drop.

8. The method of Claim 1, 2, 3, 4, 5, 6, or 7, wherein the targets are base sequence variations selected from the group consisting of single nucleotide polymorphism, multibase deletion, multibase insertion, microsatellite repeats, di-nucleotide repeats, tri-nucleotide repeats, sequence rearrangements, and chimeric sequence.

9. The method of Claim 1, 2, 3, 4, 5, 6, or 7, wherein the luminescent hybridization probes are selected to have distinguishable characteristics selected from the group consisting of luminescence emission spectral distribution, lifetime, intensity, burst duration, and polarization anisotropy.

10. The method of Claim 9, wherein the luminescent hybridization probes are formed from the group consisting of single dye molecules, energy transfer dye pairs, nano-particles, luminescent nano-crystals, intercalating dyes, and molecular beacons.

11. The method of Claim 9, wherein the form of the hybridization probe is selected from the group consisting of DNA, RNA, PNA, and LNA.

12. The method of Claim 8, wherein the luminescent hybridization probes are selected to have distinguishable characteristics selected from the group consisting of luminescence emission spectral distribution, lifetime, intensity, burst duration, and polarization anisotropy.

13. The method of Claim 12, wherein the luminescent hybridization probes are formed from the group consisting of single dye molecules, energy transfer dye pairs, nano-particles, luminescent nano-crystals, intercalating dyes, and molecular beacons.

14. The method of Claim 12, wherein the form of the hybridization probe is selected from the group consisting of DNA, RNA, PNA, and LNA.

15. The method of Claim 1, 2, 3, 4, 5, 6, or 7, where the hybridization probes are selected from the group consisting of single probes that are specific for each target or multiple probes that act together to identify the target.

16. The method of Claim 15, wherein the single probes are selected from the group consisting of oligo DNA, oligo RNA, oligo beacon, oligo PNA, oligo LNA, and chimeric oligos.

17. The method of Claim 15, wherein the multiple probes are selected from the group consisting of hybridization pairs, invader oligo pairs, ligation oligo pairs, mismatch extension 5'-exonuclease oligo pairs, energy transfer oligo pairs, and 3'-exonuclease pairs.

18. The method of Claim 12, where the hybridization probes are selected from the group consisting of single probes that are specific for each target or two probes that act together to identify the target.

19. The method of Claim 18, wherein the single probes are selected from the group consisting of oligo DNA, oligo RNA, oligo beacon, oligo PNA, oligo LNA, and chimeric oligos.

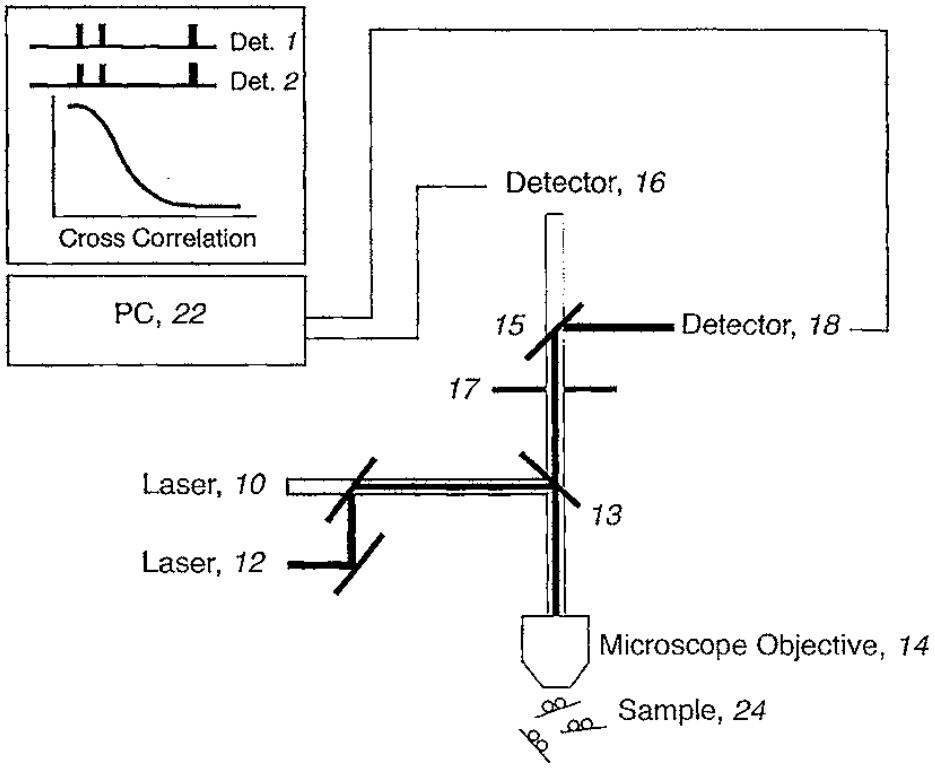
20. The method of Claim 19, wherein the two probes are selected from the group consisting of hybridization pairs, invader oligo pairs, ligation oligo pairs, mismatch extension 5'-exonuclease oligo pairs, energy transfer oligo pairs, and 3'-exonuclease pairs.

21. The method of Claim 1, 3, or 4 including forming a dilute solution to a concentration in the range of 100 nM to sub-fM of DNA or RNA fragments.

Haploid Genotyping by Two-Color, Single-Molecule Detection

Mutation	Genotype	Two-Color Probes for Mutant	Two-Color Probes for Wild Type	Two-Color Correlation Result, Mutant/Wild Type
wild type	A B / A B	-	A B Correlated Two-Color	—/+
two mutations separated on two chromosomes, heterozygote	A b / a B	A b + a B	A b + a B	—/—
two mutations on one chromosome, the second chromosome intact, heterozygote	a b / A B	a b Correlated Two-Color	A B Correlated Two-Color	+/+
two mutations on one chromosome, homozygote	a b / a b	a b Correlated Two-Color	-	+/—

Fig. 1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Det. 2
Cross Correlation
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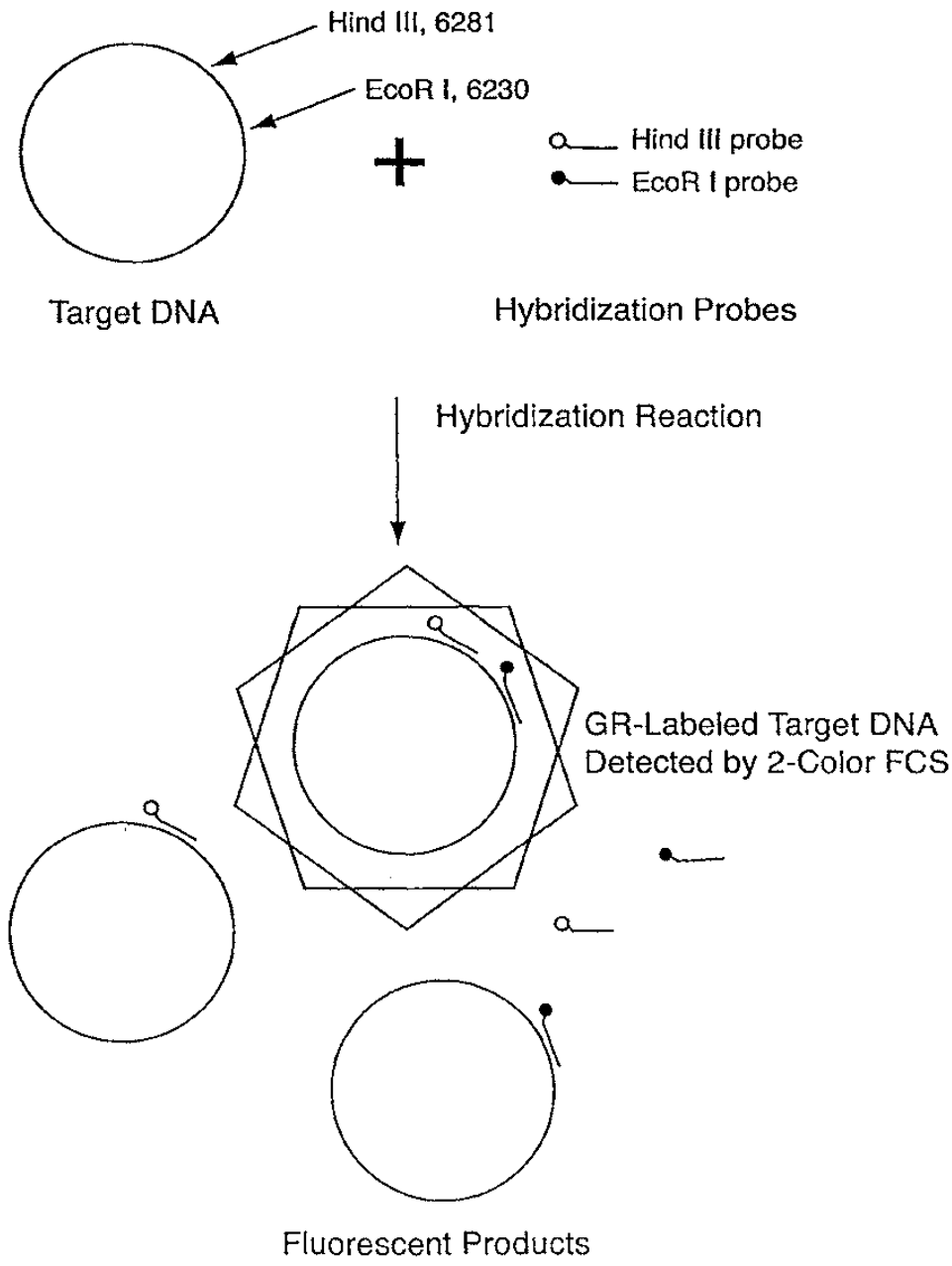
Detector, 16
15
Detector, 18
17
Laser, 10
13
Laser, 12
Microscope Objective, 14
Sample, 24

Fig. 2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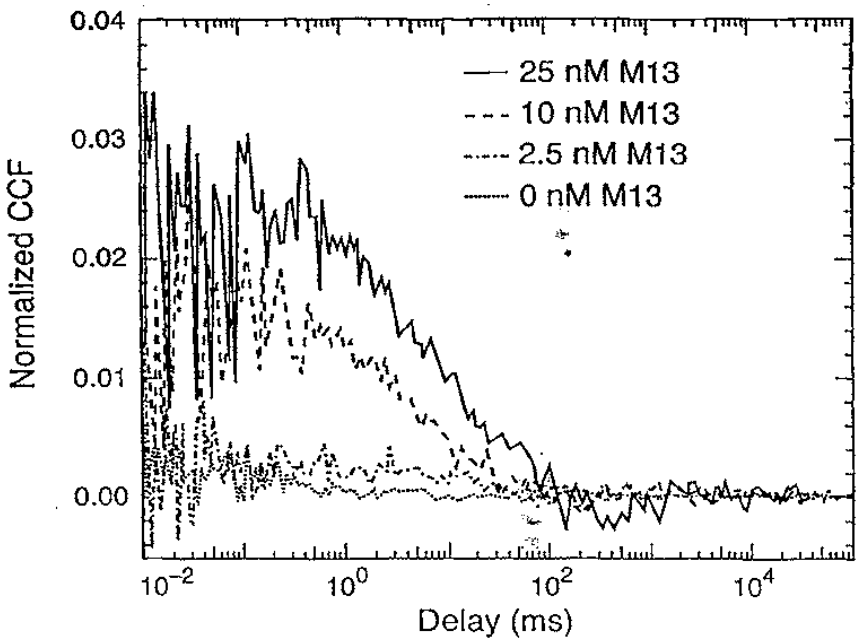
EcoR I, 6230
Hind III probe
EcoR I probe
Target DNA
Hybridization Probes
Hybridization Reaction
GR-Labeled Target DNA
Detected by 2-Color FCS
Fluorescent Products

Fig. 3A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0.02
0.01
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10^{-2}
10^{0}
10^{2}
10^{4}
Delay (ms)

Fig. 3B

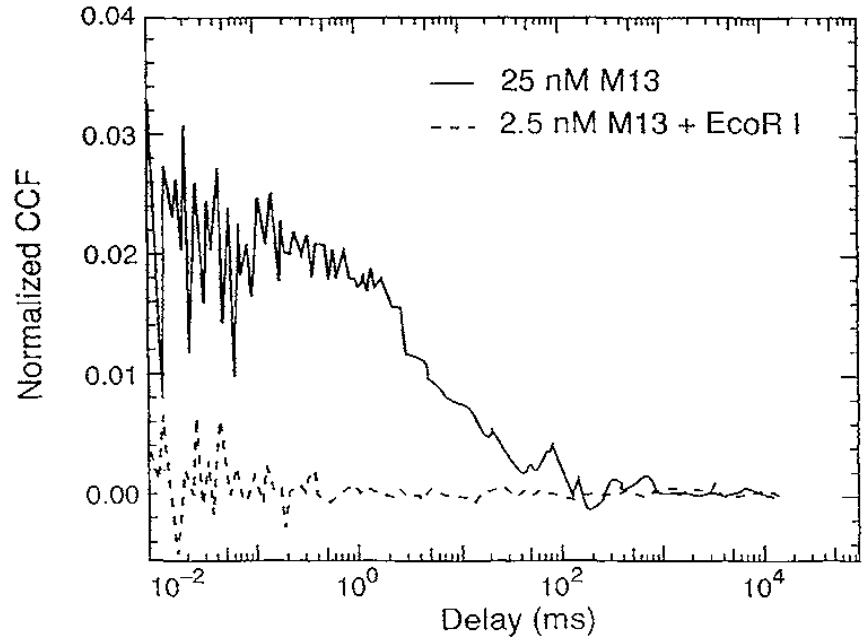
0.04
0.03
0.02
0.01
0.00
Normalized CCF
25 nM M13
2.5 nM M13 + EcoR I
10^{-2}
10^{0}
10^{2}
10^{4}
Delay (ms)

Fig. 3C

SEQUENCE LISTING

<110> Cai, Hong
Keller, Richard
Werner, James
Goodwin, Peter

<120> RAPID HAPLOTYPING BY SINGLE MOLECULE DETECTION

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/16894

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :C12Q 1/68; C07H 21/04
US CL : 435/6; 536/24.3
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
U.S. : 435/6; 536/24.3

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, DIALOG

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	KOSTRIKIS, L.G. et al. Spectral Genotyping of Human Alleles. Science. 20 February 1998, Vol. 279, No. 20, pages 1228-1229, see entire document.	1, 2, 4, 8-21 ---------- 3, 5, 6
Y	LANDEGREN, U. et al. Reading Bits of Genetic Information: Methods for Single-Nucleotide Polymorphism Analysis. Genome Research. 1998, Vol. 8, pages 769-771, entire document.	3
Y	GOODWIN, P.M. et al. Single-Molecule Detection in Liquids by Laser-Induced Fluorescence. Acc. Chem. Res. 1996, Vol. 29, pages 607-613, entire document.	5, 6

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 31 JULY 2001	Date of mailing of the international search report 29 AUG 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer TERESA STRZELECKA Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
5 August 2004 (05.08.2004)

PCT

(10) International Publication Number
WO 2004/065617 A2

(51) International Patent Classification[7]: C12Q

(21) International Application Number:
PCT/US2004/001329

(22) International Filing Date: 16 January 2004 (16.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/441,046 17 January 2003 (17.01.2003) US

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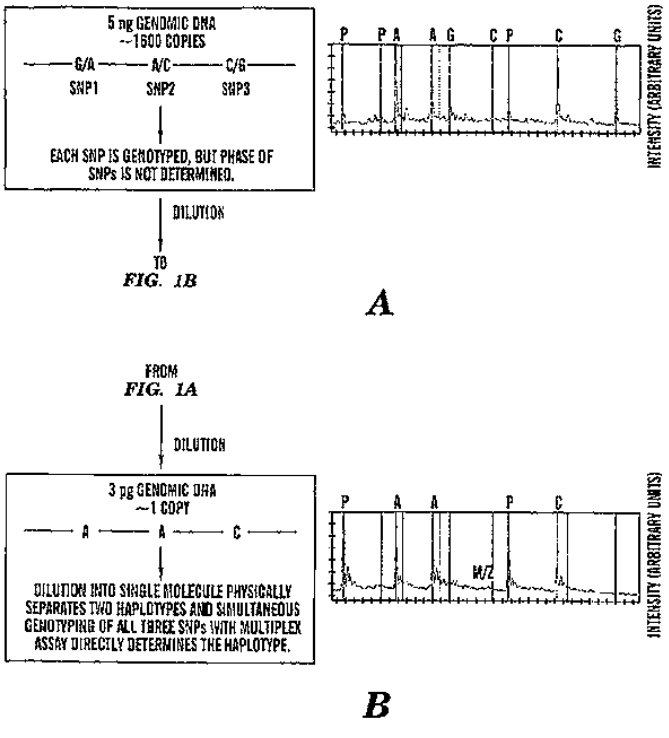
(74) Agents: **EISENSTEIN, Ronald, I.** et al.; Nixon Peabody LLP, 100 Summer Street, Boston, MA 02110 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

[Continued on next page]

(54) Title: HAPLOTYPE ANALYSIS



(57) Abstract: The present invention provides an efficient way for high throughput haplotype analysis. Several polymorphic nucleic acid markers, such as SNPs, can be simultaneously and reliably determined through multiplex PCR of single nucleic acid molecules in several parallel single molecule dilutions and the consequent statistical analysis of the results from these parallel single molecule multiplex PCR reactions results in reliable determination of haplotypes present in the subject. The nucleic acid markers can be of any distance to each other on the chromosome. In addition, an approach wherein overlapping DNA markers are analyzed can be used to link smaller haplotypes into larger haplotypes. Consequently, the invention provides a powerful new tool for diagnostic haplotyping and identifying novel haplotypes.

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Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished upon receipt of that report*

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HAPLOTYPE ANALYSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] The present application claims benefit of the U.S. provisional application Serial No. 60/441,046, filed on January 17, 2003, which is herein incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[002] Genetic polymorphisms are well recognized mechanisms underlying inter-individual differences in disease risk as well as treatment response in humans (Evans and Relling (1999) Science 286:487-491; Shields and Harris (2000) J. Clin. Onc. 18:2309-2316). Single nucleotide polymorphism (SNP) analysis has drawn much attention with the hope of identifying genetic markers for and genes involved in common diseases because of the frequency of the SNPs. Also, for many genes, the detection of SNPs known to confer loss of function provides a simple molecular diagnostic to select optimal medications and dosages for individual patients (Evans and Relling (1999) Science 286:487-491). It is common for genes to contain multiple SNPs, with haplotype structure being the principal determinant of phenotypic consequences (Collins et al. (1997) Science 278, 1580-81; Drysdale et al. (2000) Proc. Natl. Acad. Sci. 97:10483-8; Krynetski and Evans (1998) Am. J. Hum. Gen. 63:11-16). Therefore, to more accurately associate disease risks and pharmacogenomic traits with genetic polymorphisms, reliable methods are needed to unambiguously determine haplotype structure for multiple SNPs or other nucleic acid polymorphisms or mutations within genes as well as non-coding genomic regions.

[003] However, current genotyping technologies are only able to determine each polymorphism, including SNPs, separately. In other words, there is a lack of information on how several polymorphisms are associated with each other physically on a chromosome. A DNA haplotype, the phase determined association of several polymorphic markers (e.g., SNPs) is a statistically much more powerful method for disease association studies. Yet unfortunately, it is also much harder to determine a haplotype. Current experimental approaches include a physical separation of homologous chromosomes via means of mouse cell line hybrid, cloning into a plasmid and allele specific PCR. Neither of them is simple enough a method for routine high-throughput analysis. There are also ways to

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computationally determine haplotypes, but the accuracy of such computational analysis is uncertain.

[004] Approaches that can be used to haplotype SNPs or other nucleic acid polymorphisms, modifications and/or mutations that reside within relatively close proximity include, but are not limited to, single-strand conformational polymorphism (SSCP) analysis (Orita et al. (1989) Proc. Natl. Acad. Sci. USA 86:2766-2770), heteroduplex analysis (Prior et al. (1995) Hum. Mutat. 5:263-268), oligonucleotide ligation (Nickerson et al. (1990) Proc. Natl. Acad. Sci. USA 87:8923-8927) and hybridization assays (Conner et al. (1983) Proc. Natl. Acad. Sci. USA 80:278-282). A major drawback to these procedures is that they are limited to polymorphism detection along short segments of DNA and typically require stringent reaction conditions and/or labeling. Traditional Taq polymerase PCR-based strategies, such as PCR-RFLP, allele-specific amplification (ASA) (Ruano and Kidd (1989) Nucleic Acids Res. 17:8392), single-molecule dilution (SMD) (Ruano et al. (1990) Proc. Natl. Acad. Sci. USA 87:6296-6300), and coupled amplification and sequencing (CAS) (Ruano and Kidd (1991) Nucleic Acids Res. 19:6877-6882), are easily performed and highly sensitive, but these methods are also limited to haplotyping SNPs along short DNA segments (<1 kb) (Michalatos-Beloin et al. (1996) Nucleic Acids Res. 24:4841-4843; Barnes (1994) Proc. Natl. Acad. Sci. USA 91:5695-5699; Ruano and Kidd (1991) Nucleic Acids Res. 19:6877-6882).

[005] Long-range PCR (LR-PCR) offers the potential to haplotype SNPs that are separated by kilobase lengths of genomic DNA. LR-PCR products are commonly genotyped for SNPs, and haplotypes inferred using mathematical approaches (e.g., Clark's algorithm (Clark (1990) Mol. Biol. Evol. 7:111-122). However, inferring haplotypes in this manner does not yield unambiguous haplotype assignment when individuals are heterozygous at two or more loci (Hodge et al. (1999) Nature Genet. 21:360-361). Physically separating alleles by cloning, followed by sequencing, eliminates any ambiguity, but this method is laborious and expensive. Long-range allele-specific amplification negates both of these problems, but is limited to SNP-containing alleles that have heterozygous insertion/deletion anchors for PCR primers (Michalatos-Beloin et al. (1996) Nucleic Acids Res. 24:4841-4843). More complex technologies have also been used, such as monoallelic mutation analysis (MAMA) (Papadopoulos et al. (1995) Nature Genet. 11:99-102) and carbon nanotube probes (Woolley et al. (2000) Nature Biotech. 18:760-763), but these are either time consuming (MAMA), or require technology that is not widely available (nanotubes). U.S. Patent Application No. US 2002/0081598 discloses a haplotying method which involves the use of PCR amplification

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and DNA ligation to bring the polymorphic nucleic acid sites in a particular allele into close proximity to facilitate the determination of haplotypes spanning kilobase distances. However, this method relies on at least two enzymatic steps to create DNA fragments that can be ligated with other DNA fragments, and subsequently ligases to combine the DNA fragments to form one large fragment with several polymorphic sites in a shorter distance. These additional sample preparation steps make large scale use and automation of this technique cumbersome and error prone.

[006] Haplotypes, combinations of several phase-determined polymorphic markers in a chromosome, are extremely valuable for studies like disease association [1,2] and chromosome evolution. Direct molecular haplotyping has relied heavily on family data, but is limited to short genomic regions (a few kilobases). Statistical estimation of haplotype frequencies can be inconclusive and inaccurate [3].

[007] With the rapid discovery and validation of several million single nucleotide polymorphisms (SNP), it is now increasingly practical to use genome-wide scanning to find genes associated with common diseases [1,2]. However, individual SNPs have limited statistical power for locating disease susceptibility genes. Haplotypes can provide additional statistical power in the mapping of disease genes [4-7].

[008] Haplotype determination of several markers for a diploid cell is complicated since conventional genotyping techniques cannot determine the phases of several different markers. For example, a genomic region with three heterozygous markers can yield 8 possible haplotypes. This ambiguity can, in some cases, be solved if pedigree genotypes are available. However, even for a haplotype of only 3 markers, genotypes of father-mother-offspring trios can fail to yield offspring haplotypes up to 24% of the time. Computational algorithms such as expectation-maximization (EM), subtraction and PHASE are used for statistical estimation of haplotypes [4,8,9]. However, these computational methods have serious limitations in accuracy, number of markers and genomic DNA length. For example, for a haplotype of only 3 markers from doubly heterozygous individuals, the error rates of the EM and PHASE methods for haplotype reconstruction can be as high as 27% and 19%, respectively [3]. Alternatively, direct molecular haplotyping can be used based on the physical separation of two homologous genomic DNAs prior to genotyping. DNA cloning, somatic cell hybrid construction, allele specific PCR and single molecule PCR [10-12] have been used, and these approaches are largely independent of pedigree information. These methods are limited to short genomic regions (allele-specific PCR and single molecule PCR) and are prone to errors.

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[009] Therefore, a simple and more reliable method, which is also suitable for large scale and automated haplotype determination of several polymorphic alleles separated by several kilobase distances is needed to facilitate the analysis of haplotype structure in pharmacogenomic, disease pathogenesis, and molecular epidemiological studies.

SUMMARY OF THE INVENTION

[010] The present invention provides an efficient way for high throughput haplotype analysis. Several polymorphic nucleic acid markers, such as SNPs, can be simultaneously and reliably determined through multiplex PCR of single nucleic acid molecules in several parallel single molecule dilutions and the consequent statistical analysis of the results from these parallel single molecule multiplex PCR reactions results in reliable determination of haplotypes present in the subject. The nucleic acid markers can be of any distance to each other on the chromosome. In addition, an approach wherein overlapping DNA markers are analyzed can be used to link smaller haplotypes into larger haplotypes. Consequently, the invention provides a powerful new tool for diagnostic haplotyping and identifying novel haplotypes.

[011] The method of the present invention enables direct molecular haplotyping of several polymorphic markers separated by several kilobases even spanning an entire chromosome. Distances of about 1, 2, 3, 4, 5-10, 15-20, kilobases (kb) or as far as about at least 25, 30, 35, 40, 45, or 50 kb or more are preferred.

[012] Polymorphic nucleic acids useful according to the present invention include any polymorphic nucleic acids in any given nucleic acid region including, but not limited to, single nucleotide substitutions (single nucleotide polymorphisms or SNPs), multiple nucleotide substitutions, deletions, insertions, inversions, short tandem repeats including, for example, di-, tri-, and tetra-nucleotide repeats, and methylation and other polymorphic nucleic acid modification differences. Preferably the polymorphic nucleotides are SNPs.

[013] A nucleic acid sample, preferably genomic nucleic acid sample from a subject organism is first diluted to a single copy dilution. The phrase "single copy dilution" refers to a dilution wherein substantially only one molecule of nucleic acid is present or wherein one or more copies of the same allele are present. When the molecular mass of the nucleic acid is known, a dilution resulting in one single molecule dilution can be readily calculated by a skilled artisan. For example, for human genomic DNA, about 3 pg of DNA represents about one molecule. Due to stochastic fluctuation in very dilute DNA solutions, the diluted sample may have no template nucleic acid molecules or it may have two or more molecules. If no

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molecules are present in the sample, PCR amplification will not be achieved and the result will be "no genotype". If two or more molecules are present in the sample, the resulting amplification products may either be a mixture of two different alleles or represent one allele and consequently either a mixed genotype or a single allele genotype, respectively, is obtained.

[014] To obtain statistical weight to accurately determine the haplotype comprising at least two markers, more than one replica of dilutions will be needed. For example, a replicate of four independent multiplex genotyping assays using about 3-4.5 pg of human genomic DNA, including the steps of diluting the nucleic acid sample, amplifying the diluted sample, and genotyping the amplified sample, enables about 90% of direct haplotyping efficiency. Therefore, preferably at least about 4-25, more preferably at least about 6-20, 8-20, 10-18, 12-18 and most preferably about 10-12 replicates of same sample are included in the analysis according to the present invention, one replica including the steps of diluting the isolated nucleic acid sample from a subject organism, multiplex amplification of the diluted sample and genotyping the polymorphic nucleic acid sites from the amplified sample.

[015] After the step of diluting the nucleic acid sample into a substantially single nucleic acid dilution, the regions containing the polymorphic sites of interest in the nucleic acid are amplified, using, for example polymerase chain reaction (PCR) and at least two, preferably more than two primer pairs flanking at least two different polymorphic nucleic acid sites in the target molecule. The primers are selected so that they amplify a fragment of at least about 50 base pairs (bp), more preferably at least about 100, 200, 300, 400, 500, 600-1000 bp and up to about 10000 bp, wherein the fragment contains at least one polymorphic nucleotide site. Most preferably, the primer pairs are designed so that the amplification products are about 90-350 bp long, still more preferablyabout 100-250 bp long . It is preferable to maximize the efficiency of amplification from the single molecule template and therefore, at least with the current technology, the shorter fragments are preferred. However, it will be self evident to a skilled artisan that the nucleic acid amplification techniques are constantly developing and the efficiency of amplifying longer nucleic acid fragments using very small quantities of template can be perfected and consequently, primers amplifying long fragments, even longer that those indicated above, may also be used according to the present invention.

[016] After the amplification of the single molecule template with at least two different primer pairs, preferably at least 3, 4, 5, 6, 7, 8, 9, 10, primer pairs are used in a multiplex amplification reaction, the amplification product is subjected to genotyping. Use of up to at

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least about 15, 20, 30, 40, 50 or more primer pairs in one multiplex reaction is preferred on one embodiment of the invention.

[017] Genotyping can be performed by any means known to one skilled in the art including, for example, restriction fragment length polymorphism (RFLP) analysis using restriction enzymes, single-strand conformational polymorphism (SSCP) analysis, heteroduplex analysis, chemical cleavage analysis, oligonucleotide ligation and hybridization assays, allele-specific amplification, solid-phase minisequencing, or MASSARRAY™ system.

[018] The haplotype is subsequently determined by analyzing replicas of at least four dilution/amplification/genotyping reactions so as to allow statistically accurate determination of the correct haplotype in the subject. The steps including dilution, amplification and genotyping from the same subject organism sample are repeated several times to obtain a data set which can be statistically analyzed to reveal the correct haplotype in the subject organism's sample. The approach does not rely on pedigree data and does not require prior amplification of the genomic region containing the selected markers thereby simplifying the analysis and allowing speedy and automated haplotyping.

[019] In one embodiment, the invention is drawn to methods for determining a novel haplotype of nucleic acid segments, particularly of genes or other contiguous nucleic acid segments comprising at least two, preferably at least 3, 4, 5, 6, 7, 8, 9, 10-15, 20, 30, 40, 50-100 or even more distantly spaced nucleic acid polymorphisms.

[020] The methods of the present invention are useful in medicine in determining the differences in disease risk or susceptibility and determining treatment response between individual patients. The methods, however, are not limited to applications in medicine and can be used to determine the haplotype structure of a particular gene, or other contiguous DNA segment, within an organism having at least two distally spaced nucleotide polymorphisms. Thus, the methods of the invention find further use in the field of agriculture, particularly in the breeding of improved livestock and crop plants.

[021] In one embodiment, the invention provides a method of determining a haplotype in a sample obtained from an organism and comparing it to known haplotypes to diagnose a disease or disease susceptibility of an organism comprising the steps of identifying at least two polymorphic markers within a genomic region; isolating a nucleic acid sample from the subject organism and preferably purifying the isolated nucleic acid; diluting the nucleic acid sample into substantially single molecule dilution; amplifying the diluted nucleic acid sample with at least two primer pairs each capable of amplifying a different region flanking each of

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the polymorphic sites in a multiplex PCR reaction; genotyping the polymorphic sites from the amplified sample; producing at least three additional genotype replicas from the nucleic acid sample of the subject organism as described above to allow statistically accurate determination of the haplotype in the subject organism sample. In a preferred method the genotyping is performed using primer extension, terminator nucleotides and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry MALDI-TOF MS analysis. The haplotype is thereafter compared to an existing haplotype collection such as a haplotype database comprising disease- or disease susceptibility-associated haplotypes, or haplotypes associated with treatment responsiveness or unresponsiveness of the specific polymorphic markers. An non-limiting example of an existing haplotype database is a Y-STR Haplotype Reference Database which can be found at http://ystr.charite.de/index_gr.html.

[022] For example, the R117H mutation in the cystic fibrosis transmembrane receptor (CFTR) gene shows mild effect without the 5T mutation, and severe effect when the 5T mutation is present on the same chromosome. Thus, a haplotype of R117H-5T is important for clinical application to determine the severity of the prognosis of this type of cystic fibrosis. The method of the present invention allows direct determination of the haplotypes with no requirement for patient pedigree genotype information, i.e. information of the genotypes from the patient's family members. The same approach can be applied in other genetic diseases where, for example, a second mutation on the same chromosome can change the disease manifestation from the first mutation.

[023] The invention further provides a method wherein two haplotypes comprising several different polymorphic markers can be combined to form a larger haplotype covering a larger genomic region. This can be achieved by using one or more primer pairs to amplify one common polymorphic marker in two parallel multiplex amplification reactions after first diluting the sample as described above. The genotyping is performed as described above and the overlapping marker(s) provide a means to combine the two smaller haplotypes into one larger large haplotype comprising all the markers analyzed in both of the two different multiplex amplification reactions.

[024] In one embodiment, the present invention provides a method for constructing a database of haplotypes associated with one or more disease or biological trait using the methods described above. Such haplotype databases are useful for diagnostic and prognostic applications. A haplotype obtained from a subject organism suspected can be compared against the haplotype database and allows diagnosis and/or prognosis of a condition of interest. A condition may be a disease condition or a biochemical or other biological trait

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which is associated, for example, in responsiveness to a particular treatment or pharmaceutical and is determinative of choosing a treatment regime that, for example, a human patient would be responsive to.

[025] In one embodiment, the polymorphism is a nucleic acid modification, such as a methylation difference. For example, in one embodiment, the present invention provides a method of determining haplotypes comprised of markers including methylation differences. The DNA sample can be treated with any composition, for example, inorganic or organic compounds, enzymes, etc., that differentially affects the modified, for example, methylated, nucleotide to effectively create polymorphisms based on methylation states. For example, DNA sample is treated with bisulfite (Frommer, M., L. E. McDonald, D. S. Millar, C. M. Collis, F. Watt, G. W. Grigg, P. L. Molloy, and C. L. Paul. 1992. A genomic sequencing protocol that yields a positive display of 5-methylcytosine residues in individual DNA strands. Proc. Natl. Acad . Sci U.S.A. 89:1827-1831) so that unmethylated cytosine residues are converted into uracil while methylated cytosines remain the same, thus effectively creating polymorphisms based on methylation states. Haplotypes consisting polymorphisms in the DNA region next to the methylation region and the methylation region itself can be determined in a similar fashion as described above. Bisulfite treated DNA is diluted to approximately single copy, amplified by multiplex PCR (each PCR specific for each polymorphism), and genotyped by the MassARRAY system.

[026] The methylation detection procedure as described above is repeated at least 3, 4, 5, 6, 7, 8, 9, 10-15, 15-20, 30, 40, 50 or more times, preferably about 12-18 times so as to allow statistical analysis of the correct methylation haplotype in the subject organism.

[027] In the preferred embodiment, the methods of the present invention use mass spectrometry, for example, MASSARRAY™ system, to genotype the samples.

[028] Therefore in one embodiment, the present invention provides a method for determining a haplotype of a subject comprising the steps of diluting a nucleic acid sample from the subject into a single molecule dilution; amplifying the diluted single nucleotide dilution with at least two different primer pairs designed to amplify a region comprising at least two polymorphic sites in the nucleic acid template; genotyping the polymorphic sites in the single nucleic acid molecule; and determining the haplotype from the genotypes of at least the two polymorphic sites to obtain a haplotype for the subject.

[029] In one embodiment, the steps of diluting, amplifying and genotyping the nucleic acid sample from the subject are repeated at least three times from the same nucleic acid sample to obtain at least four genotype replicas from the same subject and thereafter

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comparing the at least four genotype replicas to determine the haplotype. Preferably, at least 4, 5, 6, 7, 8-10, 10-15, 15-20, 30, 50, 50-100 or more genotype replicas are obtained. In one embodiment about 12-18 replicas are obtained and the results are analyzed statistically, using for example a method of Poisson distribution.

[030] In one embodiment, the method further comprises comparing the haplotype with a haplotype from a control or a database of haplotypes from controls to determine association of the haplotype with a biological trait, which can be any biological trait including but not limited to various diseases.

[031] The polymorphisms useful according to the present invention include, but are not limited to single nucleotide polymorphisms (SNPs), deletions, insertions, substitutions or inversions. The polymorphisms may also be a combination of one or more markers selected from the group consisting of a single nucleotide polymorphism, deletion, an insertion, a substitution or an inversion or other types of nucleic acid polymorphisms.

[032] In one embodiment, the genotyping step of the method described above is performed using primer extension, preferably MASSARRAY™ technology, and mass spectrometric detection, preferably MALDI-TOF mass spectrometry.

[033] In another embodiment, the invention provides a method of diagnosing a disease condition or disease susceptibility by determining a disease related haplotype in a subject comprising the steps of diluting a nucleic acid sample from the subject into a single molecule dilution; amplifying the diluted single nucleotide dilution with at least two primer pairs designed to amplify a region comprising at least two polymorphic sites in the nucleic acid template; genotyping the polymorphic sites in the single nucleic acid molecule; determining the haplotype from the genotype of at least two polymorphic sites to obtain a haplotype for the subject; and comparing the haplotype of the subject to known disease-associated haplotypes wherein a match in the sample haplotype with a disease-associated haplotype indicates that the subject has the disease or that the subject is susceptible for the disease.

[034] In one embodiment, the method further comprises repeating the dilution, amplification and genotyping steps at least three times from the same nucleic acid sample to obtain at least four genotype replicas from the same subject and thereafter comparing the at least four genotype replicas to determine the haplotype. Preferably at least 4, 5, 6, 7, 8, 9, 10-15, 15-20, 25, 30, 40, 50-100 or more genotype replicas are produced. In one embodiment, about 12-18 replicas are produced.

[035] The invention also provides a method of determining a haplotype of a subject comprising the steps of treating a nucleic acid sample from the subject with a composition

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that differentially affects an epigenetically modified nucleotide in the nucleic acid sample to effectively create polymorphisms based on the epigenetic modification; diluting the treated nucleic acid sample into a single copy dilution; amplifying the diluted nucleic acid sample using at least two different primer pairs; genotyping the amplified sample; and determining the haplotype of the subject from the genotyped sample. The terms "epigenetic" modification or "epigenetically" modified nucleotides as described herein means nucleic acids that are modified by methylation, acetylation, or other epigenetic manner, i.e. by addition or deletion of a chemical or molecular structure on the nucleic acid which addition or deletion has an effect on the phenotype of the subject by altering the function of the modified nucleic acid.

[036] In one embodiment, the method further comprises repeating the steps of dilution, amplification and genotyping at least three times to obtain at least four genotype replicas from the same subject and thereafter determining a haplotype of the subject based on the genotype replicas. In a preferred embodiment, at least 4, 5, 6, 7, 8, 9, 10-15, 15-20, 25, 30, 40, 50-100, or more replicas are produced. In one preferred embodiment, about 12-18 replicas are produced. The method of claim 13, wherein 12-18 replicas are produced.

[037] In one embodiment, the epigenetic modification is methylation.

[038] In yet another embodiment, the epigenetic modification is methylation and the composition that is used to treat the nucleic acid is bisulfite.

[039] In another embodiment, the invention provides a method of determining a haplotype in a subject comprising the steps of: digesting a nucleic acid sample from the subject with a methylation-sensitive restriction enzyme so that either unmethylated DNA or methylated DNA is left intact, depending on which enzyme is used; diluting the digested nucleic acid sample to a single molecule concentration; amplifying the diluted nucleic acid sample with at least two different primer pairs; genotyping the amplified sample; and determining a haplotype of a methylated nucleic acid wherein at least two polymorphic markers next to the methylation site, together with the methylation site, constitutes a haplotype.

[040] In one embodiment, the methylation sensitive enzyme is HpaII.

[041] In one embodiment, the method further comprises repeating the steps of diluting, amplifying and genotyping at least three times to obtain at least four genotype replicas from the same subject and thereafter determining a haplotype of the subject based on the genotype replicas. Preferably at least 4, 5, 6, 7, 8, 9, 10-15, 4, 5, 6, 7, 8, 9, 10-15, 15-20, 25, 30, 40, 50-100, or more replicas are produced. In one preferred embodiment, about 12-18 replicas are produced. The method of claim 13, wherein 12-18 replicas are produced.

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BRIEF DESCRIPTION OF FIGURES

[042] Figures 1A-1B show a flow chart of multiplex genotyping of single DNA molecules for haplotype analysis using single nucleotide polymorphisms (SNPs) as markers. Traditional genotyping methods using a few nano-grams (ng) genomic DNA (about 1600 copies of genomic templates) yield only the genotypes of each individual SNP marker, but the phases of these SNPs are not determined (shown in top right in the mass spectra in Fig. 1A). Simultaneous genotyping of several markers using multiplex assays with single DNA molecules (Fig. 1B) allows haplotyping analysis since the two alleles can be physically separated with very dilute DNA concentrations, shown in bottom right in the mass spectra in Fig. 1B. In contrast to other molecular haplotyping methods, the entire haplotype block does not have to be amplified in this approach. Instead, only about 100 bp around each individual SNP is amplified for genotyping, resulting in very high efficiency of PCR amplification from single DNA molecules. The SNP markers can be as far apart as desired, as long as there is no significant break between them.

[043] Figure 2 shows effects of genomic DNA concentration on haplotyping efficiency. About 3 pg, 5 pg and 9 pg (or 1, 1.6 and 3 copies of human genomic templates, respectively) were used for haplotyping of three SNP markers in the CETP region. The DNA copy number in a specific reaction was estimated by the Poisson distribution. The haplotyping result can either be a failed assay, successful haplotyping, both alleles present (no phase determination for the markers), or an incomplete multiplex. Except for incomplete multiplexes, values are percentages from 54 to 144 individual multiplex assays (see specification and example for details on the calculation), followed by predicted values using the Poisson distribution.

[044] Figure 3 shows overlapping multiplex genotyping assays with single DNA molecules. Seven SNP markers (A: rs289744, B: rs2228667, C: rs5882, D: rs5880, E: rs5881, F: rs291044, G: 2033254) from an 8kb genomic region of the CETP locus were chosen (details of these SNPs, their chromosome position and oligonucleotides used for genotyping are provided in Table 2). Two 5-plex genotyping assays were designed for these 7 markers and the overlapping heterozygous SNPs were used to obtain the entire haplotype of 7 SNP markers. Assays on individual 6 were used to demonstrate how this is carried out. Multiplex assay 1 determined the haplotype of 5 SNPs as AGAGT and CGGGC. Multiplex assay 2 determined the other haplotype of 5 SNPs as GGGCT and AGGTT. Then, the genotypes of the overlapping SNPs (SNP C, E, F) were used to combine the two 5-SNP haplotypes into a haplotype of 7 SNPs covering the entire region under investigation.

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DETAILED DESCRIPTION OF THE INVENTION

[045] The present invention provides a direct molecule haplotyping approach which is based upon a surprising discovery that a single molecule dilution of genomic DNA can be used for separation of two homologous genomic DNAs and that using repeated dilutions from the same subject organisms as a starting material for multiplex amplification of different nucleic acid markers, haplotypes of any subject organisms can be determined and are statistically accurate. The diluted, amplified sample is then genotyped using, for example, the MASSARRAY™ system (Fig. 1). Parallel genotyping of several different dilutions from the same subject results in statistically accurate haplotype determination in the subject organism.

[046] The approach of the present invention differs significantly from previous single molecule PCR method in that the method of the present invention does not require the amplification of the complete genomic region containing the markers of interest; thus it is not limited to only a few kb DNA. The method of the present invention achieves close to 100% genotype and haplotype success rates for single DNA molecules. Additionally, the multiplex genotyping assay approach enables direct haplotype determination without pedigree genotype information. High throughput haplotyping can easily be achieved by incorporating the method of the present invention with any commercially available genotyping systems, such as the MASSARRAY™ system.

[047] In one embodiment, the invention provides a method of determining a haplotype of a subject comprising the steps of obtaining a nucleic acid, preferably a genomic DNA sample, diluting the nucleic acid sample into substantially a single molecule dilution, amplifying the nucleic acid sample with at least two primer pairs designed to amplify a genomic region containing a nucleic acid polymorphism on one chromosome and genotyping the amplified DNA. Repeating the steps from diluting the nucleic acid sample, at least 3 or more times and statistically analyzing the results, thereby determining the haplotype of the subject organisms.

[048] The "subject" as used in the specification refers to any organism with at least diploid genome including, but not limited to worms, fish, insects, plants, murine and other mammals including domestic animals such as cows, horse, dogs, cats, and, most preferably humans.

[049] The methods of the present invention are useful, for example, in diagnosing or determining a prognosis in a disease condition known to be associated with a specific

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haplotype(s), to map a disease or other biological trait the cause of which is currently unknown to a defined chromosomal region using haplotypes in the linkage analysis, to determine novel haplotypes, to detect haplotype associations with responsiveness to pharmaceuticals.

[050] Genomic DNA can be obtained or isolated from a subject using any method of DNA isolation known to one skilled in the art. Examples of DNA isolation methods can be found in general laboratory manuals, such as Sambrook and Russel, MOLECULAR CLONING: A LABORATORY MANUAL, 3rd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001), the entirety of which is herein incorporated by reference

[051] Polymorphic Markers and Oligonucleotides. The number of polymorphic nucleic acid useful according to the present invention is ever increasing. Currently, such markers are readily available from a variety of publicly accessible databases and new ones are constantly being added to the pool of available markers. Markers including restriction length polymorphisms, short tandem repeats such as di-, tri-, and tetra-nucleotide repeats as well as methylation status can be used as polymorphic markers according to the present invention. Such markers are well known to one skilled in the art and can be found in various publications and databases including, for example, ATCC short tandem repeat (STR) database at http://www.atcc.org/Cultures/str.cfm.

[052] Particularly useful markers according to the present invention are single nucleotide polymorphisms (SNPs). Examples of useful SNP databases include, but are not limited to Human SNP Database at http://www-genome.wi.mit.edu/snp/human, NCBI dbSNP Home Page at http://www.ncbi.nlm.nih.gov/SNP, http://lifesciences.perkinelmer.com/SNPDatabase/welcome.asp, Celera Human SNP database at http://www.celera.com/genomics/academic/home.cfm?ppage=cds&cpage=snps, the SNP Database of the Genome Analysis Group (GAN) at http://www-gan.iarc.fr/SNPdatabase.html,

[053] A number of nucleic acid primers are already available to amplify DNA fragments containing the polymorphisms and their sequences can be obtained, for example, from the above-identified databases. Additional primers can also be designed, for example, using a method similar to that published by Vieux, E.F., Kwok, P-Y and Miller, R. D. in BioTechniques (June 2002) Vol. 32. Supplement: "SNPs: Discovery of Marker Disease, pp. 28-32. Novel SNPs can also be identified using a method of MASSARRAY™ Discovery-RT (SNP-Discovery) system by SEQUENOM Inc. (San Diego, CA).

[054] A number of different nucleotide polymorphism genotyping methods useful according to the present invention are known to one skilled in the art. Methods such as

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restriction length polymorphism analysis (RFLP), single-strand conformation polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), temperature gradient gel electrophoresis (TGGE), chemical cleavage analysis, direct sequencing of nucleic acids using labels including but not limited to fluorescent and radioactive labels. All these methods have been available or at least a decade and are well known to one skilled in the art.

[055] SNP genotyping can be performed using a number of different techniques known to one skilled in the art. For example, SNP genotyping by MALDI-TOF mass spectrometry can performed using, for example, the Sequenom's mass spectrometry system, MASSARRAY™. In this method, after multiplexed PCR has been performed using more than one primer pair, each flanking different SNPs, a minisequencing primer extension reaction is performed in a single well using chain terminator nucleotides. The size of reaction products is determined directly by MALDI-TOF mass spectrometry, yielding the genotype information. It should be possible based upon this teaching. Multiplexing permits determination of, for example, at least 2, 3, 4, and 5 SNPs in a single well of a, for example 384 well plate. For example, at least 6, 7, 8, 9, 10-12-plex genotyping can be performed using the MASSARRAY™ system. The MASSARRAY™ system, for example, can be used to increase the multiplexity level of the genotyping reactions to even higher, for example at least 12-15, 20, 30, 40, and 50-100 and even higher.

[056] Alternatively, fragment analysis for SNP detection can be performed on batches of several samples on a capillary electrophoresis system, for example an ABI PRISM® 3100 GENETIC ANALYZER (Applied Biosystems, Foster City, CA). For capillary electrophoretic analysis, the primers can be labeled using dyes, including, but not limited to FAM, HEX, NED, LIZ, ROX, TAMRA, PET and VIC.

[057] Single SNP allelic discrimination can further be carried out using the ABI PRISM® 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA), which allows analysis of single nucleotide polymorphisms (SNPs) using the fluorogenic 5' nuclease assay.

[058] Yet another available method useful according to the present invention is an Arrayed Primer Extension (APEX) which is a resequencing method for rapid identification of polymorphisms that combines the efficiency of an microarray-based assay (alternative to gel-based methods, see, e.g., U.S. Patent No. 6,153,379 and Shumaker et al. Hum. Mutat. 7(4):346-354, 1996) with the Sanger nucleic acid sequencing method (Sanger et al., Proc. Natl. Acad. Sci. 74:5463-5467 (1977)). Generally, microarrays are microchips, for example

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glass slides, containing thousands of DNA segments in an ordered array, witch allows the simultaneous analysis of thousands of genetic markers.

[059] A yet another genotyping method useful according to the present invention is a solid-phase mini-sequencing technique, which is also based upon a primer extension reaction and can be used for genotyping of SNPs and can also be easily automated (U.S. Patent No. 6,013,431, Suomalainen et al. Mol. Biotechnol. Jun;15(2):123-31, 2000).

[060] In general, a primer extension reaction is a modified cycle sequencing reaction in which at least one dideoxynucleotide (terminator) is present and not all deoxynucleotides are present at any significant concentration. When a terminator is incorporated onto a DNA strand, no further extension can occur on that strand. In a standard cycle sequencing reaction, terminators are present only in small concentrations along with high concentrations of typical nucleotides. In the single base extension reactions for SNP assays, two or more fluorescently or radioactively labeled terminator nucleotides (corresponding to the two or more alleles present at the SNP to be typed) are used.

[061] The steps of the method of the present invention include diluting the nucleic acid sample into single nucleotide dilution, amplifying the diluted sample, and genotyping the amplified sample. These steps are repeated at least 3 times, preferably at least 4, 5, 6, 7, 8, 9, 10-15, 15-20, 20-25, or even 25-50 times. Preferably, the steps are repeated about 12-18 times so that the results can be statistically analyzed. The Poisson distribution analysis is used to analyze the results using the methods known to one skilled in the art. The analysis is described in detail, for example in Stephens et al. Am J Hum Genet 46: 1149-1155, 1990.

[062] Haplotype is defined as a combination of alleles or nucleic acid polymorphisms, such as SNPs of closely linked loci that are found in a single chromosome and which tend to be inherited together. Recombinations occur at different frequency in different parts of the genome and therefore, the length of the haplotypes vary throughout the chromosomal regions and chromosomes. For a specific gene segment, there are often many theoretically possible combinations of SNPs, and therefore there are many theoretically possible haplotypes.

[063] Traditionally, information about gene flow in a pedigree has been used to reconstruct likely haplotypes for families and individuals. However, even if nucleic acid samples from all the family members were available, which is rarely the case, statistics-based haplotype analysis does frequently not reveal the correct phase, i.e. haplotype, of the markers. Additionally, collection of large sample materials from, for example human families, is time consuming and expensive. In one embodiment, the present invention provides a method wherein novel haplotypes are determined using either established or novel nucleic acid

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polymorphisms. For example, novel SNPs are first identified using nucleic acid samples isolated from several subject organisms of the same species, each polymorphic SNP marker from a subject is then genotyped individually, for example using about 1-10 ng, preferably about 5 ng genomic DNA. The genomic DNA sample is then diluted into about 1 copy of genomic template per dilution. The haplotype is determined by determining the SNP's in a diluted sample, i.e., sample diluted into a substantially single molecule dilution. Alternatively, the sample can be genotyped first or in parallel for each maker using more concentrated nucleic acid solution. This can be used to verify or control the haplotype determination using the diluted sample replicas.

[064] The genomic region to be haplotyped using the method of the present invention is preferably at least about 1, 2, 3, 4, 5, 6, 7, 8, or 9 kb, more preferably at least about 10 kb or more, at least about 15 kb or more, at least about 20 kb or more. In one embodiment, the size of the region containing the polymorphic nucleotides is at least about 25 kb or more, at least about 35 kb or more, at least about 40-45 kb, or 45-50 or even about 50-100kb or more. Most preferably the genomic region is about 25 kb ore more.

[065] In determining the haplotypes, both the PCR and the genotyping reactions are preferably "multiplexed" which term is meant to include combining at least two, preferably more than at least 3, 4, 5, 6, 7, 8, 9, 10-15, or 20-25 extension primers in the same reaction are used to identify, preferably at least about 3, 4, 5, 6, 7, 8, 9, 10-15, or 20-25 polymorphic nucleic acid regions in the same genotyping reaction. In one embodiment, at least 30 primer pairs or more are used.

[066] In one embodiment, the polymorphism is at least one nucleic acid modification, such as a methylation difference. In one embodiment, the present invention provides a method of determining haplotypes comprised of markers including methylation differences. The method of haplotyping methylation differences according to the present invention comprises the steps of diluting a nucleic acid sample from a subject organism into two parallel substantially single molecule dilutions. The two dilutions are consequently subjected to a methylation detection assay, for example, an AFLP assay (see, e.g., Vos et al. Nucleic Acids Res 23: 4407-4414, 1995; Xu et al., Plant Molecular Biology Reporter 18: 361-368, 2000). The assay described by Vos et al. and Xu et al is modified to perform according the method of present invention.

[067] In short, two single molecule dilutions are digested in two parallel reactions with a mixture comprising a methylation sensitive enzyme and another enzyme, preferably a less frequent cutting restriction enzyme, wherein the less frequent cutting restriction enzyme in

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both digestion reactions is the same and the methylation sensitive enzymes added to the two parallel reactions differ in their capacity to digest methylated/non-methylated nucleic acids. For example, one dilution is digested with a combination of EcoRI and HpaII and the parallel dilution is treated digested with EcoRI and MspI. The two digested samples are then ligated using an adapter-ligation solution as described in Vos et al. and Xu et al., and amplified in parallel reactions using at least two, preferably more than two primer pairs which are capable of recognizing the restriction enzyme recognition sites in the templates. In the above-described example, EcoRI and HpaII – MspI primers are used. One of the primers is labeled so as to allow detection of the fragments from the digestions using, for example gel electrophoretic methods or mass spectrometric detection.

[068] The methylation detection procedure as described above is repeated at least 3 more times, preferably at least about 6-12 times so as to allow statistical analysis of the correct methylation haplotype in the subject organism.

[069] In light of this disclosure, other nucleic acid modification detection technologies including methylation detection techniques may be readily adapted to be used according to the principle steps of the present invention including single molecule dilution, digestion, multiplex amplification and multiplex genotyping. Methylation detection methods may also be combined to detect both methylation and other polymorphic markers, such as SNPs. In such embodiment, the amplification after restriction enzyme digestion is performed not only with methylation specific primers but also with primers designed to amplify fragments containing known nucleic acid polymorphisms, such as SNPs.

[070] In one embodiment, the invention provides a method of creating haplotypes of several polymorphic nucleotides using overlapping multiplex genotyping assays with single DNA molecules. For example, markers from a large genomic region are chosen and one or more separate multiplex amplification reactions are performed from single nucleotide dilutions and overlapping heterozygous polynucleotide markers are used to obtain the entire haplotype.

[071] For example, Figure 3 shows seven SNP markers (A: rs289744, B: rs2228667, C: rs5882, D: rs5880, E: rs5881, F: rs291044, G: 2033254) from an 8kb genomic region of the CETP locus that were chosen to determine a haplotype. Details of these SNPs, their chromosome position and oligonucleotides used for genotyping are provided in Table 2. Two 5-plex genotyping assays were designed for the 7 markers and the overlapping heterozygous SNPs were used to obtain the entire haplotype of 7 SNP markers. Assays on individual No. 6 were used to demonstrate how this is carried out. Multiplex assay 1 determined the haplotype

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of 5 SNPs as AGAGT and CGGGC. Multiplex assay 2 determined the other haplotype of 5 SNPs as GGGCT and AGGTT. Then, the genotypes of the overlapping SNPs (SNP C, E, F) were used to combine the two 5-SNP haplotypes into a haplotype of 7 SNPs covering the entire region under investigation.

EXAMPLE

[072] The effects of genomic DNA concentration on haplotyping efficiency were determined as follows. We used 3 picograms (pg), 5 pg and 9 pg (equivalent of 1, 1.6 and 3 genomic template copies) of genomic DNA for PCR amplification and genotyping of 3 SNPs in the CETP region from 12 individuals. Each 3-plex assay was repeated 12-18 times to evaluate the PCR and haplotyping efficiency. A typical assay result is summarized in Table 1. The copy number of the genomic DNA region of interest for very dilute DNA solutions is estimated by the Poisson distribution [13]. Haplotyping results were categorized into 4 groups (Table 1).

[073] Failed assays can result from either failed PCR amplification from single copy DNAs or simply no template present due to stochastic fluctuation of very dilute DNA solutions.

[074] Partially failed genotyping calls (or incomplete multiplexes) are those that have only 1 or 2 SNPs successfully genotyped. This is most likely due to unsuccessful PCR for 1 or 2 of the SNP DNA regions, since in most cases the 3 SNP markers are present or absent at the same time due to the close proximity of the SNP markers (< 628 bp). Poisson distribution may also result in the presence both alleles in the solution and hence the inability to resolve the phase of the SNPs.

[075] Successful haplotyping analysis is achieved when a single copy of the allele or multiple copies of the same allele are present and the genotyping is successful.

[076] Incomplete multiplex genotyping can be used to estimate the efficiency of genotyping from single copy DNA molecules. A partial genotyping call suggests the presence of the SNP DNA but a failure to genotype some of the SNPs. We typically observed 5-10% incomplete multiplex genotyping calls (Fig. 2), suggesting a PCR efficiency of about 90-95% with single DNA molecules. This approach may overestimate the PCR efficiency, since we did not take the completely failed assays into account. We also carried out detailed comparison between observed and theoretical values of failed assays, successful haplotyping and the presence of both alleles (Fig. 2 and see methods section for details of calculation). Theoretical values are based on the Poisson distribution of very dilute DNA

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solutions and the assumption of 100% PCR amplification efficiency. The close agreement between theoretical estimate and experimental observation substantiates the earlier estimate of extremely high PCR efficiency with single DNA molecules.

[077] High PCR efficiency is mainly due to the high efficiency of amplification of very short amplicons (typically 100 bp) and the high sensitivity of MALDI-TOF mass spectrometric detection of DNA oligonucleotides. High PCR efficiency is preferred for high-throughput haplotyping analysis. For example, with our current PCR efficiency, we can achieve 40-45% haplotyping efficiency with one single reaction using 3-4.5 pg genomic DNA. A replicate of 4 independent multiplex genotyping assays will enable about 90% of direct haplotyping efficiency.

[078] We next demonstrated an approach for determining haplotypes where there are too many markers to be determined in one multiplex genotyping assay. Overlapping informative SNPs were used to combine haplotypes from several multiplex assays. We chose six SNP markers in an 8kb CETP genomic region, and 2 overlapping 4-plex genotyping assays were used for haplotyping analysis (Fig. 3). We were able to determine the haplotypes of all 12 individuals for this genomic region, with absolutely no optimization of the assay system.

[079] The approach presented here provides a powerful and unique technology platform for direct molecular haplotyping analysis of long-range genomic regions. This approach is completely independent of pedigree genotype information.

[080] We have further incorporated this technique with the commercially available MASSARRAY™ system for high-throughput applications. This technology is extremely useful in large-scale haplotyping and haplotype-based diagnostics.

Materials and Methods

[081] Genomic DNAs and oligo nucleotides. Human genomic DNA samples used for haplotyping of the CETP locus were provided by SEQUENOM Inc. (San Diego, CA). These DNAs were isolated using the Puregene DNA isolation kit (Gentra Systems) from blood samples purchased from the Blood Bank (San Bernadino County, CA). The personal background of the blood donors is not accessible for these samples. Human genomic DNAs samples for haplotyping of a 25kb segment on chromosome 5q31 were CETP family DNAs purchased from Coriell Cell Repositories (see Table 3). Information on SNPs and oligonucleotides for genotyping is provided in Table 2.

[082] Genotyping and haplotyping analysis. Genotyping analyses were carried out using the MassArray™ system (SEQUENOM Inc.). Each SNP from every individual was

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first genotyped individually using 5 ng genomic DNA. For haplotyping analysis, multiplex genotyping assays were carried out using 3 pg (or approximately 1 copy of genomic template, unless otherwise specified) genomic DNA.

[083] Analysis of effects of genomic DNA concentration on haplotyping. To calculate the percentage of failed assays, we simply counted all failed assays (no calls for either SNP), divided by the total number of assays. We typically do 12 to 18 replicates for each 6 or 12 individuals. The percentage of incomplete assays is calculated in the same way. To calculate percentage of successful haplotyping and both alleles, we excluded the data from those individuals with homozygous haplotypes. Theoretical predictions are based on the Poisson distribution of very diluted DNA solutions, according to a published method [13].

Table 1 · Sample Haplotype analysis with triplex genotyping assay[a]

Repeat	Genotype Calls
1	GGC[b]
2	GGC
3	-[c]
4	-GC[d]
5	-
6	GGC
7	-
8	ACA
9	-GC
10	A/G C/G A/C[e]
11	ACA
12	ACA

[a]Genotypes of 3 SNP markers were determined with triplex assays from 3 pg genomic DNA.

[b]The 3 SNPs are G, G, C genotype respectively.

[c]Failed to genotype any of the 3 SNPs.

[d]Failed to genotype the first SNP, the rest two SNPs are G and C respectively.

[e]Failed to separate the two alleles, thus the genotypes are A/G, C/A and A/C for the 3 SNPs.

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Table 2. Single nucleotide polymorphism (SNP) markers, their chromosomal locations, primer pairs to amplify the markers and terminator mixes used in the reaction.

SNP ID	Chrom. Position	PCR primer 1	PCR primer 2	Extension Primer	Term. Mix
rs289741	4728 2625	TCTACCAGCTTGGCTC CCTC (SEQ ID NO.: 1)	AAGTCCATCAGCAGC AGCAG (SEQ ID NO.: 2)	GGGAGTCAGCCCAGCTC (SEQ ID NO.: 3)	ACT
rs289742	4728 2337	ACTGGTGAGACAATC CCTTC (SEQ ID NO.: 4)	CCACTGGCATTAAAGT GCTG (SEQ ID NO.: 5)	AGCCACAGAAGAAGGACTCC (SEQ ID NO.: 6)	ACT
rs289744	4728 1997	TACCAGAAACCAGAC CTCTG (SEQ ID NO.: 7)	AGTGCTGGACAGAAA GTGAG (SEQ ID NO.: 8)	TGAGGATGGTGGGAGGG (SEQ ID NO.: 9)	ACT
rs289744[a]	4728 1997	TCTACCAGAAACCAGA CCTC (SEQ ID NO.: 10)	AGTGCTGGACAGAAA GTGAG (SEQ ID NO.: 11)	ACCTCTGAGGGCCCCTTAC (SEQ ID NO.: 12)	CG
rs2228667[a]	4728 2820	CTCGAGTGATAATCTC AGGG (SEQ ID NO.: 13)	AGGTAGTGTTTACAG CCCTC (SEQ ID NO.: 14)	TGATGATGTCGAAGAGGCTCATG (SEQ ID NO.: 15)	CG
rs5882[a]	4728 4007	TTACGAGACATGACCT CAGG (SEQ ID NO.: 16)	GCATTTGATTGGCAG AGCAG (SEQ ID NO.: 17)	CTGCAGGAAGCTCTGGATG (SEQ ID NO.: 18)	CG
rs5882[b]	4728 4007	GCATTTGATTGGCAGA GCAG (SEQ ID NO.: 19)	TTACGAGACATGACCT CAGG (SEQ ID NO.: 20)	AGAGCAGCTCCGAGTCC (SEQ ID NO.: 21)	ACT
rs5880[b]	4728 5008	GCAGCACATACTGGA AATCC (SEQ ID NO.: 22)	TTTCTCTCCCCAGGAT ATCG (SEQ ID NO.: 23)	GCTTTTTCTTAGAATAGGAGG (SEQ ID NO.: 24)	ACT
rs5881[a]	4728 8087	AGATCTTGGGCATCTT GAGG (SEQ ID NO.: 25)	ACCCCTGTCTTCCACA GGTT (SEQ ID NO.: 26)	TGGGCCTGGCTGGGGAAGC (SEQ ID NO.: 27)	CG
rs5881[b]	4728 8087	ACCCCTGTCTTCCACA GGTT (SEQ ID NO.: 28)	AGATCTTGGGCATCTT GAGG (SEQ ID NO.: 29)	TGTCTTCCACAGGTTGTCGGC (SEQ ID NO.: 30)	ACT
rs291044[a]	4728	GTAAAACTGCAGCTGA	TGACTAGGTCAGGTC	GGAGTATTTAAAGGAGAGACACACTAG	CG

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	8647	GGAG (SEQ ID NO.: 31)	CCCTC (SEQ ID NO.: 32)	(SEQ ID NO.: 33)	
rs291044[b]	4728 8647	TGACTAGGTCAGGTC CCCTC (SEQ ID NO.: 34)	GTAAAACTGCAGCTG AGGAG (SEQ ID NO.: 35)	CCCTCGTGCCACAGCCT (SEQ ID NO.: 36)	ACT
rs2033254[b]	4729 0114	GGACATCAAAGGAAC AGGAC (SEQ ID NO.: 37)	ACTCACAATATTGGGC AGGC (SEQ ID NO.: 38)	CAAGGGGCTAAGGGAGAAG (SEQ ID NO.: 39)	ACT
IGR2198A _1[c]	5062 66[d]	GGGTTGCATGAGCAT TAAGT (SEQ ID NO.: 40)	CACATCAAGGATAAG ACTGC (SEQ ID NO.: 41)	ATCTCTTCAGTAGACGAAC (SEQ ID NO.: 42)	AC
IGR2175A _2	4950 82	TGGCCTTGATTCAAAC CCTG (SEQ ID NO.: 43)	AGATGAAGGAAATCC CAAGG (SEQ ID NO.: 44)	TGCCACTAACATACATAGTAAC (SEQ ID NO.: 45)	AC
IGR2150A _1	4821 71	CCTTGGCTTGATAGTC AAAC (SEQ ID NO.: 46)	ATTTGGAGGAGTGCA GAGAG (SEQ ID NO.: 47)	AGTCAAACTCTCACCAC (SEQ ID NO.: 48)	AC

[a]Multiplex Group a
[b]Multiplex Group b
[c]SNP ID from ref
[d]Position of SNP from ref

Term. Mix = terminator nucleotide mix. Chrom. Position = chromosomal position

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Table 3. DNA samples used in the Example.

Repository Number	Sample Type	Sample Description	Relation
GM12547	Lymphoblast	CEPH/FRENCH PEDIGREE 66	father
GM12548	Lymphoblast	CEPH/FRENCH PEDIGREE 66	mother
GM12549	Lymphoblast	CEPH/FRENCH PEDIGREE 66	son
GM12550	Lymphoblast	CEPH/FRENCH PEDIGREE 66	daughter
GM12551	Lymphoblast	CEPH/FRENCH PEDIGREE 66	daughter
GM12552	Lymphoblast	CEPH/FRENCH PEDIGREE 66	son
GM12553	Lymphoblast	CEPH/FRENCH PEDIGREE 66	daughter
GM12554	Lymphoblast	CEPH/FRENCH PEDIGREE 66	daughter
GM12555	Lymphoblast	CEPH/FRENCH PEDIGREE 66	son
GM12556	Lymphoblast	CEPH/FRENCH PEDIGREE 66	paternal grandfather
GM12557	Lymphoblast	CEPH/FRENCH PEDIGREE 66	paternal grandmother
GM12558	Lymphoblast	CEPH/FRENCH PEDIGREE 66	maternal grandfather
GM12559	Lymphoblast	CEPH/FRENCH PEDIGREE 66	maternal grandmother
GM07038	Lymphoblast	CEPH/UTAH PEDIGREE 1333	father
GM06987	Lymphoblast	CEPH/UTAH PEDIGREE 1333	mother
GM07004	Lymphoblast	CEPH/UTAH PEDIGREE 1333	son
GM07052	Lymphoblast	CEPH/UTAH PEDIGREE 1333	son
GM06982	Lymphoblast	CEPH/UTAH PEDIGREE 1333	son
GM07011	Lymphoblast	CEPH/UTAH PEDIGREE 1333	daughter
GM07009	Lymphoblast	CEPH/UTAH PEDIGREE 1333	son
GM07678	Lymphoblast	CEPH/UTAH PEDIGREE 1333	son
GM07026	Lymphoblast	CEPH/UTAH PEDIGREE 1333	son
GM07679	Lymphoblast	CEPH/UTAH PEDIGREE 1333	son
GM07049	Lymphoblast	CEPH/UTAH PEDIGREE 1333	paternal grandfather
GM07002	Lymphoblast	CEPH/UTAH PEDIGREE 1333	paternal grandmother
GM07017	Lymphoblast	CEPH/UTAH PEDIGREE 1333	maternal grandfather
GM07341	Lymphoblast	CEPH/UTAH PEDIGREE 1333	maternal grandmother
GM11820	Lymphoblast	CEPH/UTAH PEDIGREE 1333	daughter
GM07029	Lymphoblast	CEPH/UTAH PEDIGREE 1340	father
GM07019	Lymphoblast	CEPH/UTAH PEDIGREE 1340	mother
GM07062	Lymphoblast	CEPH/UTAH PEDIGREE 1340	daughter
GM07053	Lymphoblast	CEPH/UTAH PEDIGREE 1340	daughter
GM07008	Lymphoblast	CEPH/UTAH PEDIGREE 1340	son
GM07040	Lymphoblast	CEPH/UTAH PEDIGREE 1340	son
GM07342	Lymphoblast	CEPH/UTAH PEDIGREE 1340	son
GM07027	Lymphoblast	CEPH/UTAH PEDIGREE 1340	son
GM06994	Lymphoblast	CEPH/UTAH PEDIGREE 1340	paternal grandfather
GM07000	Lymphoblast	CEPH/UTAH PEDIGREE 1340	paternal grandmother
GM07022	Lymphoblast	CEPH/UTAH PEDIGREE 1340	maternal grandfather
GM07056	Lymphoblast	CEPH/UTAH PEDIGREE 1340	maternal grandmother
GM11821	Lymphoblast	CEPH/UTAH PEDIGREE 1340	son
GM07349	Lymphoblast	CEPH/UTAH PEDIGREE 1345	father

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GM07348	Lymphoblast CEPH/UTAH PEDIGREE 1345	mother
GM07350	Lymphoblast CEPH/UTAH PEDIGREE 1345	daughter
GM07351	Lymphoblast CEPH/UTAH PEDIGREE 1345	son
GM07352	Lymphoblast CEPH/UTAH PEDIGREE 1345	son
GM07353	Lymphoblast CEPH/UTAH PEDIGREE 1345	son
GM07354	Lymphoblast CEPH/UTAH PEDIGREE 1345	daughter
GM07355	Lymphoblast CEPH/UTAH PEDIGREE 1345	son
GM07356	Lymphoblast CEPH/UTAH PEDIGREE 1345	son
GM07347	Lymphoblast CEPH/UTAH PEDIGREE 1345	paternal grandfather
GM07346	Lymphoblast CEPH/UTAH PEDIGREE 1345	paternal grandmother
GM07357	Lymphoblast CEPH/UTAH PEDIGREE 1345	maternal grandfather
GM07345	Lymphoblast CEPH/UTAH PEDIGREE 1345	maternal grandmother

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[084] The references cited herein and throughout the specification are incorporated herein by reference in their entirety.

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CLAIMS

We claim:

1. A method for determining a haplotype of a subject comprising the steps of:
   (a) diluting a nucleic acid sample from the subject into a single molecule dilution;
   (b) amplifying the diluted single nucleotide dilution with at least two different primer pairs designed to amplify a region comprising at least two polymorphic sites in the nucleic acid template;
   (c) genotyping the polymorphic sites in the single nucleic acid molecule; and
   (d) determining the haplotype from the genotypes of at least the two polymorphic sites to obtain a haplotype for the subject.
2. The method of claim 1, further comprising repeating steps a-c at least three times from the same nucleic acid sample to obtain at least four genotype replicas from the same subject and thereafter comparing the at least four genotype replicas to determine the haplotype.
3. The method of claim 2, further comprising comparing the haplotype with a haplotype from a control or a database of haplotypes from controls to determine association of the haplotype with a biological trait.
4. The method of claim 1, wherein the polymorphism is a single nucleotide polymorphism.
5. The method of claim 1, wherein the polymorphism is a deletion, an insertion, a substitution or an inversion.
6. The method of claim 1, wherein the polymorphism is a combination of one or more markers selected from the group consisting of a single nucleotide polymorphism, deletion, an insertion, a substitution or an inversion.
7. The method of claims 1-6, wherein genotyping is performed using primer extension and mass spectrometric detection.
8. The method of claim 2, wherein 12-18 genotype replicas are produced.
9. A method of diagnosing a disease condition or disease susceptibility by determining a disease related haplotype in a subject comprising the steps of:
   (a) diluting a nucleic acid sample from the subject into a single molecule dilution;
   (b) amplifying the diluted single nucleotide dilution with at least two primer pairs designed to amplify a region comprising at least two polymorphic sites in the nucleic acid template;

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(c) genotyping the polymorphic sites in the single nucleic acid molecule;

(d) determining the haplotype from the genotype of at least two polymorphic sites to obtain a haplotype for the subject; and

(e) comparing the haplotype of the subject to known disease-associated haplotypes, wherein a match in the sample haplotype with a disease-associated haplotype indicates that the subject has the disease or that the subject is susceptible for the disease.

10. The method of claim 9, further comprising repeating steps a – c at least three times from the same nucleic acid sample to obtain at least four genotype replicas from the same subject and thereafter comparing the at least four genotype replicas to determine the haplotype.

11. The method of claim 10, wherein 12-18 replicas are produced.

12. A method of determining a haplotype of a subject comprising the steps of:

(a) treating a nucleic acid sample from the subject with a composition that differentially affects an epigenetically modified nucleotide in the nucleic acid sample to effectively create polymorphisms based on the epigenetic modification;

(b) diluting the treated nucleic acid sample into a single copy dilution;

(c) amplifying the diluted nucleic acid sample using at least two different primer pairs;

(d) genotyping the amplified sample; and

(e) determining the haplotype of the subject from the genotyped sample.

13. The method of claim 12, further comprising repeating the steps b-d at least three times to obtain at least four genotype replicas from the same subject and thereafter determining a haplotype of the subject based on the genotype replicas.

14. The method of claim 13, wherein 12-18 replicas are produced.

15. The method of claim 12, wherein the epigenetically modified nucleotide is a methylated nucleotide.

16. The method of claim 15, wherein the nucleic acid sample is treated with bisulfite.

17. A method of determining a haplotype in a subject comprising the steps of:

(a) digesting a nucleic acid sample from the subject with a methylation-sensitive restriction enzyme so that either unmethylated DNA or methylated DNA is left intact, depending on which enzyme is used;

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(b) diluting the digested nucleic acid sample to a single molecule concentration;

(c) amplifying the diluted and undiluted nucleic acid sample with at least two different primer pairs;

(d) genotyping the amplified samples; and

(e) determining a haplotype of a methylated nucleic acid wherein at least one polymorphic markers next to the methylation site, together with the methylation site, constitutes a haplotype.

18. The method of claim 17, further comprising repeating the steps b-d at least three times to obtain at least four genotype replicas from the same subject and thereafter determining a haplotype of the subject based on the genotype replicas.

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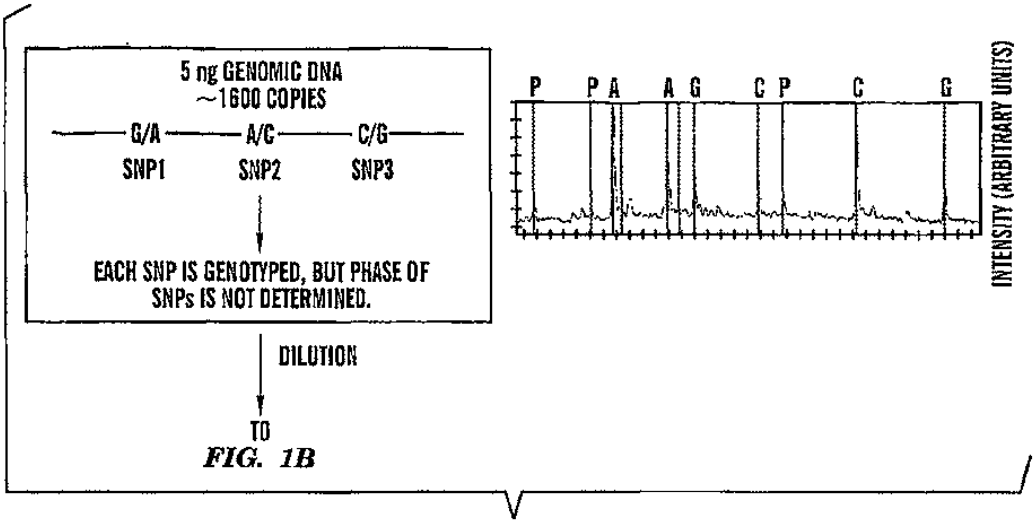

FIG. 1A

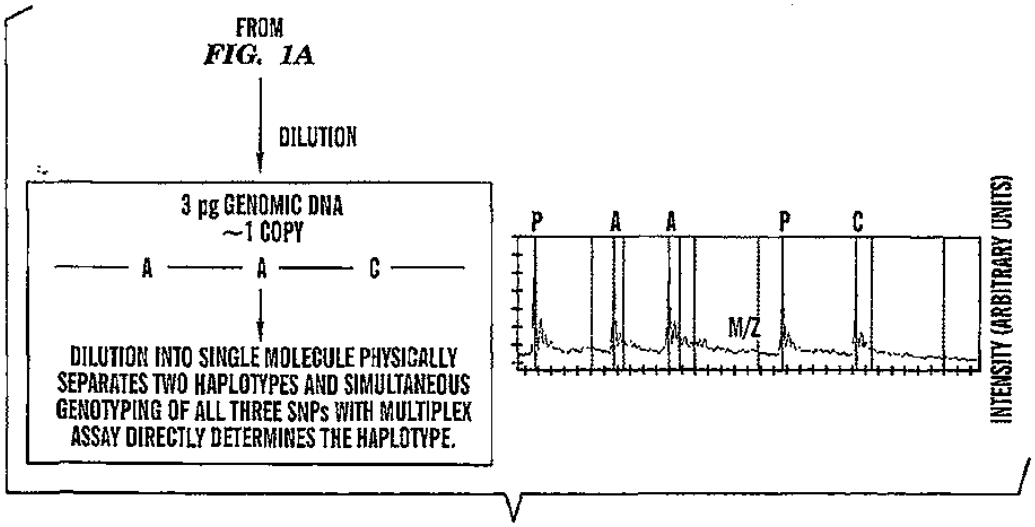

FIG. 1B

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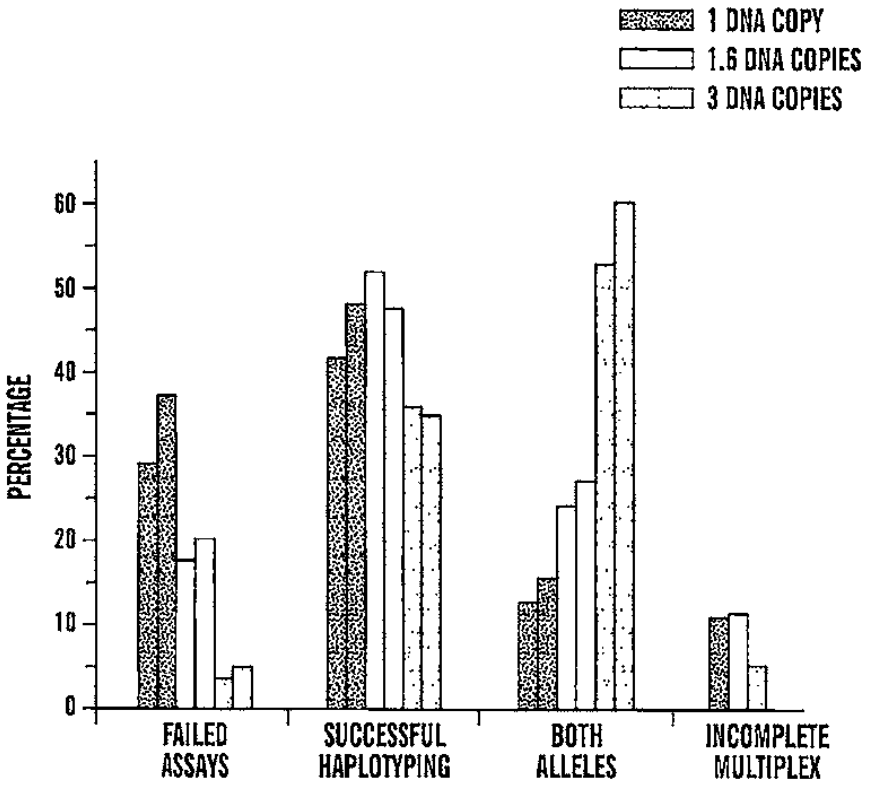

FIG. 2

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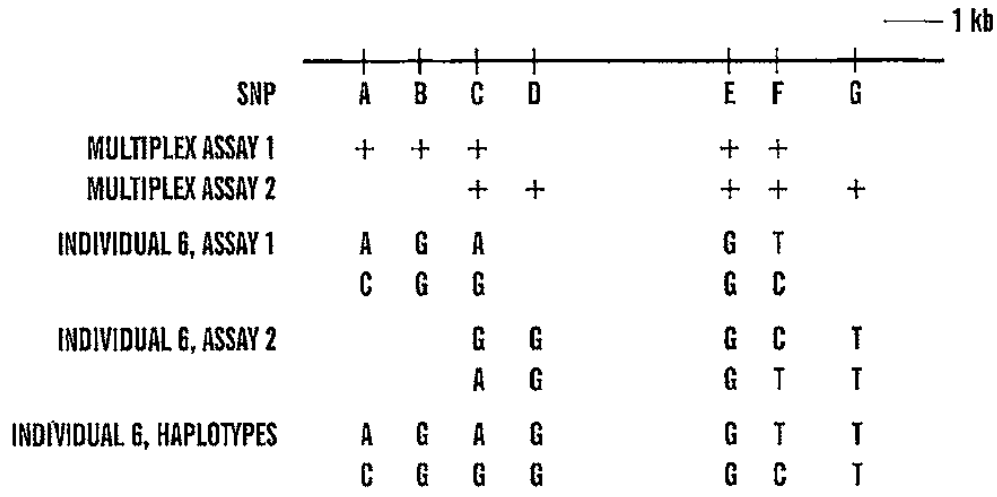

FIG. 3

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 March 2013 (14.03.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/036929 A1

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/US2012/054461

(22) International Filing Date:
10 September 2012 (10.09.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/532,882 9 September 2011 (09.09.2011) US

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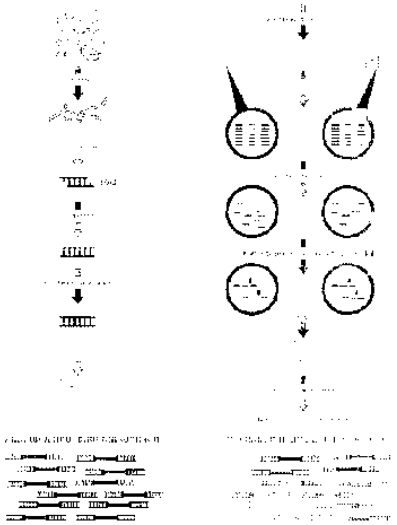
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: METHODS FOR OBTAINING A SEQUENCE

Figure 1



(57) Abstract: The invention generally relates to methods for obtaining a sequence, such as a consensus sequence or a haplotype sequence. In certain embodiments, methods of the invention involve determining an amount of amplifiable nucleic acid present in a sample, partitioning the nucleic acid based upon results of the determining step such that each partitioned portion includes, on average, a subset of unique sequences, sequencing the nucleic acid to obtain sequence reads, and assembling a consensus sequence from the reads.

WO 2013/036929 A1

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

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METHODS FOR OBTAINING A SEQUENCE

Related Application

The present application claims the benefit of and priority to U.S. provisional patent application serial number 61/532,882, filed September 9, 2011, the content of which is incorporated by reference herein in its entirety.

Government Support

This invention was made with Government support under Grant Number AG037968 awarded by the National Institute of Health (NIH). The Government has certain rights in this invention.

Field of the Invention

The invention generally relates to methods for obtaining a sequence, such as a consensus sequence or a haplotype sequence.

Background

Methods to sequence or identify significant segments of the human genome and genetic variations within those segments are becoming commonplace. However, a major impediment to understanding the health implications of genomic variation lies in the ability to correlate genomic differences with the human health consequences of those differences. Whole genome sequencing is an important first step toward elucidation of the genomic underpinnings of human health. Once sequenced, genomic DNA must be assembled or aligned to a reference sequence. A generally-accepted protocol for genome assembly involves using fosmids and BAC libraries in which long pieces of DNA are introduced into bacterial cells that are sequenced independently and reassembled. Such a process is expensive, laborious, and time consuming (e.g., a few weeks to months).

Recent advances in sequencing throughput and library preparation has allowed mammalian-sized genomes to be sequenced in a matter of days. Current sequencing technologies allow the generation of enormous amounts of sequence using short sequence reads

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(i.e., lengths of about 100bp to about 200bp). Those technologies provide up to 30GB of sequences per lane, which is equivalent to 10x coverage of the human genome.

However, application of those technologies to *de-novo* genome assemblies is limited by short sequence read length, which is insufficient to resolve complex genome structure and to produce consistent genome assembly. Further, short sequence reads cannot be used to obtain phasing data (i.e., which variants are on the same chromosome). Additionally, assembly from short reads requires construction of a de-bruign graph, which is a computationally-intensive process requiring supercomputers with large amount of RAM, which limits application to large sequencing centers with access to supercomputers. Thus, it is difficult and expensive to use short sequence reads to get quality *de-novo* reference genome assemblies.

Summary

The invention generally relates to methods for obtaining a sequence, such as a consensus sequence or a haplotype sequence. Methods of the invention allow for sequencing of long continuous (kilobase scale) nucleic acid fragments using conventional short read sequencing technologies. Methods of the invention are accomplished by determining an amount of amplifiable nucleic acid present in a sample, partitioning the nucleic acid based upon results of the determining step such that each partitioned portion includes, on average, a subset of unique sequences, sequencing the nucleic acid to obtain sequence reads, and assembling a consensus sequence from the reads. Limiting the number of amplifiable molecules per partitioned portion so that almost 100% of all amplifiable molecules are present as single copies greatly reduces or eliminates chances of having a repeated or homologous sequence within a partitioned portion. Thus, sample complexity is significantly reduced, which reduces ambiguity in the reconstruction of a consensus sequence. In some cases, the reconstruction can achieve complete unambiguity. In this manner, methods of the invention allow conversion of short sequence reads (about 10 bp to about 200 bp) into intermediate sized fragments (about 10,000 bp) that can be assembled into full chromosomes to provide reference quality assemblies. In some embodiments, the fraction of the unique sequences in the sample is greater than 10%, 20%, 50%, or 95%.

Nucleic acid obtained from biological samples typically is fragmented to produce suitable fragments for analysis. Thus, methods of the invention may further involve an initial step of fragmenting obtained nucleic acid. To further provide for unambiguous reconstruction of a

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consensus sequence, methods of the invention may also involve attaching unique marker identifiers to ends of each fragment, thus ensuring that homologous fragments, for example originating from homologous copies of chromosomes, can be detected based upon the unique markers that are attached to each fragment. In other embodiments, To further provide for unambiguous reconstruction of a consensus sequence, methods of the invention may also involve attaching labels to the nucleic acids in each partitioned portion. Exemplary labels include nucleic acid binding proteins, optical labels, nucleotide analogs, and others known in the art. In preferred embodiments, the labels are bar code sequences. In some embodiments, the labels are adaptor primer sequences. These adaptor sequences described in the invention, in some embodiments, allow resolving assembly ambiguities by linking the related sequence information of sequence segments together. In some embodiments, the adaptor sequences adjacent to the ends of the one or more nucleic acids are different. In some embodiments, the one or more target polynucleotides comprise at least a first target polynucleotide adjacent to a first known nucleotide sequence at at least one end and a second target polynucleotide adjacent to a second known nucleotide sequence at at least one end, wherein the first known nucleotide sequence is not the same as the second known nucleotide sequence. In some embodiments, the first target polynucleotide further comprises a third known nucleotide sequence at at least one end, wherein the second target polynucleotide further comprises a fourth known nucleotide sequence at at least one end, wherein the third known nucleotide sequence is dependent on the first known nucleotide sequence and wherein the fourth known nucleotide sequence is dependent on the second known nucleotide sequence. In some embodiments, relating sequence information from the plurality of fragments into the first target polynucleotide comprises linking the first and the third known nucleotide sequences. In some embodiments, the first and third known nucleotide sequences are different from the second and fourth known nucleotide sequences.

The nucleic acid obtained from biological samples may originate from genomic DNA. In some embodiments, the genomic DNA may originate from a polyploidy genome. The nucleic acid obtained from biological samples may comprise a portion of a major histocompatibility complex gene. In some embodiments, the nucleic acid may originate from fetal DNA.

Partitioning of the fragments into partitioned portions may be by any method known in the art. For example, partitioning may involve dispensing the sample into different wells of a

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microwell plate, or partitioning may involve segmenting the sample into droplets. In particular embodiments, partitioning is performed under microfluidic control.

After partitioning, the fragmented nucleic acids may be amplified by any methods known in the art. In particular embodiments, PCR is used to amplify the fragments. The amplified fragments in each partitioned portion may then be fragmented and bar code sequences are attached to these fragments. Fragmenting may be by any method known in the art, such as restriction digesting or by application of mechanical force, e.g., sonication. In some embodiments, the bar code sequences may be nucleic acid sequences. The length of the bar code sequences may be greater than 3 nucleotide long. In certain embodiments, the fragments are longer than 10 bp or 250 bp, or shorter than 1000 bp or 2000 bp.

After bar codes have been incorporated into the nucleic acid templates, the templates are sequenced. Sequencing may be by any method known in the art. In certain embodiments, sequencing is sequencing by synthesis. In other embodiments, sequencing is single molecule sequencing by synthesis. In some embodiments, sequencing is ion semiconductor sequencing. In some embodiments, sequencing is nanopore sequencing. In some embodiments, sequencing is sequencing by electron microscopy. In certain embodiments, sequencing involves hybridizing a primer to the template to form a template/primer duplex, contacting the duplex with a polymerase enzyme in the presence of a detectably labeled nucleotides under conditions that permit the polymerase to add nucleotides to the primer in a template-dependent manner, detecting a signal from the incorporated labeled nucleotide, and sequentially repeating the contacting and detecting steps at least once, wherein sequential detection of incorporated labeled nucleotide determines the sequence of the nucleic acid. In some embodiments, the sequencing comprises obtaining paired end reads. The accuracy or average accuracy of the sequence information may be greater than 80%, 90%, 95%, 99% or 99.98%. In some embodiments, the sequence information obtained is more than 50 bp, 100 bp or 200 bp. The sequence information may be obtained in less than 1 month, 2 weeks, 1 week 1 day, 3 hours, 1 hour, 30 minutes, 10 minutes, or 5 minutes. The sequence accuracy or avegare accuracy may be greater than 95% or 99%. The sequence coverage may be greater than 20 fold or less than 500 fold. Exemplary detectable labels include radiolabels, florescent labels, enzymatic labels, etc. In particular embodiments, the detectable label may be an optically detectable label, such as a fluorescent label. Exemplary fluorescent labels include cyanine, rhodamine, fluorescien, coumarin,

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BODIPY, alexa, or conjugated multi-dyes. In some embodiments, the nucleotide is flagged if one or more of its sequence segments are substantially similar to one or more sequence segments of another nucleotide within the same partition.

Another aspect of the invention provides methods for assembling a consensus sequence that involve obtaining nucleic acid, fragmenting the nucleic acid, determining an amount of amplifiable nucleic acid present in a sample, partitioning the fragmented nucleic acids based upon results of the determining step, amplifying the partitioned nucleic acids, attaching bar codes to the amplified nucleic acid, sequencing the nucleic acid to obtain bar coded sequence reads, and assembling a consensus sequence from the reads. In certain embodiments, each partitioned portion includes, on average, a unique subset of nucleic acids.

In one aspect, the invention relates to a method for relating sequence components in a target polynucleotide, the method comprising: (a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length, and wherein the known nucleotide sequence is capable of serving as an amplification target; (b) partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 99.999%; (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments; (d) obtaining partial or complete sequence information from at least a subset of the fragments; and (e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides. In a similar aspect, the invention relates to a method for relating sequence components in a target polynucleotide, the method comprising: (a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length of greater than 30 bp, and wherein the known nucleotide sequence is capable of serving as an amplification target; (b) partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 100%; (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments; (d) obtaining partial or complete sequence information from at

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least a subset of the fragments; and (c) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides. In some embodiments, the methods comprise subjecting at least one partition to nucleic acid amplification using the known nucleotide sequence as an amplification target thereby amplifying the one or more target polynucleotides into amplicons such that at least a fraction of the sequence segments originating from the at least one or more target polynucleotides or the amplicons in the at least one partition is estimated to be present as a single copy prior to amplification in the at least one partition with a likelihood that is less than 99.999%. In some embodiments, the at least one sample comprises a first target polynucleotide and a second target polynucleotide each adjacent to a first known nucleotide sequence and a second known nucleotide sequence at at least one end, wherein the first known nucleotide sequence is not the same as the second known nucleotide sequence. In some embodiments the sequence segment length is greater than about 30bp. In some embodiments, the sequence segment length is greater than about 50bp. In some embodiments, the sequence segment length is less than about 100bp. In some embodiments, the fraction is greater than 10%. In some embodiments, the fraction is greater than 20%. In some embodiments, the fraction is greater than 50%. In some embodiments, the fraction is 95%. In some embodiments, the likelihood is greater than 80%. In some embodiments, likelihood is 99%. In some embodiments, upon partitioning at least one sequence segment is present in multiple copies in the at least one partition. In some embodiments, the method further comprises amplifying the target polynucleotide prior to subjecting the partition to polynucleotide fragmentation. In some embodiments, the target polynucleotide is adjacent to a known nucleotide sequence at both ends. In some embodiments, the known sequence is introduced onto the target polynucleotide by ligating an adaptor oligonucleotide. In some embodiments, on average, the fragments are longer than 10 bp. In some embodiments, on average, the fragments are shorter than 2000 bp. In some embodiments, on average, the fragments are shorter than 1000 bp. In some embodiments, on average, the fragments are longer than 250 bp. In some embodiments, on average, the one or more target polynucleotides are longer than 5000 bp. In some embodiments,on average, the one or more target polynucleotides are longer than 10000 bp. In some embodiments, the fragments within a partition are labeled with one or more partition specific barcodes. In some embodiments, the barcodes are nucleic acid sequences. In some embodiments, the barcodes are greater than 3 nucleotides long. In some embodiments, the barcodes are greater than 5 nucleotides long. In

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some embodiments, the one or more partition specific barcodes comprise 2 barcodes that are each greater than 2 nucleotides long. In some embodiments, all two partition specific barcodes comprise at least two differences in the nucleic acid sequence. In some embodiments, the sequence information comprises sequence reads obtained by sequencing. In some embodiments,the sequence information comprises an accuracy of greater than 99%. In some embodiments, the sequence information comprises an accuracy of greater than 95%. In some embodiments, the sequence information comprises an accuracy of greater than 90%. In some embodiments, the sequence information comprises an accuracy of greater than 80%. In some embodiments, the sequence information comprises an average accuracy of greater than 99%. In some embodiments, the sequence information comprises an average accuracy of greater than 95%. In some embodiments, the sequence information comprises an average accuracy of greater than 90%. In some embodiments, the sequence information comprises an average accuracy of greater than 80%. In some embodiments, the sequence reads comprise an accuracy of greater than 99.98%. In some embodiments, the sequence information spans more than 50 bp. In some embodiments, the sequence information spans more than 100 bp. In some embodiments, the sequence information spans more than 200 bp. In some embodiments, all sequence information is obtained in less than 1 month. In some embodiments, all sequence information is obtained in less than 2 weeks. In some embodiments, all sequence information is obtained in less than 1 week. In some embodiments, all sequence information is obtained in less than 1 day. In some embodiments, all sequence information is obtained in less than 3 hours. In some embodiments, all sequence information is obtained in less than 1 hour. In some embodiments, all sequence information is obtained in less than 30 minutes. In some embodiments, all sequence information is obtained in less than 10 minutes. In some embodiments, all sequence information is obtained in less than 5 minutes. In some embodiments, the relating step comprises an average accuracy of at least 95%. In some embodiments, the relating step comprises an average accuracy of at least 99%. In some embodiments, the target polynucleotide within the sample is flagged if one or more of its sequence segments are substantially similar to one or more sequence segments of a second target polynucleotide partitioned into the same partition. In some embodiments, the methods further comprise a sequence coverage of greater than 20 fold. In some embodiments, the methods further comprise an average sequence coverage of less than 500 fold. In some embodiments, the sequencing comprises sequencing by synthesis. In some embodiments, the

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sequencing comprises ion semiconductor sequencing. In some embodiments, the sequencing comprises single molecule real time sequencing. In some embodiments, the sequencing comprises nanopore sequencing. In some embodiments, the sequencing comprises sequencing by electron microspcopy. In some embodiments, the target polynucleotide originates from genomic DNA. In some embodiments, the genomic DNA originates from a polyploid genome. In some embodiments, the target polypeptide comprises a portion of a major histocompatibility complex gene. In some embodiments, the target polypeptide originates from fetal DNA. In some embodiments, the sequencing comprises obtaining paired end reads.

In some embodiments, the methods further comprise utilizing computing resources that are delivered over a network to improve detection of sequence variants and detection average accuracy. In some embodiments, the one or more target polynucleotides originate from a single molecule, and wherein the related sequence information links two or more positions on the single molecule. In some embodiments, the two or more positions on the single molecule are separated by more than 5000 bp. In some embodiments, the two or more positions on the single molecule are separated by more than 10000 bp. In some embodiments, the one or more target polynucleotides comprise a first target polynucleotide and a second polynucleotide and the related sequence information to the first target polynucleotide and the related sequence information to the second target polynucleotide are linked.

In some embodiments, the methods further comprise detecting a genomic structural variation.

In some embodiments, the one or more target polynucleotides originate from one or more tissue samples, wherein relating sequence information comprises detecting a plurality of sequence variants in the one or more tissue samples, and wherein the plurality of sequence variants from one or more tissue sample are compared.

In some embodiments, the methods further comprise providing a diagnosis based on the related sequence information. In some embodiments, the diagnosis is directed to a disease selected from the group consisting of allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic eczema, atopic dermatitis, food allergy, severe combined immunodeficiency (SCID), hypereosinophilic syndrome, chronic granulomatous disease, leukocyte adhesion deficiency I and II, hyper IgE syndrome, Chediak Higashi, neutrophilias, neutropenias, aplasias, Agammaglobulinemia, hyper-IgM syndromes, DiGeorge/Velocardial-facial syndromes and Interferon gamma-TH1 pathway

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defects, rheumatoid arthritis, diabetes, systemic lupus erythematosus, Graves' disease, Graves ophthalmopathy, Crohn's disease, multiple sclerosis, psoriasis, systemic sclerosis, goiter and struma lymphomatosa (Hashimoto's thyroiditis, lymphadenoid goiter), alopecia aerata, autoimmune myocarditis, lichen sclerosis, autoimmune uveitis, Addison's disease, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritis nodosa, and inflammatory bowel disease, allograft rejection and tissue destructive from allergic reactions to infectious microorganisms or to environmental antigens, hemangiomatosis in newborns, secondary progressive multiple sclerosis, chronic progressive myelodegenerative disease, neurofibromatosis, ganglioneuromatosis, keloid formation, Paget's Disease of the bone, fibrocystic disease (e.g., of the breast or uterus), sarcoidosis, Peronies and Duputren's fibrosis, cirrhosis, atherosclerosis and vascular restenosis, hematologic malignancies and solid tumors, 21 hydroxylase deficiency, cystic fibrosis, Fragile X Syndrome, Turner Syndrome, Duchenne Muscular Dystrophy, Down Syndrome or other trisomies, heart disease, single gene diseases, HLA typing, phenylketonuria, sickle cell anemia, Tay-Sachs Disease, thalassemia, Klinefelter Syndrome, Huntington Disease, autoimmune diseases, lipidosis, obesity defects, hemophilia, inborn errors of metabolism, and diabetes.

In some embodiments, the one or more target polynucleotides comprise at least a first target polynucleotide adjacent to a first known nucleotide sequence at at least one end and a second target polynucleotide adjacent to a second known nucleotide sequence at at least one end, wherein the first known nucleotide sequence is not the same as the second known nucleotide sequence. In some embodiments, the first target polynucleotide further comprises a third known nucleotide sequence at at least one end, wherein the second target polynucleotide further comprises a fourth known nucleotide sequence at at least one end, wherein the third known nucleotide sequence is dependent on the first known nucleotide sequence and wherein the fourth known nucleotide sequence is dependent on the second known nucleotide sequence. In some embodiments, relating sequence information from the plurality of fragments into the first target polynucleotide comprises linking the first and the third known nucleotide sequences. In some embodiments, the first and third known nucleotide sequences are different from the second and fourth known nucleotide sequences.

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In some embodiments, the methods further comprise identifying the presence of a pathogen in the at least one sample. In some embodiments, the pathogen is selected from the group consisting of a bacterial agent, a virus, a parasite, and a fungus. In some embodiments, the bacterial agent is selected from the group consisting of Escherichia coli, Salmonella, Shigella, KlESBiella, Pseudomonas, Listeria monocytogenes, Mycobacterium tuberculosis, Mycobacterium aviumintracellulare, Yersinia, Francisella, Pasteurella, Brucella, Clostridia, Bordetella pertussis, Bacteroides, Staphylococcus aureus, Streptococcus pneumonia, B-Hemolytic strep., Corynebacteria, Legionella, Mycoplasma, Ureaplasma, Chlamydia, Neisseria gonorrhea, Neisseria meningitides, Hemophilus influenza, Enterococcus faecalis, Proteus vulgaris, Proteus mirabilis, Helicobacter pylori, Treponema palladium, Borrelia burgdorferi, Borrelia recurrentis, Rickettsial pathogens, Nocardia, and Acitnomycetes. In some embodiments, the fungus is selected from the group consisting of Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Paracoccidioides brasiliensis, Candida albicans, Aspergillus fumigautus, Phycomycetes (Rhizopus), Sporothrix schenckii, Chromomycosis, and Maduromycosis. In some embodiments, the virus is selected from the group consisting of human immunodeficiency virus, human T-cell lymphocytotrophic virus, hepatitis viruses (e.g., Hepatitis B Virus and Hepatitis C Virus), Epstein-Barr Virus, cytomegalovirus, human papillomaviruses, orthomyxo viruses, paramyxo viruses, adenoviruses, corona viruses, rhabdo viruses, polio viruses, toga viruses, bunya viruses, arena viruses, rubella viruses, and reo viruses. In some embodiments, the parasite is selected from the group consisting of Plasmodium falciparum, Plasmodium malaria, Plasmodium vivax, Plasmodium ovale, Onchoverva volvulus, Leishmania, Trypanosoma spp., Schistosoma spp., Entamoeba histolytica, Cryptosporidum, Giardia spp., Trichimonas spp., Balatidium coli, Wuchereria bancrofti, Toxoplasma spp., Enterobius vermicularis, Ascaris lumbricoides, Trichuris trichiura, Dracunculus medinesis, trematodes, Diphyllobothrium latum, Taenia spp., Pneumocystis carinii, and Necator americanis. In some embodiments, the pathogen comprises a drug resistant pathogen. In some embodiments, the drug resistant pathogen is selected from the group consisting of vancomycin-resistant Enterococcus faecium, methicillin-resistant Staphylococcus aureus, penicillin-resistant Streptococcus pneumoniae, multi-drug resistant Mycobacterium tuberculosis, and AZT-resistant human immunodeficiency virus.

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In a similar aspect with related embodiments, the invention relates to a method method of relating sequence components in a target polynucleotide comprising: (a) providing at least one sample comprising one or more target polynucleotides wherein each target polynucleotide comprises one or more sequence segments with a sequence length; (b) partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 99.999%; (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments; (d) obtaining partial or complete sequence information from the fragments; and (e) relating sequence information from a plurality of fragments into the target polynucleotides. In some embodiments, a fraction of said one or more target polynucleotides in the sample are each attached to one or more labels. In some embodiments, said label is nucleic acid binding proteins, optical labels, nucleotide analogs, or oligonucleotides.

In another similar aspect with related embodiments, the invention relates to a method for relating sequence components in a target polynucleotide, the method comprising: (a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length; (b) partitioning the sample into a finite plurality of partitions and subjecting at least one partition to nucleic acid amplification thereby amplifying the one or more target polynucleotides into amplicons such that at least a fraction of the sequence segments originating from the at least one or more target polynucleotides or the amplicons in the at least one partition is estimated to be present as a single copy prior to amplification in the at least one partition with a likelihood that is less than 99.999%; (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments; (d) obtaining partial or complete sequence information from at least a subset of the fragments; and (e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides. In yet another similar aspect with related embodiments, the invention relates to a method for relating sequence components in a target polynucleotide, the method comprising: (a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length of greater than 30 bp; (b) partitioning the sample into a finite plurality of partitions and

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subjecting at least one partition to nucleic acid amplification thereby amplifying the one or more target polynucleotides into amplicons such that at least a fraction of the sequence segments originating from the at least one or more target polynucleotides or the amplicons in the at least one partition is estimated to be present as a single copy prior to amplification in the at least one partition with a likelihood that is less than 100%; (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments; (d) obtaining partial or complete sequence information from at least a subset of the fragments; and (e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides.

In any aspect of the invention, the method may comprise partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments within a target polynucleotide or within an amplifiable or amplified, for example exponentially amplifiable or amplified, target polynucleotide, in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is lower than 100%, 99.999%, 99.99%, 99.98%, 99.95%, 99.9%, 99.5%, 99.0%, 95%, 90% or less. In any aspect of the invention, the method may comprise partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments within a target polynucleotide or within an amplifiable or amplified, for example exponentially amplifiable or amplified, target polynucleotide, in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is higher than 80%, 90% , 95%, 99%, 99.5%, 99.95%, 99.98%, 99.99%, 99.999%, or more. In any aspect, sequence segment length can be greater than about 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 bp or more. In any aspect, the fraction of the sequence segments estimated to be present as a single copy in a partition can be greater than 5, 10, 20, 30, 40, 50 , 60, 70, 80, 90, 95, 99% or greater. In any aspect, the fraction of the sequence segments within amplifiable or amplified, for example exponentially amplifiable or amplified, target polynucleotides, estimated to be present as a single copy in a partition can be greater than 5, 10, 20, 30, 40, 50 , 60, 70, 80, 90, 95, 99% or greater. In any aspect, the fragments and/or the target polynucleotides can be longer than 10, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000, 2000 bp or more. In any aspect, the fragments and/or the target polynucleotides can be shorter than 30, 40, 50, 100, 200, 300, 400, 500, 1000, 2000, 3000, 4000, 5000, 10000, 20000, 30000, 40000, 50000 bp or more. In any aspect, the barcodes can be 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20 nucleotides long or longer. In any aspect, the partition specific barcodes may comprise 1, 2, 3, 4,

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5, 6, 7, 8, 9, 10 or more barcodes. In any aspect, the sequence information may comprise an accuracy or average accuracy of 80, 90, 95, 98, 99, 99.5, 99.8, 99.9, 99.99, 99.995% or higher. In any aspect, the sequence information may span or on average span more than 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 180, 200, 250, 300, 400, 500 bp or more. In any aspect the sequence information may be obtained in less than 1 month, 2 weeks, 1 week, 1 day, 3, hours, 1 hour, 30 minutes, 10 minutes, 5 minutes, 1 minute, or less. In any aspect, the relating step may comprise an accuracy or average accuracy of 80, 90, 95, 98, 99, 99.5, 99.8, 99.9, 99.99, 99.995% or higher. In any aspect, the method may comprise a sequence coverage of greater than 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 fold or more. In any aspect, the method may comprise a sequence coverage of less than 500, 400, 300, 200, 100, 90, 80, 70, 60, 50, 40, 30, 25, 20, 15, 12, 10, 9, 8, 7, 6, 5, 4, 3, 2 fold or less.

In another related aspect, the invention relates to a kit for relating sequence components in the one or more target polynucleotides, comprising (a) one or more restriction endonucleases; (b) an enzyme capable of repairing at least one end of polynucleotides; (c) one or more ligases capable of ligating an oligonucleotide sequence to the one or more target polynucleotides; (d) one or more known nucleotide sequences capable of serving as an amplification target; (e) a system capable of selecting a subset of the one or more target polynucleotides of a desired length; and (f) one or more polymerases capable of polynucleotide synthesis.
In another aspect, the invention relates to a for relating sequence components in a target polynucleotide, comprising (a) a device comprising a substrate with one or more reaction volumes comprising one or more restriction endonucleases capable of polynucleotide fragmentation; (b) a device comprising a substrate with one or more reaction volumes comprising one or more oligonucleotides with a known sequence; and (c) a device comprising a substrate with one or more reaction volumes comprising one or more polymerases capable of polynucleotide synthesis.

Another aspect of the invention relates to a method of forming a linear nucleic acid molecule comprising a target polynucleotide with an adaptor oligonucleotide at each end, comprising (a) providing a target polynucleotide and an intermediate polynucleotide, wherein the intermediate polynucleotide comprises at least two adaptor oligonucleotides, (b) forming a circular polynucleotide construct by combining the target polynucleotide with the intermediate

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polynucleotide at each end, and (c) cleaving the circular polynucleotide construct within the intermediate polynucleotide to form a linearized molecule. In some embodiments, the target polynucleotide is subjected to a size selection technique for a particular sized polynucleotide at about 50, 100, 250, 500, 1000, 2500, 5000, or 10,000 nucleotides. In some embodiments, the target polynucleotide is created by fragmentation of a large double stranded polynucleotide by mechanical shearing, chemical or enzymatic treatment. The target polynucleotide, in certain embodiments, is created by a polymerase and nucleotide triphosphates. In some embodiments, the target polynucleotide is subjected to melting temperature thereby producing a single stranded target polynucleotide. The target polynucleotide, in some embodiments, comprises a sticky end that pairs sufficiently complementary with the intermediate polynucleotide. In some embodiments, the target polynucleotide comprises a blunt end. In some embodiments, the blunt end is generated by fragmentation and enzymatic end repair. In some embodiments, the enzymatic end repair comprises a polymerase and one or more nucleotide triphosphates. In some embodiments, the target polynucleotide comprises a poly-N-tail. In some embodiments, the poly-N-tail comprises one or more adenine, thymine, guanine or cytosine nucleotide bases at either its 3' or 5'end that pair sufficiently complementary with the intermediate polynucleotide. In some embodiments, the poly-N-tail is at a 3' end of the target polynucleotide. In some embodiments, the intermediate polynucleotide is sufficiently complementary to the poly-N-tail. In some embodiments, in step (a) the target polynucleotide and the intermediate polynucleotide are present in a ratio of about 1:1, 1:2, 1:3, 1:4, 1:6, 1:8, 1:10 or 1:20. In some embodiments, in step (b) the target polynucleotide and the intermediate polynucleotide are ligated in a ratio of 1:1. In some embodiments, the adaptor oligonucleotide is single or double stranded. In some embodiments, the circular polynucleotide construct is single or double stranded. In some embodiments, the adaptor oligonucleotides at each end of the target polynucleotide are substantially the same. In some embodiments, the adaptor oligonucleotides at each end of the target polynucleotide are different. In some embodiments, at least 3 bases of the adaptor oligonucleotides at each end of the target polynucleotide are different. In some embodiments, at least 4 bases of the adaptor oligonucleotides at each end of the target polynucleotide are different. In some embodiments, there are more than one adaptor oligonucleotides at each end. In some embodiments, the adaptor oligonucleotide comprises one or more identification elements. In some embodiments, at least one of the one or more identification elements comprises a unique

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identifying tag. In some embodiments, at least one of the one or more identification elements comprises a multiple cloning site. In some embodiments, at least one of the one or more identification elements comprises a universal priming site. In some embodiments, at least one of the one or more identification elements comprises a recognition site for a polymerase. In some embodiments, at least one of the one or more identification elements comprises a nick in the adaptor oligonucelotide. In some embodiments, at least one of the one or more identification elements comprises a molecular binding site. In some embodiments, at least one of the one or more identification elements comprises a recognition site for a topoisomerase enzyme and wherein the topoisomerase is capable of attaching to the recognition site a 3' end of the recognition site. In some embodiments, the attaching comprises forming a covalent bond. In some embodiments, the adaptor oligonucleotide further comprises a combination of the one or more identification elements described earlier in any order. In some embodiments, the intermediate polynucleotide is cleaved using a restriction endonuclease. In some embodiments, ligation of blunt or sticky ends comprises a ligase. In some embodiments, cleaving the circular polynucleotide construct comprises adenine-thymine or guanine-cytosine complementary base pairing. In some embodiments, forming a circular polynucleotide comprises using a topoisomerase enzyme. In some embodiments, the methods in the invention further comprises an additional recovery step employing affinity capture to a molecular binding site in an adaptor oligonucleotide. In some embodiments, the affinity capture is employed after the step wherein the circular polynucleotide construct within the intermediate polynucleotide is cleaved. In some embodiments, the one or more identification elements allow for identification or isolation of the target polynucleotide.

In another aspect, the invention relates to a composition capable of creating a linear nucleic acid molecule comprising a target polynucleotide with an adaptor oligonucleotide at each end for the identification and isolation of a target polynucleotide, comprising (a) the target polynucleotide, (b) an intermediate polynucleotide comprising at least two adaptor oligonucleotides, wherein the intermediate polynucleotide further comprises at least one or more elements that allow for circularization, linearization, identification, amplification or isolation. In some embodiments, the elements of the composition are selected from the group consisting of a unique identifying tag, a multiple cloning site, a universal priming site, a recognition site for a polymerase, a molecular binding site, and a topoisomerase enzyme covalently attached at 3' end

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to its recognition site. In some embodiments, the composition comprises the intermediate polynucleotide and the target polynucleotide in a ratio of about 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 8:1, 10:1, or 20:1. In some embodiments, the target polynucleotide is rendered into a circular molecule. In some embodiments, the circular molecule in the composition further comprises the intermediate polynucleotide. In related aspects, the invention relates to a kit comprising the composition capable of creating the linear nucleic acid molecule comprising the target polynucleotide with an adaptor oligonucleotide at each end, further comprising one or more components selected from the group consisting of one or more polymerases, one or more ligases, one or more restriction endonucleases, one or more primers complementary to a universal priming site, one or more molecular binding molecules that recognize a molecular binding site, one or more topoisomerases, one or more single nucleotide triphosphates and one or more terminal transferases. In some embodiments, the kit further comprises one or more class II transposons. In some embodiments, the kit further comprises a sequencing adaptor, a sequencing primer, or a barcode adaptor.

In another aspect, the invention relates to a method for obtaining a sequence, comprising determining an amount of amplifiable nucleic acid present in a sample, partitioning the nucleic acid based upon results of the determining step such that each partitioned portion comprises, on average, a subset of unique sequences, sequencing the nucleic acid to obtain sequence reads, and obtaining a sequence from the reads. In some embodiments, prior to the determining step, the method further comprises fragmenting the nucleic acid. In some embodiments, The method further comprises attaching a set of unique marker identifier to ends of each fragment. In some embodiments, the unique marker identifiers comprise bar code sequences that are part of adapter sequences. In some embodiments, the bar code sequences are the same. In some embodiments, the bar code sequences are different. In some embodiments, the method further comprises attaching labels to the nucleic acids in each partitioned portion. In some embodiments, the labels are bar code sequences. In some embodiments, prior to the attaching labels step, the method further comprises amplifying the nucleic acids in each partitioned portion. In some embodiments, after the amplifying step, the method further comprises fragmenting the amplified nucleic acids in each partitioned portion. In some embodiments, fragmenting comprises restriction digesting. In some embodiments, fragmenting comprises mechanically fragmenting. In some embodiments, fragmenting comprises using an in vitro translocation enzyme. In some embodiments,

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partitioning comprises dispensing the sample into different wells of a microwell plate. In some embodiments, partitioning comprises segmenting the sample into droplets. In some embodiments, partitioning is performed under microfluidic control. In some embodiments, sequencing is sequencing-by-synthesis. In some embodiments, sequencing is single molecule sequencing-by-synthesis. In some embodiments, the sequence is a consensus sequence. In some embodiments, the sequence is a haplotype sequence.

In another aspect of the invention, a method for obtaining a sequence is described, comprising obtaining nucleic acid, fragmenting the nucleic acid, determining an amount of amplifiable nucleic acid present in a sample, partitioning the fragmented nucleic acids based upon results of the determining step, amplifying the partitioned nucleic acids, attaching bar codes to the amplified nucleic acid, sequencing the nucleic acid to obtain bar coded sequence reads, and obtaining a sequence from the reads. In some embodiments, each partitioned portion comprises, on average, a unique subset of nucleic acids. In some embodiments, the method further comprises attaching marker identifiers to ends of the fragments. In some embodiments, fragmenting comprises restriction digesting. In some embodiments, fragmenting comprises mechanically fragmenting. In some embodiments, fragmenting comprises using an in vitro translocation enzyme. In some embodiments, partitioning comprises dispensing the sample into different wells of a microwell plate. In some embodiments, partitioning comprises segmenting the sample into droplets. In some embodiments, partitioning is performed under microfluidic control. In some embodiments, sequencing is sequencing-by-synthesis. In some embodiments, sequencing is single molecule sequencing-by-synthesis. In some embodiments, the sequence is a consensus sequence. In some embodiments, the sequence is a haplotype sequence.

In yet another aspect, a system for reagent dispensing is disclosed that comprises a first vessel having a flow through hole on a bottom portion of the vessel, and a second vessel, wherein the system is configured such that the first vessel is situated above the second vessel such that the second vessel is capable of receiving a reagent from the first vessel. In some embodiments, the first and second vessels are multiwell plates. In some embodiments, the multiwell plates are 96 or 384 well plates. In some embodiments, the first vessel further comprises a cover. In some embodiments, the system further comprises a centrifuge. In some embodiments, the system further comprises a permeable membrane, wherein the membrane is situated between the first

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and second vessels. In some embodiments, force generated by the centrifuge causes a reagent in the first vessel to pass through the membrane and into the second vessel.

In another aspect of the invention, a method for dispensing reagents is described that comprises providing a system comprising a first vessel having a flow through hole on a bottom portion of the vessel, a second vessel, wherein the system is configured such that the first vessel is situated above the second vessel such that the second vessel is capable of receiving a reagent from the first vessel, dispensing a reagent into the first vessel, and applying centrifugal force to the system to cause the reagent to pass into the second vessel. In some embodiments, prior to the providing step, the method further comprises dispensing a sample into the second vessel. In some embodiments, the first and second vessels are multiwell plates. In some embodiments, the multiwell plates are 96 or 384 well plates. In some embodiments, the first vessel further comprises a cover. In some embodiments, the centrifugal force is generated by a centrifuge. In some embodiments, the system further comprises a permeable membrane, wherein the membrane is situated between the first and second vessels.

Brief Description of the Drawings

Figure 1 is a diagram showing an exemplary embodiments of methods of the invention.

Figure 2 is a set of graphs showing statistics for a sample, obtained by mapping reads to a reference genome.

Figure 3 is a graph showing assembly statistics.

Figure 4 shows structural variation detected using methods of the invention. Methods of the invention allowed detection of novel variants by comparing assembled long fragments with reference sequences. Single molecule amplification also allowed haplotype-resolved variant calling since each fragment originated from one of two chromosomes.

Figures 5A-B are schematics showing that end markers can be attached by circularizing long fragments and using a pool of circularization adapters that contain matched pairs of known sequences that are ligated to opposite ends of long fragments. Figure 5A shows a method that uses PCR and Figure 5B shows a method that uses a restriction enzyme.

Figure 6 demonstrates an example of attaching adapters to target polynucleotide according to some embodiments of the invention.

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Figure 7 illustrates an example for a workflow for sequence assembly according to someembodiments of the invention.

Figure 8 illustrates application of hypermapping according to some embodiments of the invention.

Figure 9 illustrates an exemplary embodiment comprising a phasing algorithm.

Figure 10 illustrates an example method for Poor Man's Mate Pair (PMMP) according to some embodiments of the invention.

Figure 11 illustrates an exemplary embodiment comprising an algorithm for cancer detection according to some embodiments of the invention.

Figure 12 illustrates various components of a generalized computer system according to some embodiments of the present invention.

Figure 13 is a block diagram illustrating an example architecture of a computer system that can be used in connection with example embodiments of the present invention.

Figure 14 is a diagram illustrating a computer network that can be used in connection with example embodiments of the present invention.

Figure 15 is a block diagram illustrating another example architecture of a computer system that can be used in connection with example embodiments of the present invention.

Detailed Description

Methods of the invention provide a highly-scalable library construction method that allows accurate reconstruction of intermediate sized genomic fragments from short paired reads. According to embodiments of the invention, genomic DNA is converted into a library of intermediately sized fragments 8-10kb that are amplified inside partitioned portions after artificially limiting number of template molecules per portion. Resulting amplicon libraries are fragmented and converted to sequencing libraries labeled with unique bar codes to allow reads to be split according to partitioned portion after sequencing. Long fragments are then reassembled using a sequencing algorithm from the short paired reads.

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Figure 1 provides an exemplary embodiment of methods of the invention. In one embodiment, nucleic acid template molecules (e.g., DNA or RNA) are isolated from a biological sample containing a variety of other components, such as proteins, lipids and non-template nucleic acids. Nucleic acid template molecules can be obtained from any cellular material, obtained from an animal, plant, bacterium, fungus, or any other cellular organism. Biological samples for use in the present invention include viral particles or preparations. Nucleic acid template molecules can be obtained directly from an organism or from a biological sample obtained from an organism, e.g., from blood, urine, cerebrospinal fluid, seminal fluid, saliva, sputum, stool and tissue. Any tissue or body fluid specimen may be used as a source for nucleic acid for use in the invention. Nucleic acid template molecules can also be isolated from cultured cells, such as a primary cell culture or a cell line. The cells or tissues from which template nucleic acids are obtained can be infected with a virus or other intracellular pathogen. A sample can also be total RNA extracted from a biological specimen, a cDNA library, viral, or genomic DNA. A sample may also be isolated DNA from a non-cellular origin, e.g. amplified/isolated DNA from the freezer.

Nucleic acid template molecules can be obtained as described in U.S. Patent Application Publication Number US2002/0190663 A1, published Oct. 9, 2003. Generally, nucleic acid can be extracted from a biological sample by a variety of techniques such as those described by Maniatis, et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor, N.Y., pp. 280-281 (1982).

In specific aspects, the present invention introduces a concept of multiplexing two or more enzymatic processes in one reaction, and teaches how to optimize a highly multiplexed enzymatic process. In particular embodiments, the present invention is directed to compositions and methods for simultaneous processing of DNA molecules with a combination of enzymes in a one-step-one-tube reaction and producing either a collection of molecules suitable for further processing, for example for amplification, or in some cases, the methods and compositions of the invention result in amplified DNA molecules. In particular embodiments, the methods of the invention can be easily applied to any type of fragmented double stranded DNA including but not limited to, for example, free DNA isolated from plasma, serum, and/or urine; apoptotic DNA from cells and/or tissues; DNA fragmented enzymatically in vitro (for example, by DNase I and/or restriction endonuclease); and/or DNA fragmented by mechanical forces (hydro-shear,

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sonication, nebulization, etc.). Additional suitable methods and compositions of producing nucleic acid molecules comprising stem-loop oligonucleotides are further described in detail in US Patent No. 7,803,550, which is herein incorporated by reference in its entirety.

In other embodiments, the invention can be easily applied to any high molecular weight double stranded DNA including, for example, DNA isolated from tissues, cell culture, bodily fluids, animal tissue, plant, bacteria, fungi, viruses, etc.

Nucleic acid obtained from biological samples typically is fragmented to produce suitable fragments for analysis. Template nucleic acids may be fragmented or sheared to desired length, using a variety of mechanical, chemical and/or enzymatic methods. DNA may be randomly sheared via sonication, e.g. Covaris method, brief exposure to a DNase, or using a mixture of one or more restriction enzymes, or a transposase or nicking enzyme. RNA may be fragmented by brief exposure to an RNase, heat plus magnesium, or by shearing. The RNA may be converted to cDNA. If fragmentation is employed, the RNA may be converted to cDNA before or after fragmentation. In one embodiment, nucleic acid from a biological sample is fragmented by sonication. In another embodiment, nucleic acid is fragmented by a hydroshear instrument. Generally, individual nucleic acid template molecules can be from about 2 kb bases to about 40 kb. In a particular embodiment, nucleic acids are about 6kb-10 kb fragments. Nucleic acid molecules may be single-stranded, double-stranded, or double-stranded with single-stranded regions (for example, stem- and loop-structures).

A biological sample as described herein may be homogenized or fractionated in the presence of a detergent or surfactant. The concentration of the detergent in the buffer may be about 0.05% to about 10.0%. The concentration of the detergent can be up to an amount where the detergent remains soluble in the solution. In one embodiment, the concentration of the detergent is between 0.1% to about 2%. The detergent, particularly a mild one that is nondenaturing, can act to solubilize the sample. Detergents may be ionic or nonionic. Examples of nonionic detergents include triton, such as the Triton® X series (Triton® X-100 t-Oct-C_6H_4-$(OCH_2$-$CH_2)_xOH$, x=9-10, Triton® X-100R, Triton® X-114 x=7-8), octyl glucoside, polyoxyethylene(9)dodecyl ether, digitonin, IGEPAL® CA630 octylphenyl polyethylene glycol, n-octyl-beta-D-glucopyranoside (betaOG), n-dodecyl-beta, Tween® 20 polyethylene glycol

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sorbitan monolaurate, Tween® 80 polyethylene glycol sorbitan monooleate, polidocanol, n-dodecyl beta-D-maltoside (DDM), NP-40 nonylphenyl polyethylene glycol, C12E8 (octaethylene glycol n-dodecyl monoether), hexaethyleneglycol mono-n-tetradecyl ether (C14E06), octyl-beta-thioglucopyranoside (octyl thioglucoside, OTG), Emulgen, and polyoxyethylene 10 lauryl ether (C12E10). Examples of ionic detergents (anionic or cationic) include deoxycholate, sodium dodecyl sulfate (SDS), N-lauroylsarcosine, and cetyltrimethylammoniumbromide (CTAB). A zwitterionic reagent may also be used in the purification schemes of the present invention, such as Chaps, zwitterion 3-14, and 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulf-onate. It is contemplated also that urea may be added with or without another detergent or surfactant.

Lysis or homogenization solutions may further contain other agents, such as reducing agents. Examples of such reducing agents include dithiothreitol (DTT), .beta.-mercaptoethanol, DTE, GSH, cysteine, cysteamine, tricarboxyethyl phosphine (TCEP), or salts of sulfurous acid.

Size selection of the nucleic acids may be performed to remove very short fragments or very long fragments. The nucleic acid fragments can be partitioned into fractions comprising a desired number of fragments using any suitable method known in the art. In some embodiments, the fractions include about 1, 2, 5, 10, 50, 100, 250, 500, 750, 1000, 1500, 2000, 5000 or 10,000 molecules. Suitable methods to limit the fragment size in each fragment are known in the art. In various embodiments of the invention, the fragment size is limited to 1, 2, 3, 4, 5, 7, 10, 12, 15, 20, 25, 30, 50, 100 kb or longer.

In various embodiments, the fragments are amplified after partitioning. Any amplification method known in the art may be used. Examples of amplification techniques that can be used include, but are not limited to, quantitative PCR, quantitative fluorescent PCR (QF-PCR), multiplex fluorescent PCR (MF-PCR), real time PCR (RTPCR), single cell PCR, restriction fragment length polymorphism PCR (PCR-RFLP), PCK-RFLPIRT-PCR-IRFLP, hot start PCR, nested PCR, in situ polonony PCR, in situ rolling circle amplification (RCA), bridge PCR, picotiter PCR and emulsion PCR. Other suitable amplification methods include the liguse chain reaction (LCR), transcription amplification, self-sustained sequence replication, selective amplification of target polynucleotide sequences, consensus sequence primed polymerase chain reaction (CP-PCR), arbitrarily primed polymerase chain reaction (AP-PCR), degenerate oligonucleotide-primed PCR (DOP-PCR) and nucleic acid based sequence amplification

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(NABSA). Other amplification methods that can be used herein include those described in U.S. Patent Nos. 5,242,794; 5,494,810; 4,988,617; and 6,582,938.

In particular embodiments, PCR is used to amplify DNA molecules after they are dispensed into individual partitions. In some cases, one or more specific priming sequences within amplification adapters are utilized for PCR amplification. The amplification adapters may be ligated to fragmented DNA molecules before or after dispensing into individual partitions. Polynucleotides comprising amplification adapters with suitable priming sequences on both ends can be PCR amplified exponentially. Typically, polynucleotides with only one suitable priming sequence, for example due to imperfect ligation efficiency of amplification adapters comprising priming sequences would only undergo linear amplification. Further, polynucleotides can be eliminated from amplification, for example PCR amplification, all together, if no adapters comprising suitable priming sequences are ligated. In some embodiments, the number of PCR cycles vary between 10-30, but can be as low as 9, 8, 7, 6, 5, 4, 3, 2 or less or as high as 40, 45, 50, 55, 60 or more. As a result, exponentially amplifiable fragments carrying amplification adapters with a suitable priming sequence can be present in much higher (1000 fold or more) concentration compared to linearly amplifiable or un-amplifiable fragments, after a PCR amplification. Benefits of PCR, as compared to whole genome amplification techniques (such as amplification with randomized primers or Multiple Displacement Amplification using phi29 polymerase) include, but are not limited to a more uniform relative sequence coverage - as each fragment can be copied at most once per cycle and as the amplification is controlled by thermocycling program, a substantially lower rate of forming chimeric molecules than for example MDA (**Lasken et al, 2007, BMC Biotechnology**) - as chimeric molecules pose significant challenges for accurate sequence assembly by presenting nonbiological sequences in the assembly graph, which may result in higher rate of misassemblies or highly ambigious and fragmented assembly, reduced sequence specific biases that may result from binding of randomized primers commonly used in MDA versus using specific priming sites with a specific sequence, a higher reproducibility in the amount of final amplified DNA product, which can be controlled by selection of the number of PCR cycles, and a higher fidelity in replication with the polymerases that are commonly used in PCR as compared to common whole genome amplification techniques known in the art.

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In some embodiments, end repair is performed to generate blunt end 5' phosphorylated nucleic acid ends using commercial kits, such as those available from Epicentre Biotechnologies (Madison, WI).

An adapter oligonucleotide includes any oligonucleotide having a sequence, at least a portion of which is known, that can be joined to a target polynucleotide. Adapter oligonucleotides can comprise DNA, RNA, nucleotide analogues, non-canonical nucleotides, labeled nucleotides, modified nucleotides, or combinations thereof. Adapter oligonucleotides can be single-stranded, double-stranded, or partial duplex. In general, a partial-duplex adapter comprises one or more single-stranded regions and one or more double-stranded regions. Double-stranded adapters can comprise two separate oligonucleotides hybridized to one another (also referred to as an "oligonucleotide duplex"), and hybridization may leave one or more blunt ends, one or more 3′ overhangs, one or more 5′ overhangs, one or more bulges resulting from mismatched and/or unpaired nucleotides, or any combination of these. In some embodiments, a single-stranded adapter comprises two or more sequences that are able to hybridize with one another. When two such hybridizable sequences are contained in a single-stranded adapter, hybridization yields a hairpin structure (hairpin adapter). When two hybridized regions of an adapter are separated from one another by a non-hybridized region, a "bubble" structure results. Adapters comprising a bubble structure can consist of a single adapter oligonucleotide comprising internal hybridizations, or may comprise two or more adapter oligonucleotides hybridized to one another. Internal sequence hybridization, such as between two hybridizable sequences in an adapter, can produce a double-stranded structure in a single-stranded adapter oligonucleotide. Adapters of different kinds can be used in combination, such as a hairpin adapter and a double-stranded adapter, or adapters of different sequences. Hybridizable sequences in a hairpin adapter may or may not include one or both ends of the oligonucleotide. When neither of the ends are included in the hybridizable sequences, both ends are "free" or "overhanging." When only one end is hybridizable to another sequence in the adapter, the other end forms an overhang, such as a 3′ overhang or a 5′ overhang. When both the 5′-terminal nucleotide and the 3′-terminal nucleotide are included in the hybridizable sequences, such that the 5′-terminal nucleotide and the 3′-terminal nucleotide are complementary and hybridize with one another, the end is referred to as "blunt." Different adapters can be joined to target

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polynucleotides in sequential reactions or simultaneously. For example, the first and second adapters can be added to the same reaction. Adapters can be manipulated prior to combining with target polynucleotides. For example, terminal phosphates can be added or removed.

Adapters can contain one or more of a variety of sequence elements, including but not limited to, one or more amplification primer annealing sequences or complements thereof, one or more sequencing primer annealing sequences or complements thereof, one or more barcode sequences, one or more common sequences shared among multiple different adapters or subsets of different adapters, one or more restriction enzyme recognition sites, one or more overhangs complementary to one or more target polynucleotide overhangs, one or more probe binding sites (e.g. for attachment to a sequencing platform, such as a flow cell for massive parallel sequencing, such as developed by Illumina, Inc.), one or more random or near-random sequences (e.g. one or more nucleotides selected at random from a set of two or more different nucleotides at one or more positions, with each of the different nucleotides selected at one or more positions represented in a pool of adapters comprising the random sequence), and combinations thereof. Two or more sequence elements can be non-adjacent to one another (e.g. separated by one or more nucleotides), adjacent to one another, partially overlapping, or completely overlapping. For example, an amplification primer annealing sequence can also serve as a sequencing primer annealing sequence. Sequence elements can be located at or near the 3′ end, at or near the 5′ end, or in the interior of the adapter oligonucleotide. When an adapter oligonucleotide is capable of forming secondary structure, such as a hairpin, sequence elements can be located partially or completely outside the secondary structure, partially or completely inside the secondary structure, or in between sequences participating in the secondary structure. For example, when an adapter oligonucleotide comprises a hairpin structure, sequence elements can be located partially or completely inside or outside the hybridizable sequences (the "stem"), including in the sequence between the hybridizable sequences (the "loop"). In some embodiments, the first adapter oligonucleotides in a plurality of first adapter oligonucleotides having different barcode sequences comprise a sequence element common among all first adapter oligonucleotides in the plurality. In some embodiments, all second adapter oligonucleotides comprise a sequence element common among all second adapter oligonucleotides that is different from the common sequence element shared by the first adapter oligonucleotides. A difference in sequence elements can be any such that at least a portion of different adapters do not completely align, for example,

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due to changes in sequence length, deletion or insertion of one or more nucleotides, or a change in the nucleotide composition at one or more nucleotide positions (such as a base change or base modification). In some embodiments, an adapter oligonucleotide comprises a 5′ overhang, a 3′ overhang, or both that is complementary to one or more target polynucleotides. Complementary overhangs can be one or more nucleotides in length, including but not limited to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more nucleotides in length. Complementary overhangs may comprise a fixed sequence. Complementary overhangs may comprise a random sequence of one or more nucleotides, such that one or more nucleotides are selected at random from a set of two or more different nucleotides at one or more positions, with each of the different nucleotides selected at one or more positions represented in a pool of adapters with complementary overhangs comprising the random sequence. In some embodiments, an adapter overhang is complementary to a target polynucleotide overhang produced by restriction endonuclease digestion. In some embodiments, an adapter overhang consists of an adenine or a thymine.

Adapter oligonucleotides can have any suitable length, at least sufficient to accommodate the one or more sequence elements of which they are comprised. In some embodiments, adapters are about, less than about, or more than about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90, 100, 200, or more nucleotides in length.

The terms "joining" and "ligation" as used herein, with respect to two polynucleotides, such as an adapter oligonucleotide and a target polynucleotide, refers to the covalent attachment of two separate polynucleotides to produce a single larger polynucleotide with a contiguous backbone. Methods for joining two polynucleotides are known in the art, and include without limitation, enzymatic and non-enzymatic (e.g. chemical) methods. Examples of ligation reactions that are non-enzymatic include the non-enzymatic ligation techniques described in U.S. Pat. Nos. 5,780,613 and 5,476,930, which are herein incorporated by reference. In some embodiments, an adapter oligonucleotide is joined to a target polynucleotide by a ligase, for example a DNA ligase or RNA ligase. Multiple ligases, each having characterized reaction conditions, are known in the art, and include, without limitation NAD^+-dependent ligases including tRNA ligase, Taq DNA ligase, *Thermus filiformis* DNA ligase, *Escherichia coli* DNA ligase, Tth DNA ligase, *Thermus scotoductus* DNA ligase (I and II), thermostable ligase, Ampligase thermostable DNA ligase, VanC-type ligase, 9° N DNA Ligase, Tsp DNA ligase, and novel ligases discovered by

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bioprospecting; ATP-dependent ligases including T4 RNA ligase, T4 DNA ligase, T3 DNA ligase, T7 DNA ligase, Pfu DNA ligase, DNA ligase I, DNA ligase III, DNA ligase IV, and novel ligases discovered by bioprospecting; and wild-type, mutant isoforms, and genetically engineered variants thereof. Ligation can be between polynucleotides having hybridizable sequences, such as complementary overhangs. Ligation can also be between two blunt ends. Generally, a 5′ phosphate is utilized in a ligation reaction. The 5′ phosphate can be provided by the target polynucleotide, the adapter oligonucleotide, or both. 5′ phosphates can be added to or removed from polynucleotides to be joined, as needed. Methods for the addition or removal of 5′ phosphates are known in the art, and include without limitation enzymatic and chemical processes. Enzymes useful in the addition and/or removal of 5′ phosphates include kinases, phosphatases, and polymerases. In some embodiments, both of the two ends joined in a ligation reaction (e.g. an adapter end and a target polynucleotide end) provide a 5′ phosphate, such that two covalent linkages are made in joining the two ends. In some embodiments, only one of the two ends joined in a ligation reaction (e.g. only one of an adapter end and a target polynucleotide end) provides a 5′ phosphate, such that only one covalent linkage is made in joining the two ends. In some embodiments, only one strand at one or both ends of a target polynucleotide is joined to an adapter oligonucleotide. In some embodiments, both strands at one or both ends of a target polynucleotide are joined to an adapter oligonucleotide. In some embodiments, 3′ phosphates are removed prior to ligation. In some embodiments, an adapter oligonucleotide is added to both ends of a target polynucleotide, wherein one or both strands at each end are joined to one or more adapter oligonucleotides. When both strands at both ends are joined to an adapter oligonucleotide, joining can be followed by a cleavage reaction that leaves a 5′ overhang that can serve as a template for the extension of the corresponding 3′ end, which 3′ end may or may not include one or more nucleotides derived from the adapter oligonucleotide. In some embodiments, a target polynucleotide is joined to a first adapter oligonucleotide on one end and a second adapter oligonucleotide on the other end. In some embodiments, two ends of a target polynucleotide are joined to the opposite ends of a single adapter oligonucleotide. In some embodiments, the target polynucleotide and the adapter oligonucleotide to which it is joined comprise blunt ends. In some embodiments, separate ligation reactions are carried out for each sample, using a different first adapter oligonucleotide comprising at least one barcode sequence for each sample, such that no barcode sequence is joined to the target polynucleotides of more

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than one sample. A target polynucleotide that has an adapter oligonucleotide joined to it is considered "tagged" by the joined adapter.

In some embodiments, joining of an adapter to a target polynucleotide produces a joined product polynucleotide having a 3′ overhang comprising a nucleotide sequence derived from the adapter.

In some embodiments, after joining at least one adapter oligonucleotide to a target polynucleotide, the 3′ end of one or more target polynucleotides is extended using the one or more joined adapter oligonucleotides as template. For example, an adapter comprising two hybridized oligonucleotides that is joined to only the 5′ end of a target polynucleotide allows for the extension of the unjoined 3′ end of the target using the joined strand of the adapter as template, concurrently with or following displacement of the unjoined strand. Both strands of an adapter comprising two hybridized oligonucleotides may be joined to a target polynucleotide such that the joined product has a 5′ overhang, and the complementary 3′ end can be extended using the 5′ overhang as template. As a further example, a hairpin adapter oligonucleotide can be joined to the 5′ end of a target polynucleotide. In some embodiments, the 3′ end of the target polynucleotide that is extended comprises one or more nucleotides from an adapter oligonucleotide. For target polynucleotides to which adapters are joined on both ends, extension can be carried out for both 3′ ends of a double-stranded target polynucleotide having 5′ overhangs. This 3′ end extension, or "fill-in" reaction, generates a complementary sequence, or "complement," to the adapter oligonucleotide template that is hybridized to the template, thus filling in the 5′ overhang to produce a double-stranded sequence region. Where both ends of a double-stranded target polynucleotide have 5′ overhangs that are filled in by extension of the complementary strands' 3′ ends, the product is completely double-stranded. Extension can be carried out by any suitable polymerase known in the art, such as a DNA polymerase, many of which are commercially available. DNA polymerases can comprise DNA-dependent DNA polymerase activity, RNA-dependent DNA polymerase activity, or DNA-dependent and RNA-dependent DNA polymerase activity. DNA polymerases can be thermostable or non-thermostable. Examples of DNA polymerases include, but are not limited to, Taq polymerase, Tth polymerase, Tli polymerase, Pfu polymerase, Pfutubo polymerase, Pyrobest polymerase, Pwo polymerase, KOD polymerase, Bst polymerase, Sac polymerase, Sso polymerase, Poc

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polymerase, Pab polymerase, Mth polymerase, Pho polymerase, ES4 polymerase, VENT polymerase, DEEPVENT polymerase, EX-Taq polymerase, LA-Taq polymerase, Expand polymerases, Platinum Taq polymerases, Hi-Fi polymerase, Tbr polymerase, Tfl polymerase, Tru polymerase, Tac polymerase, Tne polymerase, Tma polymerase, Tih polymerase, Tfi polymerase, Klenow fragment, and variants, modified products and derivatives thereof 3′ end extension can be performed before or after pooling of target polynucleotides from independent samples.

In some embodiments, the fill-in reaction is followed by or performed as part of amplification of one or more target polynucleotides using a first primer and a second primer, wherein the first primer comprises a sequence that is hybridizable to at least a portion of the complement of one or more of the first adapter oligonucleotides, and further wherein the second primer comprises a sequence that is hybridizable to at least a portion of the complement of one or more of the second adapter oligonucleotides. Each of the first and second primers may be of any suitable length, such as about, less than about, or more than about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 90, 100, or more nucleotides, any portion or all of which may be complementary to the corresponding target sequence (e.g. about, less than about, or more than about 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, or more nucleotides). "Amplification" refers to any process by which the copy number of a target sequence is increased. Methods for primer-directed amplification of target polynucleotides are known in the art, and include without limitation, methods based on the polymerase chain reaction (PCR). Conditions favorable to the amplification of target sequences by PCR are known in the art, can be optimized at a variety of steps in the process, and depend on characteristics of elements in the reaction, such as target type, target concentration, sequence length to be amplified, sequence of the target and/or one or more primers, primer length, primer concentration, polymerase used, reaction volume, ratio of one or more elements to one or more other elements, and others, some or all of which can be altered. In general, PCR involves the steps of denaturation of the target to be amplified (if double stranded), hybridization of one or more primers to the target, and extension of the primers by a DNA polymerase, with the steps repeated (or "cycled") in order to amplify the target sequence. Steps in this process can be optimized for various outcomes, such as to enhance yield, decrease the formation of spurious products, and/or increase or decrease specificity of primer annealing.

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Methods of optimization are well known in the art and include adjustments to the type or amount of elements in the amplification reaction and/or to the conditions of a given step in the process, such as temperature at a particular step, duration of a particular step, and/or number of cycles. In some embodiments, an amplification reaction comprises at least 5, 10, 15, 20, 25, 30, 35, 50, or more cycles. In some embodiments, an amplification reaction comprises no more than 5, 10, 15, 20, 25, 35, 50, or more cycles. Cycles can contain any number of steps, such as 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 or more steps. Steps can comprise any temperature or gradient of temperatures, suitable for achieving the purpose of the given step, including but not limited to, 3′ end extension (e.g. adapter fill-in), primer annealing, primer extension, and strand denaturation. Steps can be of any duration, including but not limited to about, less than about, or more than about 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 70, 80, 90, 100, 120, 180, 240, 300, 360, 420, 480, 540, 600, or more seconds, including indefinitely until manually interrupted. Cycles of any number comprising different steps can be combined in any order. In some embodiments, different cycles comprising different steps are combined such that the total number of cycles in the combination is about, less that about, or more than about 5, 10, 15, 20, 25, 30, 35, 50, or more cycles. In some embodiments, amplification is performed following the fill-in reaction. Amplification can be performed before or after pooling of target polynucleotides from independent samples.

In some embodiments, target polynucleotides from independent samples are pooled after the joining step. Pooling can be performed immediately after the joining step, or following one or more intervening steps between joining and pooling. Pools can comprise any fraction of the total target polynucleotides from a joining reaction, including the whole reaction volume. Samples can be pooled evenly or unevenly. Target polynucleotides can be further processed before or after pooling, for example to purify desired products or eliminate undesired products. Pools can comprise polynucleotides from any number of independent samples, such as at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24, 28, 32, 36, 40, 50, 60, 70, 80, 90, 100, 128, 192, 384, 500, 1000 or more samples. In some embodiments, target polynucleotides are pooled based on the barcodes to which they are joined. In some embodiments, target polynucleotides from independent samples are pooled such that all four bases are evenly represented at one or more positions along the barcode, among barcodes included in the pool. In some embodiments, target polynucleotides from independent samples are pooled such that all four bases are evenly

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represented at every position along the barcode, among barcodes included in the pool. Where only one barcode is joined to polynucleotides of each sample, samples can be pooled in multiples of four in order to represent all four bases at one or more positions along the barcode evenly, for example 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 96, 128, 192, 256, 384, and so on. Where two barcodes are included in the joining reaction for each sample, such as two different first adapter oligonucleotides or one first adapter oligonucleotide and one second adapter oligonucleotide each having barcodes, samples can be pooled in multiples of two in order to evenly represent all four bases at one or more positions along the barcode, for example 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 48, 64, 96, 128, 256, 384, and so on. All combinations of the number of barcodes included in the joining reaction for target polynucleotides from each sample and the multiples in which samples are pooled in order to evenly represent all four nucleotides at one or more positions along the barcode are contemplated by the methods of the invention.

In some embodiments, pooling of target polynucleotides is followed by sequencing one or more polynucleotides in the pool. Sequencing processes are generally template dependent. Nucleic acid sequence analysis that employs template dependent synthesis identifies individual bases, or groups of bases as they are added during a template mediated synthesis reaction, such as a primer extension reaction, where the identity of the base is complementary to the template sequence to which the primer sequence is hybridized during synthesis. Other such processes include ligation driven processes, where oligonucleotides or polynucleotides are complexed with an underlying template sequence, in order to identify the sequence of nucleotides in that sequence. Typically, such processes are enzymatically mediated using nucleic acid polymerases, such as DNA polymerases, RNA polymerases, reverse transcriptases, and the like, or other enzymes such as in the case of ligation driven processes, e.g., ligases.

Amplification adapters may be attached to the fragmented nucleic acid. Amplification adapters may be attached prior or subsequent to partitioning the nucleic acid. Adapters may be commercially obtained, such as from Integrated DNA Technologies (Coralville, IA). In certain embodiments, the adapter sequences are attached to the template nucleic acid molecule with an enzyme. The enzyme may be a ligase or a polymerase. The ligase may be any enzyme capable of ligating an oligonucleotide (RNA or DNA) to the template nucleic acid molecule. Suitable

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ligases include T4 DNA ligase and T4 RNA ligase (such ligases are available commercially, from New England Biolabs). The polymerase may be any enzyme capable of adding nucleotides to the 3' and the 5' terminus of template nucleic acid molecules. Alternatively, amplification adapters can be added to the target polynucleotide of interest via an intermediate polynucleotide that is comprised of two or more amplification adapters.

The adapters can be added by ligating a target polynucleotide to an intermediate polynucleotide comprised of compatible adapter ends. The compatible adapter ends can be kept under ligation conditions usually including a ligase, which facilitates the nucleic acid ends to intermolecularly ligate, thereby producing a circularized nucleic acid molecule. In some embodiments, the intermediate polynucleotide comprises a cleavable adapter thereby allowing the transformation of the circular polynucleotide into a linearized molecule with adapters located at each end (Figure 6 A, B,C). The cleavable adapter may comprise a restriction endonuclease recognition site specific for a restriction endonuclease. The intermediate polynucleotide may comprise a cleavable adapter, for example a nicked adapter. For another example, the adaptor may comprise a cleavable adapter. The cleavable site in the adapter may be a deoxyuridine nucleotide which can be cleaved by uracil DNA glycosylase (UDG) and an AP-lyase. The cleavable adapter may comprise a 3' phosphorothiolate linkage cleaved by a metal ion, included but not limited to Ag^{1}, Hg^{2+} or Cu^{2+}. The cleavage reaction may be at a pH of at least about 5 to 9. The temperature for the cleavage reaction may be selected at a temperature of about 22° to 37° degrees Celsius.

There are several ligation methods that can be employed to attach the adapters to a target polynucleotide. Ligation methods can include directional cloning, which uses "sticky ends". Sticky can be are generated by treating a polynucleotide with restriction enzymes to create complementary over-hanging ends. In the presence of a ligase complementary over-hanging ends may be ligated together. Ligation can be performed using non-directional cloning methods by the use of "blunt ends". In certain embodiments, following fragmentation, the ends of the fragments may be repaired, trimmed (e.g. using an exonuclease), or filled (e.g., using a polymerase and dNTPs), to form blunt ends. The blunt ends may have phosphates at the 5' ends and a hydroxyl at each 3' end of the target polynucleotide and the intermediate polynucleotide; alternatively, one or more 5' ends may lack a 5' phosphate.. In the presence of a ligase enzyme, the blunt ends phosphates at the 5' ends and hydroxyl at the 3' ends may be ligated together. In

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certain embodiments, single strand overhangs can be removed to form blunt ends by the use of particular exonucleases that cut free single strand nucleic acids but do not cut double strand nucleic acids. Examples of such exonucleases include, but are not limited to: Exo VII, Exonuclease I, Exonuclease T, Lambda Exonuclease, and T7 Exonuclease.

Alternatively, one could ligate the target polynucleotide and the intermediate polynucleotide using T-A end cloning method. T-A cloning is a subcloning technique that does not use restriction enzymes generated sticky ends. Upon generating blunt ends, the ends can be treated with a polymerase and dATP to form a template independent addition to the 3'-end and the 5'-end of the fragments, thus producing a single A overhanging. The T-A cloning technique relies on the ability of adenine (A) and thymine (T) to complementary base pair on different DNA fragments to hybridize and, in the presence of ligase to form a circular polynucleotide. Alternatively, an investigator can use PCR generated fragments that already contain an "A" overhang by employing a DNA polymerase that leaves an adenine "A" nucleotide at the 3'end during amplification, such as Taq DNA polymerase or equivalents. Thermostable polymerases containing extensive 3´ to 5´ exonuclease activity are not suitable for this purpose, as they do not leave the 3´ adenine-overhangs. The probability probability of Taq DNA polymerase adding the terminal adenosine overhang may be increased by usinf PCR primers that have guanines at the 5' end. In another example, thymines (T) can be added using a dideoxythymidine triphosphate (ddTTP) and a terminal transferase. This tailing leaves the vector with a single 3'-overhanging thymine residue on each blunt end. Similarly, one could use G-C cloning in the presence of ligase to form a circular polynucleotide. Commercialized kits with pre-prepared reagents and terminal transferases are available T-A or G-C cloning and well known in the art. T-A/G-C cloning are best utilized when directional cloning is not a requirement.

According to one method the target polynucleotide can be ligated by PCR to the intermediate polynucleotide, by generating a circularized form using a topoisomerase using an intermediate ploynucleotide with adapters. In some embodiments, the adapters containa 5´-(C/T)CCTT-3' recognition site at the 3' ends. The intermediate polynucleotide may contain a topoisomerase enzyme covalently attached to the recognition site generating an intermediate polynucleotide-TOPO modified molecule. The intermediate-TOPO polynucleotide may be mixed with target polynucleotides generated by PCR, allowing for recognition of the intermediate polynucleotide-TOPO 3' by the 5' ends. The strands may be covalently linked by

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the topoisomerase to form a circular polynucleotide.

In some applications, amplification adapters are added to a target polynucleotide. The target polynucleotide can be single or double stranded. accordingly, the adapters can be either single stranded or double stranded depending on whether the target polynucleotide employed is single or double stranded. A single strand target template may originate from RNA or DNA. CircLigase™ II is a thermostable ssDNA ligase that catalyzes intramolecular ligation of ssDNA templates having a 5′-phosphate and a 3′-hydroxyl group (Epicentre). The target polynucleotide can be further obtained from fragmentation of large DNA or RNA molecules, PCR amplification or from cloned vectors containing the target sequence of interest, such as a commercial cloned gene expression libraries of RNA or DNA.

In some embodiments of the invention, end markers/adapters can be attached by circularizing long fragments and using a pool of circularization adapters that contain matched pairs of known sequences that are ligated to opposite ends of long fragments. Such paired adapters may be attached to long fragments allowing for validation of long fragment assembly, for example by checking whether a correctly matching pair of adapters is found on opposite ends of a reconstructed fragment (Figures 5A-B).

The ratio of the target polynucleotide and the intermediate polynucleotide within the circular polynucleotide may be varied. In such cases, reiterative steps described above may be performed using multiple cloning site identification elements or nicked identification elements contained within the adapters. Accordingly, a circular polynucleotide containing more than a 1:1 target polynucleotide: intermediate polynucleotide ratio may be generated. In some embodiments, target polynucleotide and the intermediate polynucleotide are present at a 1:2, 1:3, 1:4, 1:6, 1:8, 1:10 or 1:20 ratio.

Adapters containing particular identification elements may be used and may be useful in downstream analysis of the target polynucleotide. More specifically, one could use adapters that contain a unique tag identification element. Tags can include, but are not limited to, for example, a fluorophore, a quantum dot, a dendrimer, a nanowire, a bead, a peptide, a protein, a magnetic bead, a methyl group, a methyltransferase, a non-cutting restriction enzyme, a zinc-finger protein, an antibody, a transcription factor, a DNA binding protein, a hairpin polyamide, a triplex-forming oligodeoxynucleotide, a peptide nucleic acid, a nucleic acid or the equivalents thereof. The methods may include the use of two or more different tags, and a single molecule

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may accordingly include multiple tags. In some embodiments, a unique tag can be a synthetic or a unique sequence of natural nucleotides that allows for easy identification of the target polynucleotide within a complicated pool of oligonucleotides containing various sequences. In certain embodiments, unique identifiers are attached to the nucleic acid fragments prior to attaching the adapter sequences. In a some embodiments, unique marker identifiers are contained within adapter sequences such that the unique marker sequence is partially contained in the sequencing reads obtained from boundaries of long fragments. This ensures that homologous fragments can be detected based upon the unique markers that are attached to each fragment, thus further providing for unambiguous reconstruction of a consensus sequence. Homologous fragments may occur for example by chance due to genomic repeats, two fragments originating homologous chromosomes, or fragments originating from overlapping locations on the same chromosome. Such fragments may be discarded to ensure that long fragment assembly can be computed unambiguously. The markers may be attached as described above for the adapter sequences. The markers may be included in the adapter sequences.

In some cases, samples may need multiple additional manipulations. An adapter, such as one described above, with a multiple cloning site identification element may be used for additional steps. A multiple cloning site, is a short segment of DNA which contains many,for example up to ~20 restriction enzyme recognition sites. This feature in the adapter can be used for iterative rounds of molecular cloning or subcloning to allow for insertion of a piece of DNA or several pieces of DNA into the multiple cloning site identification elements. This method can be used to vary the ratio of the target polynucleotide and adapter sequences. Alternatively, it can be used to tailor an adapter sequence with specific identification elements within the adapter. In another embodiment, one can modify or concatenate particular identification elements comprising the adapter using nicked or single nucleotide regions site contained in the adapter identification element.

In some applications, parallel amplification of the target polynucleotides is desirable. End adapters with a universal priming site for a DNA polymerase may be utilized for parallel amplification. With adapters located at each end, the target polynucleotides can be simultaneously amplified using universal primers that are sufficiently complementary to a universal priming site allowing for hybridization to upstream and downstream universal priming

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sequences in the adapters.

In some instances, more controlled amplification of a target polynucleotide may be facilitated, by using an adapter comprising a specific recognition site for a transcription factor. Specifically, an adapter containing a specific transcriptional promoter sequence that is recognized by a particular polymerase can be utilized. Examples of such polymerases include, but are not limited to T7, T3, SP6, or homologues thereof. . Such methods can further be employed when it is desirable to transform a single stranded molecule into a double stranded molecule.

In some embodiments, the adapter sequences can contain a molecular binding site identification element to facilitate identification and isolation of the target polynucleotide for downstream applications. Molecular binding as affinity mechanism allows for the interaction between two molecules to result in a stable association complex. Molecules that can participate in molecular binding reactions include: proteins, nucleic acids, carbohydrates, lipids, and small organic molecules such as ligands, peptides or drugs.

One example of protein-protein molecular binding is affinity mechanism is the avidin-biotin system. Avidin, has a high binding affinity for the molecule, biotin. A biotinylated adapter may be used in the intermediate polynucleotide by synthesizing the adapter sequence with biotinyalted-dNTPs, which are well known in the art. Following the ligation of the target polynucleotide to the biotinaltyed adapters, the biotinaltyed target polynucleotide can be captured using streptavidin magnetic beads. In another embodiment, the molecular binding site is selected from the group consisting of, digoxigenin, a hapten, a ligand, a peptide and a nucleic acid.

When a nucleic acid molecular binding site is used as part of the adapter, it can be used to employ selective hybridization to isolate the target sequence. Selective hybridization may restrict substantial hybridization to target polynucleotides containing the adapter with the molecular binding site and capture nucleic acids, which are sufficiently complementary to the molecular binding site. Thus, through "selective hybridization" one can detect the presence of the target polynucleotide in an unpure sample containing a pool of many polynucleotides. An example of a nucleotide-nucleotide selective hybridization isolation system comprises a system with several

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capture nucleotides, which are complementary sequences to the molecular binding identification elements, and are optionally immobilized to a solid support. In other embodiments, the capture polynucleotides could be complementary to the target sequences itself or a barcode or unique tag contained within the adapter. The capture polynucleotides can be immobilized to various solid supports, such as inside of a well of a plate, mono-dispersed spheres, microarrays, or any other suitable support surface known in the art. The hybridized complementary adapter polynucleotides attached on the solid support can be isolated, by washing away the undesirable non-binding polynucleotides, leaving the desirable target polynucleotides behind. If complementary adapter molecules are fixed to paramagnetic spheres or similar bead technology for isolation, then spheres can then be mixed in a tube together with the target polynucleotide containing the adapters. When the adapter sequences have been hybridized with the complementary sequences fixed to the spheres, undesirable molecules can be washed away while spheres are kept in the tube with a magnet or similar agent. The desired target molecules can be subsequently released by increasing the temperature, changing the pH, or by using any other suitable elution method known in the art.

In some embodiments, the adapter comprises a nicked adapter. Accordingly, the adapter may contain a single-stranded region within a predominantly double stranded adapter. Such single-stranded regions can take the form of gaps interior to a duplex, or alternatively can be located at the ends forming terminal single-stranded regions. Nicked adapters can be made by several methods. One method is by the use of nickases. Nickases are endonucleases that recognize a specific recognition sequence in double-stranded nucleic acid molecules, and cut one strand at a specific location relative to the recognition sequence, thereby giving rise to single-stranded gaps in duplex DNA. The nicking enzyme may nick one or more of a DNA duplex, an RNA/DNA hybrid and an RNA duplex. Three major sources obtaining sequence-specific DNA nicking enzymes include nicking enzymes from Chlorella algae viruses, from which N.CviQXI (CviNY2A) and N.CviPII (CviNYSI) were originally found (Zhang Y. et al. Virology, 240:366-375 (1998); Xia Y. et al. Nucl. Acids Res. 16:9477-9487 (1988)),bacteria in which N.BstNBI and N.BstSEI were discovered (Morgan R. D. et al. Biol. Chem. 381:1123-5 (2000); Abdurashitov, et al., Mol. Biol. (Mosk) 30:1261-1267 (1996)), and enzymes generated by protein engineering from existing Type IIA restriction enzymes. Examples of nickases that can be used include but are not limited to Nb.BsrDI, Nb.BsmI, Nt.BbvCI, Nb.Bbv.Nb.BtsI and Nt.BstNBI.

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Site-specific DNA nicking endonucleases are used to form the single-stranded regions by nicking at the boundaries of the single-strand regions, either on opposing DNA strands (creating terminal single-stranded regions) or on the same strand (creating a single-strand gap). The skilled artisan will appreciate that any other site-specific nicking enzyme would give equivalent results. In other aspect of the invention, a nicked adapter can be made by incorporating uracil into one strand of an adaptor sequence and nicking is accomplished subsequently by using uracil-DNA glycosylase which acts by liminating uracil from DNA molecules by cleaving the N-glycosylic bond.

In other aspects of the invention, nicked regions can also be used for several applications including: joining, detecting, cutting and purifying the unpaired adapter regions containing the nick site. Such application can be carried out by restriction enzymes which preferentially cleave single stranded nucleic acids. In one aspect the nicked adapter can used to make a preferred cleavage site for a restriction endonuclease thereby linearizing the circularized polynucleotide. In general, various restriction enzymes can cut single stranded nucleic acids under the correct conditions. Examples of restriction endonucleases that preferentially cleave single-stranded nucleotide regions include, but are not limited, HhaI and CfoI, or equivalents thereof. Alternatively, a general restriction enzyme can be employed to cleave single stranded nucleic acids.

Single-stranded nicked regions within the adapter can facilitate the assembly of multiple nucleic acid fragments and intermediate polynucleotides. This is useful in the construction of intermediate polynucleotide with particular adapter identification elements discussed herein. These applications include strand displacement DNA amplification. Strand displacement DNA amplification, includes introducing a specific nick in the target polynucleotide by a nicking enzyme. Strand displacement DNA polymerase or other equivalent DNA polymerases can initiate a new strand synthesis at the nick and displace the nicked strand, resulting in linear DNA amplification products.

Nicked DNA can also be used to facilitate recombinant DNA technology for gene fragment assembly. Staggered nicks can be introduced in top and bottom strands to generate large cohesive ends (e.g. 8 to 20 nt long). The complementary cohesive ends can anneal together and bypass the ligation step. Nicking enzymes can also be used in preparation of ssDNA ends for

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DNA fragment assembly in linear or circular form. Strand-specific DNA nicking enzymes can be used to form single-stranded regions by nicking at the boundaries of the single-stranded regions, either on opposing DNA strands, creating terminal single-stranded regions, or on the same strand, creating single-stranded gap regions. Duplex DNA containing a single nick exhibits altered migration through agarose or ploycrylamide gel-based assays. The altered migration characteristic can be used for isolation and purification of the target polynucleotide using standard nucleic acid purification techniques known in the art.

As used herein, the term "barcode" refers to a known nucleic acid sequence that allows some feature of a polynucleotide with which the barcode is associated to be identified. In some embodiments, the feature of the polynucleotide to be identified is the sample from which the polynucleotide is derived. In some embodiments, barcodes are at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, or more nucleotides in length. In some embodiments, barcodes are shorter than 10, 9, 8, 7, 6, 5, or 4 nucleotides in length. In some embodiments, barcodes associated with some polynucleotides are of different length than barcodes associated with other polynucleotides. In general, barcodes are of sufficient length and comprise sequences that are sufficiently different to allow the identification of samples based on barcodes with which they are associated. In some embodiments, a barcode, and the sample source with which it is associated, can be identified accurately after the mutation, insertion, or deletion of one or more nucleotides in the barcode sequence, such as the mutation, insertion, or deletion of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more nucleotides. In some embodiments, each barcode in a plurality of barcodes differ from every other barcode in the plurality at least two nucleotide positions, such as at least 2, 3, 4, 5, 6, 7, 8, 9, 10, or more positions. In some embodiments, both a first adapter and a second adapter comprise at least one of a plurality of barcode sequences. In some embodiments, barcodes for second adapter oligonucleotides are selected independently from barcodes for first adapter oligonucleotides. In some embodiments, first adapter oligonucleotides and second adapter oligonucleotides having barcodes are paired, such that adapters of the pair comprise the same or different one or more barcodes. In some embodiments, the methods of the invention further comprise identifying the sample from which a target polynucleotide is derived based on a barcode sequence to which the target polynucleotide is joined. In general, a barcode may

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comprise a nucleic acid sequence that when joined to a target polynucleotide serves as an identifier of the sample from which the target polynucleotide was derived.

Figures 5A-B show an embodiment in which a short bar code (for example 4bp) is added to the end markers. In certain embodiments, the same end-signal bar code is on both sides of the 10kb molecule. Thus, after assembling the 10kb reads, one can tell that there's no misassembly by making sure that the two ends have the same bar code. In other embodiments, the bar codes on both ends are different. In these embodiments, it is only important that the relationship between the two bar codes be known. So one could use a set of bar codes, for example "A-primer-B" and "Q-primer-R" (here A, B , Q, and R represent a short bar code, e.g. 4-nt long sequence), as long as the links A-B and Q-R are known.

In certain embodiments, ligation is used to place the same barcode on both sides (Figure 5A, bar codes are denoted "A" and the results goes "A-primer-A"). The nucleic acid is then circularize and amplified from the primer site in the middle (in both directions; Figure 5A). Alternatively, one could ligate a construct of the form "A-primer1-restriction-primer2-A" and then after circularization use a restriction enzyme to cut at the "restriction" size, followed by PCR of primer1 and primer2 to amplify (Figure 5B). Methods of the invention involve determining an amount of amplifiable nucleic acid present in a sample. Any known method may be used to quantify amplifiable nucleic acid, and an exemplary method is the polymerase chain reaction (PCR), specifically quantitative polymerase chain reaction (QPCR). QPCR is a technique based on the polymerase chain reaction, and is used to amplify and simultaneously quantify a targeted nucleic acid molecule. QPCR allows for both detection and quantification (as absolute number of copies or relative amount when normalized to DNA input or additional normalizing genes) of a specific sequence in a DNA sample. The procedure follows the general principle of polymerase chain reaction, with the additional feature that the amplified DNA is quantified as it accumulates in the reaction in real time after each amplification cycle. QPCR is described, for example, in Kurnit et al. (U.S. patent number 6,033,854), Wang et al. (U.S. patent number 5,567,583 and 5,348,853), Ma et al. (The Journal of American Science, 2(3), 2006), Heid et al. (Genome Research 986-994, 1996), Sambrook and Russell (Quantitative PCR, Cold Spring Harbor Protocols, 2006), and Higuchi (U.S. patent numbers 6,171,785 and 5,994,056). The

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contents of these are incorporated by reference herein in their entirety.

Two common methods of quantification are: (1) use of fluorescent dyes that intercalate with double-stranded DNA, and (2) modified DNA oligonucleotide probes that fluoresce when hybridized with a complementary DNA. In the first method, a DNA-binding dye binds to all double-stranded (ds)DNA in PCR, resulting in fluorescence of the dye. An increase in DNA product during PCR therefore leads to an increase in fluorescence intensity and is measured at each cycle, thus allowing DNA concentrations to be quantified. The reaction is prepared similarly to a standard PCR reaction, with the addition of fluorescent (ds)DNA dye. The reaction is run in a thermocycler, and after each cycle, the levels of fluorescence are measured with a detector; the dye only fluoresces when bound to the (ds)DNA (i.e., the PCR product). With reference to a standard dilution, the (ds)DNA concentration in the PCR can be determined. Like other real-time PCR methods, the values obtained do not have absolute units associated with it. A comparison of a measured DNA/RNA sample to a standard dilution gives a fraction or ratio of the sample relative to the standard, allowing relative comparisons between different tissues or experimental conditions. To ensure accuracy in the quantification, it is important to normalize expression of a target gene to a stably expressed gene. This allows for correction of possible differences in nucleic acid quantity or quality across samples.

The second method uses a sequence-specific RNA or DNA-based probe to quantify only the DNA containing the probe sequence; therefore, use of the reporter probe significantly increases specificity, and allows quantification even in the presence of some non-specific DNA amplification. This allows for multiplexing, i.e., assaying for several genes in the same reaction by using specific probes with differently colored labels, provided that all genes are amplified with similar efficiency.

This method is commonly carried out with a DNA-based probe with a fluorescent reporter (e.g. 6-carboxyfluorescein) at one end and a quencher (e.g., 6-carboxy-tetramethylrhodamine) of fluorescence at the opposite end of the probe. The close proximity of the reporter to the quencher prevents detection of its fluorescence. Breakdown of the probe by the 5' to 3' exonuclease activity of a polymerase (e.g., Taq polymerase) breaks the reporter-quencher proximity and thus allows unquenched emission of fluorescence, which can be detected. An increase in the product targeted by the reporter probe at each PCR cycle results in a proportional increase in fluorescence due to breakdown of the probe and release of the reporter.

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The reaction is prepared similarly to a standard PCR reaction, and the reporter probe is added. As the reaction commences, during the annealing stage of the PCR both probe and primers anneal to the DNA target. Polymerization of a new DNA strand is initiated from the primers, and once the polymerase reaches the probe, its 5'-3'-exonuclease degrades the probe, physically separating the fluorescent reporter from the quencher, resulting in an increase in fluorescence. Fluorescence is detected and measured in a real-time PCR thermocycler, and geometric increase of fluorescence corresponding to exponential increase of the product is used to determine the threshold cycle in each reaction.

Relative concentrations of DNA present during the exponential phase of the reaction are determined by plotting fluorescence against cycle number on a logarithmic scale (so an exponentially increasing quantity will give a straight line). A threshold for detection of fluorescence above background is determined. The cycle at which the fluorescence from a sample crosses the threshold is called the cycle threshold, C_t. Since the quantity of DNA doubles every cycle during the exponential phase, relative amounts of DNA can be calculated, e.g. a sample with a C_t of 3 cycles earlier than another has $2^3 = 8$ times more template. Amounts of nucleic acid (e.g., RNA or DNA) are then determined by comparing the results to a standard curve produced by a real-time PCR of serial dilutions (e.g. undiluted, 1:4, 1:16, 1:64) of a known amount of nucleic acid.

In certain embodiments, the QPCR reaction involves a dual fluorophore approach that takes advantage of fluorescence resonance energy transfer (FRET), e.g., LIGHTCYCLER hybridization probes, where two oligonucleotide probes anneal to the amplicon (e.g. see U.S. patent number 6,174,670). The oligonucleotides are designed to hybridize in a head-to-tail orientation with the fluorophores separated at a distance that is compatible with efficient energy transfer. Other examples of labeled oligonucleotides that are structured to emit a signal when bound to a nucleic acid or incorporated into an extension product include: SCORPIONS probes (e.g., Whitcombe et al., Nature Biotechnology 17:804-807, 1999, and U.S. patent number 6,326,145), Sunrise (or AMPLIFLOUR) primers (e.g., Nazarenko et al., Nuc. Acids Res. 25:2516-2521, 1997, and U.S. patent number 6,117,635), and LUX primers and MOLECULAR BEACONS probes (e.g., Tyagi et al., Nature Biotechnology 14:303-308, 1996 and U.S. patent number 5,989,823).

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In other embodiments, the QPCR reaction uses fluorescent Taqman methodology and an instrument capable of measuring fluorescence in real time (e.g., ABI Prism 7700 Sequence Detector). The Taqman reaction uses a hybridization probe labeled with two different fluorescent dyes. One dye is a reporter dye (6-carboxyfluorescein), the other is a quenching dye (6-carboxy-tetramethylrhodamine). When the probe is intact, fluorescent energy transfer occurs and the reporter dye fluorescent emission is absorbed by the quenching dye. During the extension phase of the PCR cycle, the fluorescent hybridization probe is cleaved by the 5'-3' nucleolytic activity of the DNA polymerase. On cleavage of the probe, the reporter dye emission is no longer transferred efficiently to the quenching dye, resulting in an increase of the reporter dye fluorescent emission spectra. Any nucleic acid quantification method, including real-time methods or single-point detection methods may be use to quantify the amount of nucleic acid in the sample. The detection can be performed several different methodologies (e.g., staining, hybridization with a labeled probe; incorporation of biotinylated primers followed by avidin-enzyme conjugate detection; incorporation of 32P-labeled deoxynucleotide triphosphates, such as dCTP or dATP, into the amplified segment), as well as any other suitable detection method known in the art for nucleic acid quantification. The quantification may or may not include an amplification step.

The results of the quantitation can be used to determine the proper dilution for partitioning before the sequencing steps. The quantitation may not be experimental. The amount of nucleic acid in the pre-partitioned sample can be determined using various methods or the sample may be supplied with the amount of nucleic acid predetermined. In various embodiments, the fractioned sample is amplified, e.g. using a PCR step. Particularly, the fragmented nucleic acids are partitioned based upon results of the determining step such that each partitioned portion includes, on average, a subset of unique sequences. Limiting the number of amplifiable molecules per partitioned portion greatly reduces or eliminates chances of having a repeated sequence within a partitioned portion. Thus, sample complexity within each partitioned portion is significantly reduced as compared to the original sample, which allows for unambiguous reconstruction of a consensus sequence.

In certain embodiments, the partitioning is performed under microfluidic control. In other embodiments, partitioning involves dispensing the sample into different wells of a microwell plate. Such diluting and dispensing is described for example in Brown et al. (U.S.

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patent numbers 6,143,496 and 6,391,559), the content of each of which is incorporated by reference herein in its entirety. In certain embodiments, there is, on average, only a single nucleic acid fragment in each well.

In other embodiments, partitioning involves segmenting the sample into droplets. In certain embodiments, there is only a single nucleic acid fragment in each droplet. Droplet forming methods are known in the art and described for example in Davies et al. (U.S. patent numbers 7,993,911; 7,622,076 and U.S. patent application numbers 2010/0304446; 2010/0109320; 2010/0092973; 2010/0075312; and 2008/0277494); Griffiths et al. (U.S. patent numbers 6,489,103; 6,808,882; 7,138,233; 7,252,943; 7,582,446; 7,638,276; 7,897,341; and 7,968,287 and U.S. patent application numbers 2010/0210479; 2009/0325236; and 2009/0197772); Link et al. (U.S. patent application numbers 2011/0000560; 2010/0137163; and 2010/0105866); Stone et al. (U.S. patent number 7,708,949 and U.S. patent application number 2010/0172803), and Anderson et al. (U.S. patent number 7,041,481 and which reissued as RE41,780), the content of each of which is incorporated by reference herein in its entirety.

Generally, a sample fluid becomes dispersed into co-flowing streams of an immiscible fluid, such as an oil) to form monodisperse droplets. These droplets can be flowed through channels and reactions can be conducted in the droplets. Briefly, droplet forming devices generally include an inlet channel, and outlet channel, and at least one carrier fluid channel. The channels are configured to meet at a junction. The inlet channel flows sample fluid to the junction, and the carrier fluid channels flow a carrier fluid that is immiscible with the sample fluid to the junction. The inlet channel narrows at its distal portion where it connects to the junction. The inlet channel is oriented to be perpendicular to the carrier fluid channels. Droplets are formed as sample fluid flows from inlet channel to the junction, where the sample fluid interacts with the flowing carrier fluid provided to the junction by carrier fluid channels, thus forming droplets of sample fluid in the carrier fluid that flow to the outlet channel.

The fragmented nucleic acids are then amplified in each partitioned portion. Amplification refers to production of additional copies of a nucleic acid sequence and is generally carried out using polymerase chain reaction or other technologies well known in the art (e.g., Dieffenbach and Dveksler, PCR Primer, a Laboratory Manual, Cold Spring Harbor Press, Plainview, N.Y. [1995]). The amplification reaction may be any amplification reaction known in the art that amplifies nucleic acid molecules, such as polymerase chain reaction, nested

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polymerase chain reaction, polymerase chain reaction-single strand conformation polymorphism, ligase chain reaction (Barany F. (1991) PNAS 88:189-193; Barany F. (1991) PCR Methods and Applications 1:5-16), ligase detection reaction (Barany F. (1991) PNAS 88:189-193), strand displacement amplification and restriction fragments length polymorphism, transcription based amplification system, nucleic acid sequence-based amplification, rolling circle amplification, and hyper-branched rolling circle amplification.

In certain embodiments, the amplification reaction is the polymerase chain reaction. Polymerase chain reaction (PCR) refers to methods by K. B. Mullis (U.S. patent numbers 4,683,195 and 4,683,202, hereby incorporated by reference) for increasing concentration of a segment of a target sequence in a mixture of genomic DNA without cloning or purification. The process for amplifying the target sequence includes introducing an excess of oligonucleotide primers to a DNA mixture containing a desired target sequence, followed by a precise sequence of thermal cycling in the presence of a DNA polymerase. The primers are complementary to their respective strands of the double stranded target sequence.

Primers can be prepared by a variety of methods including but not limited to cloning of appropriate sequences and direct chemical synthesis using methods well known in the art (Narang et al., Methods Enzymol., 68:90 (1979); Brown et al., Methods Enzymol., 68:109 (1979)). Primers can also be obtained from commercial sources such as Operon Technologies, Amersham Pharmacia Biotech, Sigma, and Life Technologies. The primers can have an identical melting temperature. The lengths of the primers can be extended or shortened at the 5' end or the 3' end to produce primers with desired melting temperatures. Also, the annealing position of each primer pair can be designed such that the sequence and, length of the primer pairs yield the desired melting temperature. The simplest equation for determining the melting temperature of primers smaller than 25 base pairs is the Wallace Rule (Td=2(A+T)+4(G+C)). Computer programs can also be used to design primers, including but not limited to Array Designer Software (Arrayit Inc.), Oligonucleotide Probe Sequence Design Software for Genetic Analysis (Olympus Optical Co.), NetPrimer, and DNAsis from Hitachi Software Engineering. The TM (melting or annealing temperature) of each primer is calculated using software programs such as Oligo Design, available from Invitrogen Corp.

To effect amplification, the mixture is denatured and the primers then annealed to their complementary sequences within the target molecule. Following annealing, the primers are

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extended with a polymerase so as to form a new pair of complementary strands. The steps of denaturation, primer annealing and polymerase extension can be repeated many times (i.e., denaturation, annealing and extension constitute one cycle; there can be numerous cycles) to obtain a high concentration of an amplified segment of a desired target sequence. The length of the amplified segment of the desired target sequence is determined by relative positions of the primers with respect to each other, and therefore, this length is a controllable parameter.

With PCR, it is possible to amplify a single copy of a specific target sequence in genomic DNA to a level that can be detected by several different methodologies (e.g., staining, hybridization with a labeled probe; incorporation of biotinylated primers followed by avidin-enzyme conjugate detection; incorporation of 32P-labeled deoxynucleotide triphosphates, such as dCTP or dATP, into the amplified segment). In addition to genomic DNA, any oligonucleotide sequence can be amplified with the appropriate set of primer molecules. In particular, the amplified segments created by the PCR process itself are, themselves, efficient templates for subsequent PCR amplifications. Amplified target sequences can be used to obtain segments of DNA (e.g., genes) for insertion into recombinant vectors.

Methods for performing PCR in droplets are shown for example in Link et al. (U.S. patent application numbers 2008/0014589, 2008/0003142, and 2010/0137163) and Anderson et al. (U.S. patent number 7,041,481 and which reissued as RE41,780), the content of each of which is incorporated by reference herein in its entirety.

Other amplification methods and strategies can also be utilized to detect nucleic acids in biological fluids. For example, another approach would be to combine PCR and the ligase chain reaction (LCR). Since PCR amplifies faster than LCR and requires fewer copies of target DNA to initiate, PCR can be used as first step followed by LCR. The amplified product could then be used in a LCR or ligase detection reaction (LDR) in an allele-specific manner that would indicate if a mutation was present. Another approach is to use LCR or LDR for both amplification and allele-specific discrimination. The later reaction is advantageous in that it results in linear amplification. Thus the amount of amplified product is a reflection of the amount of target DNA in the original specimen and therefore permits quantitation.

LCR utilizes pairs of adjacent oligonucleotides which are complementary to the entire length of the target sequence (Barany F. (1991) PNAS 88:189-193; Barany F. (1991) PCR Methods and Applications 1:5-16). If the target sequence is perfectly complementary to the

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primers at the junction of these sequences, a DNA ligase will link the adjacent 3' and 5' terminal nucleotides forming a combined sequence. If a thermostable DNA ligase is used with thermal cycling, the combined sequence will be sequentially amplified. A single base mismatch at the junction of the oligonucleotides will preclude ligation and amplification. Thus, the process is allele-specific. Another set of oligonucleotides with 3' nucleotides specific for the mutant would be used in another reaction to identify the mutant allele. A series of standard conditions could be used to detect all possible mutations at any known site. LCR typically utilizes both strands of genomic DNA as targets for oligonucleotide hybridization with four primers, and the product is increased exponentially by repeated thermal cycling.

A variation of the reaction is the ligase detection reaction (LDR) which utilizes two adjacent oligonucleotides which are complementary to the target DNA and are similarly joined by DNA ligase (Barany F. (1991) PNAS 88:189-193). After multiple thermal cycles the product is amplified in a linear fashion. Thus the amount of the product of LDR reflects the amount of target DNA. Appropriate labeling of the primers allows detection of the amplified product in an allele-specific manner, as well as quantitation of the amount of original target DNA. One advantage of this type of reaction is that it allows quantitation through automation (Nickerson et al. (1990) PNAS 87: 8923-8927).

The amplified nucleic acid in each partitioned portion may then be fragmented. Bar code sequences may be attached to these fragments. In various embodiments, the bar code sequences label the nucleic acid fragments in a partition specific manner. Lengths and sequences of bar code sequences can be designed to achieve a desired level of accuracy determining the identity of the partition. Bar code sequences can be designed such that after a tolerable number of point mutations, the identity of the partition can still be deduced with a desired accuracy. The amplified nucleic acid may be fragmented or sheared to a desired length using a variety of mechanical, chemical and/or enzymatic methods. In certain embodiments, a Tn-5 transposase (commercially available from Epicentre Biotechnologies; Madison, WI) cuts the amplified nucleic acid into fragments and inserts short pieces of DNA into the cuts. The short pieces of DNA are used to incorporate the bar code sequences.

Attaching bar code sequences to nucleic acid templates is shown in Kahvejian et al. (U.S. patent application number 2008/0081330), and Steinman et al. (International patent application number PCT/US09/64001), the content of each of which is incorporated by reference herein in

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its entirety. Methods for designing sets of bar code sequences and other methods for attaching bar code sequences are shown in U.S. patent numbers 6,138,077; 6,352,828; 5,636,400; 6,172,214; 6235,475; 7,393,665; 7,544,473; 5,846,719; 5,695.934; 5,604,097; 6,150,516; RE39,793; 7,537,897; 6172,218; and 5,863,722, the content of each of which is incorporated by reference herein in its entirety. In certain embodiments, a single bar code is attached to each fragment. In other embodiments, a plurality of bar codes, e.g., two bar codes, are attached to each fragment.

The bar code sequence generally includes certain features that make the sequence useful in sequencing reactions. For example the bar code sequences are designed to have minimal or no homopolymer regions, i.e., 2 or more of the same base in a row such as AA or CCC, within the bar code sequence. The bar code sequences are also designed so that they are at least one edit distance away from the base addition order when performing base-by-base sequencing, ensuring that the first and last base do not match the expected bases of the sequence.

The bar code sequences are designed such that each sequence is correlated to nucleic acid in a particular portioned portion, allowing sequence reads to be correlated back to the partitioned portion from which they came. Methods of designing sets of bar code sequences is shown for example in Brenner et al. (U.S. patent number 6.235,475), the contents of which are incorporated by reference herein in their entirety. In certain embodiments, the bar code sequences range from about 5 nucleotides to about 15 nucleotides. In a particular embodiment, the bar code sequences range from about 4 nucleotides to about 7 nucleotides. Since the bar code sequence is sequenced along with the template nucleic acid, the oligonucleotide length should be of minimal length so as to permit the longest read from the template nucleic acid attached. Generally, the bar code sequences are spaced from the template nucleic acid molecule by at least one base (minimizes homopolymeric combinations).

Methods of the invention involve attaching the bar code sequences to the template nucleic acids. In certain embodiments, the bar code sequences are attached to the template nucleic acid molecule with an enzyme. The enzyme may be a ligase or a polymerase. The ligase may be any enzyme capable of ligating an oligonucleotide (RNA or DNA) to the template nucleic acid molecule. Suitable ligases include T4 DNA ligase and T4 RNA ligase (such ligases are available commercially, from New England Biolabs). Methods for using ligases are well known in the art. The polymerase may be any enzyme capable of adding nucleotides to the 3'

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and the 5' terminus of template nucleic acid molecules.

The ligation may be blunt ended or via use of complementary over hanging ends. In certain embodiments, following fragmentation, the ends of the fragments may be repaired, trimmed (e.g. using an exonuclease), or filled (e.g., using a polymerase and dNTPs), to form blunt ends. Upon generating blunt ends, the ends may be treated with a polymerase and dATP to form a template independent addition to the 3'-end and the 5-end of the fragments, thus producing a single A overhanging. This single A is used to guide ligation of fragments with a single T overhanging from the 5'-end in a method referred to as T-A cloning.

Alternatively, because the possible combination of overhangs left by the restriction enzymes are known after a restriction digestion, the ends may be left as is, i.e., ragged ends. In certain embodiments double stranded oligonucleotides with complementary over hanging ends are used. In particular embodiments, bar code sequences are incorporated using limited cycle PCR.

According to some embodiments of the invention, the templates are sequenced after incorporating bar codes to nucleic acid templates. Various methods can be used to determine the identity of a partition allowing for easier assembly of sequences into larger fragments. In some embodiments, the partitions remain physically separated. In some embodiments, the nucleic acids are labeled with a dye. Appropriate numbers of partitions can be pooled together allowing for the identification of the partition origin of a sequence. The number of partitions that can be pooled together while allowing for the identification of the partition origin of a nucleic acid sequence may depend on the method of labeling the nucleic acids. Sequencing may be by any method known in the art. DNA sequencing techniques include classic dideoxy sequencing reactions (Sanger method) using labeled terminators or primers and gel separation in slab or capillary, sequencing by synthesis using reversibly terminated labeled nucleotides, pyrosequencing, 454 sequencing, allele specific hybridization to a library of labeled oligonucleotide probes, sequencing by synthesis using allele specific hybridization to a library of labeled clones that is followed by ligation, real time monitoring of the incorporation of labeled nucleotides during a polymerization step, polony sequencing, and SOLiD sequencing. Sequencing of separated molecules has more recently been demonstrated by sequential or single extension reactions using polymerases or ligases as well as by single or sequential differential hybridizations with libraries of probes.

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A sequencing technique that can be used in the methods of the provided invention includes, for example, Helicos True Single Molecule Sequencing (tSMS) (Harris T. D. et al. (2008) Science 320:106-109). In the tSMS technique, a DNA sample is cleaved into strands of approximately 100 to 200 nucleotides, and a polyA sequence is added to the 3' end of each DNA strand. Each strand is labeled by the addition of a fluorescently labeled adenosine nucleotide. The DNA strands are then hybridized to a flow cell, which contains millions of oligo-T capture sites that are immobilized to the flow cell surface. The templates can be at a density of about 100 million templates/cm^2. The flow cell is then loaded into an instrument, e.g., HeliScope.TM. sequencer, and a laser illuminates the surface of the flow cell, revealing the position of each template. A CCD camera can map the position of the templates on the flow cell surface. The template fluorescent label is then cleaved and washed away. The sequencing reaction begins by introducing a DNA polymerase and a fluorescently labeled nucleotide. The oligo-T nucleic acid serves as a primer. The polymerase incorporates the labeled nucleotides to the primer in a template directed manner. The polymerase and unincorporated nucleotides are removed. The templates that have directed incorporation of the fluorescently labeled nucleotide are detected by imaging the flow cell surface. After imaging, a cleavage step removes the fluorescent label, and the process is repeated with other fluorescently labeled nucleotides until the desired read length is achieved. Sequence information is collected with each nucleotide addition step. Further description of tSMS is shown for example in Lapidus et al. (U.S. patent number 7,169,560), Lapidus et al. (U.S. patent application number 2009/0191565), Quake et al. (U.S. patent number 6,818,395), Harris (U.S. patent number 7,282,337), Quake et al. (U.S. patent application number 2002/0164629), and Braslavsky, et al., PNAS (USA), 100: 3960-3964 (2003), the contents of each of these references is incorporated by reference herein in its entirety.

Another example of a DNA sequencing technique that can be used in the methods of the provided invention is 454 sequencing (Roche) (Margulies, M et al. 2005, Nature, 437, 376-380). 454 sequencing involves two steps. In the first step, DNA is sheared into fragments of approximately 300-800 base pairs, and the fragments are blunt ended. Oligonucleotide adaptors are then ligated to the ends of the fragments. The adaptors serve as primers for amplification and sequencing of the fragments. The fragments can be attached to DNA capture beads, e.g., streptavidin-coated beads using, e.g., Adaptor B, which contains 5'-biotin tag. The fragments attached to the beads are PCR amplified within droplets of an oil-water emulsion. The result is

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multiple copies of clonally amplified DNA fragments on each bead. In the second step, the beads are captured in wells (pico-liter sized). Pyrosequencing is performed on each DNA fragment in parallel. Addition of one or more nucleotides generates a light signal that is recorded by a CCD camera in a sequencing instrument. The signal strength is proportional to the number of nucleotides incorporated. Pyrosequencing makes use of pyrophosphate (PPi) which is released upon nucleotide addition. PPi is converted to ATP by ATP sulfurylase in the presence of adenosine 5' phosphosulfate. Luciferase uses ATP to convert luciferin to oxyluciferin, and this reaction generates light that is detected and analyzed.

Another example of a DNA sequencing technique that can be used in the methods of the provided invention is SOLiD technology (Applied Biosystems). In SOLiD sequencing, genomic DNA is sheared into fragments, and adaptors are attached to the 5' and 3' ends of the fragments to generate a fragment library. Alternatively, internal adaptors can be introduced by ligating adaptors to the 5' and 3' ends of the fragments, circularizing the fragments, digesting the circularized fragment to generate an internal adaptor, and attaching adaptors to the 5' and 3' ends of the resulting fragments to generate a mate-paired library. Next, clonal bead populations are prepared in microreactors containing beads, primers, template, and PCR components. Following PCR, the templates are denatured and beads are enriched to separate the beads with extended templates. Templates on the selected beads are subjected to a 3' modification that permits bonding to a glass slide. The sequence can be determined by sequential hybridization and ligation of partially random oligonucleotides with a central determined base (or pair of bases) that is identified by a specific fluorophore. After a color is recorded, the ligated oligonucleotide is cleaved and removed and the process is then repeated.

Another example of a DNA sequencing technique that can be used in the methods of the provided invention is Ion Torrent sequencing (U.S. patent application numbers 2009/0026082, 2009/0127589, 2010/0035252, 2010/0137143, 2010/0188073, 2010/0197507, 2010/0282617, 2010/0300559), 2010/0300895, 2010/0301398, and 2010/0304982), the content of each of which is incorporated by reference herein in its entirety. In Ion Torrent sequencing, DNA is sheared into fragments of approximately 300-800 base pairs, and the fragments are blunt ended. Oligonucleotide adaptors are then ligated to the ends of the fragments. The adaptors serve as primers for amplification and sequencing of the fragments. The fragments can be attached to a surface and is attached at a resolution such that the fragments are individually resolvable.

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Addition of one or more nucleotides releases a proton (H^+), which signal detected and recorded in a sequencing instrument. The signal strength is proportional to the number of nucleotides incorporated.

Another example of a sequencing technology that can be used in the methods of the provided invention is Illumina sequencing. Illumina sequencing is based on the amplification of DNA on a solid surface using fold-back PCR and anchored primers. Genomic DNA is fragmented, and adapters are added to the 5' and 3' ends of the fragments. DNA fragments that are attached to the surface of flow cell channels are extended and bridge amplified. The fragments become double stranded, and the double stranded molecules are denatured. Multiple cycles of the solid-phase amplification followed by denaturation can create several million clusters of approximately 1,000 copies of single-stranded DNA molecules of the same template in each channel of the flow cell. Primers, DNA polymerase and four fluorophore-labeled, reversibly terminating nucleotides are used to perform sequential sequencing. After nucleotide incorporation, a laser is used to excite the fluorophores, and an image is captured and the identity of the first base is recorded. The 3' terminators and fluorophores from each incorporated base are removed and the incorporation, detection and identification steps are repeated.

Another example of a sequencing technology that can be used in the methods of the provided invention includes the single molecule, real-time (SMRT) technology of Pacific Biosciences. In SMRT, each of the four DNA bases is attached to one of four different fluorescent dyes. These dyes are phospholinked. A single DNA polymerase is immobilized with a single molecule of template single stranded DNA at the bottom of a zero-mode waveguide (ZMW). A ZMW is a confinement structure which enables observation of incorporation of a single nucleotide by DNA polymerase against the background of fluorescent nucleotides that rapidly diffuse in an out of the ZMW (in microseconds). It takes several milliseconds to incorporate a nucleotide into a growing strand. During this time, the fluorescent label is excited and produces a fluorescent signal, and the fluorescent tag is cleaved off. Detection of the corresponding fluorescence of the dye indicates which base was incorporated. The process is repeated.

Another example of a sequencing technique that can be used in the methods of the provided invention is nanopore sequencing (Soni G V and Meller A. (2007) Clin Chem 53: 1996-2001). A nanopore is a small hole, of the order of 1 nanometer in diameter. Immersion of a

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nanopore in a conducting fluid and application of a potential across it results in a slight electrical current due to conduction of ions through the nanopore. The amount of current which flows is sensitive to the size of the nanopore. As a DNA molecule passes through a nanopore, each nucleotide on the DNA molecule obstructs the nanopore to a different degree. Thus, the change in the current passing through the nanopore as the DNA molecule passes through the nanopore represents a reading of the DNA sequence.

Another example of a sequencing technique that can be used in the methods of the provided invention involves using a chemical-sensitive field effect transistor (chemFET) array to sequence DNA (for example, as described in US Patent Application Publication No. 20090026082). In one example of the technique, DNA molecules can be placed into reaction chambers, and the template molecules can be hybridized to a sequencing primer bound to a polymerase. Incorporation of one or more triphosphates into a new nucleic acid strand at the 3' end of the sequencing primer can be detected by a change in current by a chemFET. An array can have multiple chemFET sensors. In another example, single nucleic acids can be attached to beads, and the nucleic acids can be amplified on the bead, and the individual beads can be transferred to individual reaction chambers on a chemFET array, with each chamber having a chemFET sensor, and the nucleic acids can be sequenced.

Another example of a sequencing technique that can be used in the methods of the provided invention involves using a electron microscope (Moudrianakis E. N. and Beer M. Proc Natl Acad Sci USA. 1965 March; 53:564-71). In one example of the technique, individual DNA molecules are labeled using metallic labels that are distinguishable using an electron microscope. These molecules are then stretched on a flat surface and imaged using an electron microscope to measure sequences.

The obtained sequence reads can be split according to their bar code, i.e., demultiplexed, and reads originating from individual wells can be saved into separate files. Fragments amplified within each partitioned portion can be reconstructed using a de-novo assembly or by aligning to known reference sequence if such sequence exists. Methods of the invention may take advantage of pair-end reads and sequencing quality scores that represent base calling confidence to reconstruct full length fragments.

To begin the reconstruction process, short reads may be stitched together bioinformatically, .e.g. by finding overlaps and extending them. To be able to do that

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unambiguously, one may ensure that long fragments that were amplified within each partitioned portion are distinct enough, and do not have similar stretches of DNA that will make assembly from short fragments ambiguous, which can occur, for example, if two molecules in the same well originated from overlapping positions on homologous chromosomes, overlapping positions of same chromosome, or a genomic repeat. Such fragments can be detected during sequence assembly process by observing multiple possible ways to extend the fragment, one of which containing a sequence specific to an end marker. End markers can be chosen such that an end marker sequence is not frequently found in DNA fragments of a sample that is analyzed. A probabilistic framework utilizing quality scores can be applied to decide whether a possible sequence extension way represents an end maker and thus the end of a fragment.

Overlapping fragments may be computationally discarded since they no longer represent the same initial long molecule. This process allows to treat a population of molecules resulting after amplification as a clonally amplified population of disjoint molecules with no significant overlap or homology, which enables sequencing errors to be corrected to achieve very high consensus accuracy and allows unambiguous reconstruction of long fragments. If overlaps are not discarded, then one can take into consideration that reads may be originating from fragments originating from two homologous chromosomes or overlapping regions of the same chromosome (in case of diploid organism) which makes error correction difficult and ambiguous.

Computational removal of overlapping fragments also allows use of quality scores to resolve nearly-identical repeats. Resulting long fragments may be assembled into full genomes using any of the algorithms known in the art for genome sequence assembly that can utilize long reads.

In addition to de-novo assembly fragments can be used to obtain phasing (assignment to homologous copies of chromosomes) of genomic variants, by observing that under conditions of experiment described in the preferred embodiment long fragments originate from either one of chromosomes, which enables to correlate and co-localize variants detected in overlapping fragments obtained from distinct partitioned portions.

Figure 7 illustrates an example for a workflow for sequence assembly. Accordingly, a demultiplexing step may be applied to separate reads into their fractions of origin, for example, by using the tags/barcodes on the reads. An optional filtering step may filter out or trim reads if they are of too low quality, for example with sequencer quality (Q) values of higher than 15, 12,

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10, 8, 6, or 5, are detected as sequencing artifacts, or have a low sequence complexity. A complexity analysis may be optionally incorporated, for example by using end markers to identify reads that originate from the beginning or end of an original fragment. The sequence immediately after the end marker may be used to estimate the number of fragments each fraction contained. Sequencing errors may be corrected for overlapping reads, for example based on the base quality reported by the sequencer for the overlapping reads. A sequence overlap graph may be constructed, for example bye using overlaps between sequences to infer the connectivity and ordering of sequences. The graph may be corrected using the end-markers, by restricting the connection of reads to other reads in a single chosen direction. The reads may be assembled into original fragments, for example by tracing a path along the graph that is consistent with paired reads (if available) to reconstruct the original fragment. Optionally, an assembly validation may be performed. For example, the original reads may be aligned to the assembled fragment, every base along the fragment may be assessed for the presence of supporting reads covering it, and, optionally for the presence of paired reads which map upstream and/or downstream of that base. A cross-fragment analysis may be performed comparing fragments originating from different fractions to detect any possible mis-assemblies.

Methods and systems described herein are equipped to provide sequence information with very high per base accuracies, for example per base accuracies of greater than 80, 90, 95, 99, 99.9, 99.98, 99.99%, 99.999% or higher. The per base accuracies may depend on sequence coverage with underlying short reads, and/or average accuracies for stretches of sequences, for example average accuracies of greater than 80, 90, 95, 99, 99.9, 99.98, 99.99% or higher may be achieved. Sequencing errors affecting per base and average accuracy of sequence information due to underlying sequencing platform may be substantially or completely corrected by majority calls by the assembly methods and systems described herein, such as a computer acting as an assembler. An output with a single long read may be produced from putting together multiple long reads.

Further, methods and systems described herein may allow for increased assembly accuracy; one contributing factor being higher read accuracies allowing for resolution of nearly identical repeats and thus preventing incorrect read assemblies. Genome assembly based on the longer and more accurate reads/sequences described herein would result in higher assembly accuracies compared to traditional genomic reads known in the art. For example, methods and

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systems of the invention can achieve average assembly accuracies of greater than 90, 95, 99, 99.9, 99.98, 99.99%, or higher.

Further yet, methods and systems described herein may allow for increased genome resequencing accuracies. In various embodiments, hypermapping, phase resolved sequencing, and/or local reassembly is made possible due to reduced sample complexity and multiple short reads covering the sequence reads described herein. In some embodiments, hypermapping may be utilized allowing to cover larger fractions of the genome, for example identical repeats and copy number variations spanned by a common sequence which cannot be uniquely covered with short reads that map equally well to multiple genomic locations.

Figure 8 illustrates application of hypermapping according to some embodiments of the invention. Hypermapping may be applied to genome resequencing, phasing, cancer analysis, and any other suitable sequencing methods known in the art..Typically, a genome may contain many sequence repeats, some of which are identical or nearly identical. Accordingly, short reads originating from these repeat regions may have multiple equally confident alignments to a reference genome, therefore making it extremely hard to establish which exact copy of the repeat they originated from. Most genome analysis pipelines known in the art place these reads randomly in an effort to preserve coverage depth.

Methods and systems described herein may allow for short reads to originate from a reduced representation of a genome, for example a set of amplifiable fragments in a given fraction. Proper mapping of reads that originate from repeat regions may be achieved by selecting a repeat locus such the repeat locus is spanned by uniquely mapped reads, consistent with the amplifiable fragment originating from that region.

According to various embodiments of the invention, hypermapping effectively reduces the complexity of the genome by only considering parts of the genome that are covered by amplifiable fragments, for example the amplifiable fragments within a specific sample volume/fraction. Accordingly, a much higher fraction of the genome may be accessible to mapping, and incorrect read mappings may be reduced, thereby improving resequencing accuracy.

Methods and systems described herein allow for genome phasing based on reduced genome representation strategies. Each sample volume/fraction may contain a reduced subset of the genome organized as continuous regions of the genome. In various embodiments, each of the

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sequences originating from a region/fragment within a sample volume/fraction can be deduced to have originated from a single chromosome and thus will only contain variants present on that chromosome. Accordingly, it is possible to reconstruct local chromosome phasing, for example by finding overlapping fragments that share heterozygous variants. Gaps, for example those resulting from a long stretch of homozygous variants, can be covered, for example by using HapMap data and Linkage Disequilibrium.

Various embodiments of the invention utilize cloud based phasing (see for example Shedure et al. Nat Biotechnol. 2011 Jan;29(1):59-63). Alternatively, external data, for example data from the 1000 Genomes Project, may be utilized to phase regions relative to each other, for example based on a concept of "Linkage Disequilibrium". Without being bound by theory, DNA is typically passed to offspring in large blocks that are mixture of blocks derived from parents. Accordingly, a few blocks in previously fully phased individuals, for example by trio sequencing or any other suitable method known in the art, may be utilized for finding overlaps with locally phased blocks described herein and proper phasing can be inferred.

Figure 9 illustrates an exemplary embodiment comprising a phasing algorithm. Accordingly, an initial sequencing quality control round can be followed by demultiplexing the sequencing results into multiple data depositories, such as files, databases, tables, or any other suitable data storage system known in the art. The demultiplexing can be guided by the barcodes that identify the origin of a sequence read, such as a partition. The demultiplexed information can then be analyzed individually from here on.

The demultiplexed sequence information can be aligned to a reference genome and fragment bounderies and/or overlaps can be detected. A hypermapping algorithm may improve the alignment of the correct reads to the correct parts of the genome. The fragment boundaries and overlaps can be updated accordingly.

Overlapping fragments, such as those that originated from a single partition with two target polynucleotide comprising overlapping sequence segments above a certain length (e.g. over 20, 30, 40, 50, 60, 70, 80, 90, 100 or more bp) may be discarded from the data and a new analysis round may be employed comprising one or more of the detection of fragment boundaries and/or overlaps, hypermapping, and alignment to a reference genome steps.

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The detection of fragment boundaries and overlaps may allow for calling diploid genome variants. Auxiliary information, such as shotgun sequencing data, may be incorporated in the genome variant analysis.

Sequence information related to each fragment can be accumulated at all or selected positions, for example at variant positions. Phasing information for variants can be determined and output. Haplotypes can be locally phased. In addition, external data, such as from HapMap, may be combined with local phasing information, for example phasing information covering a range of less than 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 3000, 4000, or 5000 bp, extending phased regions with external haplotype data over a range of more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100 kb or more.

Various embodiments of the invention allow for detection of structural variants, for example using standard suitable methods known in the art. Accordingly, relying on the reduced representation methods described herein may reduce noise and increase accuracy of SV detection.

According to various embodiments of the invention, only a fraction of the genome is amplified in each reaction volume/fraction/partition, resulting in fewer repeats interfering with a local reassembly process. Accordingly, parts of the genome that are substantially different from a reference can be locally reconstructed for example by de-novo, reference assisted assembly or using algorithms based on paired end information.

Multiple sample fractions each with a reduced genome representation of a genome, in various embodiments, allows for new kinds of algorithms to be employed. For example, it is possible to resolve some repeats, finding a correct assembly across repeat regions by establishing whether regions spanning the repeat are in proximity to each other.

Figure 10 illustrates an example method for Poor Man's Mate Pair (PMMP). Two fractions have fragments that contain an identical repeat (R). Within each well, an unambiguous assembly is not possible because two different assemblies would be equally supported by the short reads (ARB and CRD in Fraction 1, and ERF and CRD in Fraction 2). However, by noticing that CRD is found in Fraction 1, and also in Fraction 2, and that neither of sequences "A" or "B" is found in Fraction 2, it can be reasoned that sequences C and D are found in close proximity to each other and thus CRD is the right assembly. Therefore, one can also reconstruct "ARB" and "ERF" assemblies in Fractions 1 and 2. This is a significant improvement over

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samples with larger or full genome representations. Accordingly, additional information may be obtained by having multiple wells with reduced representations as described herein.

Methods

De-novo assembly

Complex and repetitive regions of genomes are especially hard to assemble across to generate long sequences. The low accuracy in this process makes it especially hard to differentiate between very similar repeats. In addition, this process is computationally expensive and in some cases not practical.

The long reads obtained using the methods and systems described herein provide long enough sequences to bridge across most known repetitive elements, thus making it possible to assemble very long contigs without breaking at repeat regions. The high accuracy of reads described herein similar repetitive regions can be distinguished avoiding mis-assembly. For example, nearly identical genomic repeat regions with 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 variations in their sequence can be distinguished using the methods and systems described herein. In some embodiments, the methods described herein can discriminate and quantitate genomic DNA regions. The methods described herein can discriminate and quantitate at least 1; 2; 3; 4; 5; 10, 20; 50; 100; 200; 500; 1,000; 2,000; 5,000; 10,000, 20,000; 50,000; 100,000; 200,000; 300,000; 400,000; 500,000; 600,000; 700,000; 800,000; 900,000; 1,000,000; 2,000,000 or 3,000,000 different genomic DNA regions. The methods described herein can discriminate and quantitate genomic DNA regions varying by 1 nt or more than 1, 2, 3, 5, 10, 15, 20, 21, 22, 24, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nt. Further, the computation requirements, for example memory, CPU runtime of the de-novo assembly from very long reads are much lower than those of, for example, shotgun assembly.

The use of the single-molecule sequencing technologies described herein allows for obtaining reads to originating from a single haplotype. Taken together with the extremely low error rate and long read span phasing of polyploid genomes may be facilitated, allowing for phased de-novo assembly.

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The methods and systems described herein facilitate the use of reduced representations of a genome in each individual volume thus decreasing "sample complexity", for example by 10, 100, 1000, 10000, 100000 fold or more, relative to the full genome.

The assembly and post-assembly analysis of reads or clouds using the methods and systems described herein may be enhanced in conjunction with other sequencing technologies known in the art, such as shotgun sequencing, paired-end sequencing or mate-pair sequencing.

In some cases, the methods described herein are used to detect and/or quantify genomic DNA regions such as a region containing a DNA polymorphism. A polymorphism refers to the occurrence of two or more genetically determined alternative sequences or alleles in a population. A polymorphic marker or site is the locus at which divergence occurs. Preferred markers have at least two alleles, each occurring at a frequency of preferably greater than 1%, and more preferably greater than 10% or 20% of a selected population. A polymorphism may comprise one or more base changes, an insertion, a repeat, or a deletion. A polymorphic locus may be as small as one base pair. Polymorphic markers include single nucleotide polymorphisms (SNP's), restriction fragment length polymorphisms (RFLP's), short tandem repeats (STRs), variable number of tandem repeats (VNTR's), hypervariable regions, minisatellites, dinucleotide repeats, trinucleotide repeats, tetranucleotide repeats, simple sequence repeats, and insertion elements such as Alu. A polymorphism between two nucleic acids can occur naturally, or be caused by exposure to or contact with chemicals, enzymes, or other agents, or exposure to agents that cause damage to nucleic acids, for example, ultraviolet radiation, mutagens or carcinogens.

Methods and systems described herein can be used to discriminate and quantitate a DNA region containing a DNA polymorphism. The methods described herein can discriminate and quantitate at least 1, 2, 3, 4, 5, 10, 20, 50, 100, 200, 500, 1,000, 2,000, 5,000, 10,000, 20,000, 50,000, 100,000, 200,000, 300,000, 400,000, 500,000, 600,000, 700,000, 800,000, 900,000, 1,000,000, 2,000,000, 3,000,000 or more DNA polymorphisms originating from one or more samples. In some embodiments, the methods described herein can discriminate and quantitate at least 1, 2, 3, 4, 5, 10, 20, 50, 100, 200, 500, 1,000, 2,000, 5,000, 10,000, 20,000, 50,000, 100,000, 200,000, 300,000, 400,000, 500,000, 600,000, 700,000, 800,000, 900,000, 1,000,000, 2,000,000, 3,000,000, or more different polymorphic markers originating form one or more samples._In some embodiments, the methods described herein can discriminate and quantitate at least 1, 2, 3, 4, 5, 10, 20, 50, 100, 200, 500, 1,000, 2,000, 5,000, 10,000, 20,000, 50,000,

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100,000, 200,000, 300,000, 400,000, 500,000, 600,000, 700,000, 800,000, 900,000, 1,000,000, 2,000,000, 3,000,000, or more different SNPs originating from one or more samples.

In some embodiments, the methods described herein are used to detect and/or quantify genomic DNA regions by mapping the region to the genome of a species in the case where the transplant donor and the transplant recipient are not from the same species (e.g., xenotransplants). In some embodiments, the methods described herein can discriminate and quantitate a DNA region from a species. The methods described herein can discriminate and quantitate of at least 1, 2, 3, 4, 5, 10, 20, 50, 100, 200, 500, 1,000, 2,000, 5,000, 10,000, 20,000, 50,000, 100,000, 200,000, 300,000, 400,000, 500,000, 600,000, 700,000, 800,000, 900,000, 1,000,000, 2,000,000, 3,000,000, or more DNA regions from a species.

Methods and systems described herein may comprise the detection of genetic variants. In some instances, at least about 2, at least about 3, at least about 4, at least about 5, at least about 10, at least about 15, at least about 20, at least about 30, at least about 40, at least about 50, at least about 100, at least about 200, at least about 300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, or at least about 1000 genetic variants are detected in a single reaction. In another example, at least about 2000, at least about 5000, at least about 10000, at least about 15000, at least about 20000, at least about 30000, at least about 40000, at least about 50000, at least about 100000, at least about 200000, at least about 300000, at least about 400000, at least about 500000, at least about 600000, at least about 700000, at least about 800000, at least about 900000, or at least about 1000000 genetic variants are detected in a single reaction. De novo assembly comprising an N50 value or median of 50, 75, 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000 kilobases or more can be achieved using the methods and systems described herein. Genetic variants within these assembled sequences can be identified according to the methods of the invention.

Genome phasing

Phasing across continuous regions of sequences is greatly facilitated by longer read lengths. Many sequencing based technologies known in the art lack read length to phase across continuous regions, such as regions longer than 200, 300, 400, 500, 700, 1000, 2000, 3000, or more nucleotides. Computational approaches may prove inaccurate and unable to phase low frequency variants, which were not measured across reference populations. In addition, phasing

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based on trio sequencing, for example including an individual and parents, can be expensive and impractical, requiring access to parents' DNA and cannot reliably establish phasing in locations heterozygous in both parents and a child.

In contrast, methods and systems described herein facilitate generation of long sequences originating from single molecule amplification and spanning across multiple heterozygous sites. Thus, shorter sequence reads, for example reads less than 20, 25, 30, 40, 50, 100, 200, or 300 can be utilized and assembled into longer sequences. Accurate phasing of long sequences by the methods and systems described herein may increase variant calling accuracy, for example by using haploid error models. Further, methods and systems described herein allow for the phasing of low frequency variants not present in reference SNP chips.

In particular embodiments, phasing is done by aliquoting an intermediate amount of amplifiable fragments, for example exponentially amplifiable fragments, in each partition, for example between about 1-10 MB and about 100-200MB or more, and sequencing them to an intermediate coverage of 2-5 fold. Fragment boundaries can be detected by detecting reads grouping at the specific parts of the genome, and overlapping fragments within a partition can be discarded with the use of the end marker sequence. Unphased SNPs can be identified from alignments of read clouds that are produced by fragments or using standard whole genome sequencing. For each fragment, variants that are supported by reads that originated from this variant can be recorded. This capability is largely supported by the very high probability (>90%, >99%, >99.9%, or higher, depending on the number of amplifiable fragments per partition) that clouds would originate from a single haplotype, that variant phases are mostly consistent within a cloud, and that a probabilistic model, such as Hidden Markov Model can be used to establish the most likely sequence of variant phases across a region on the chromosome. Accordingly, disjoint phased segments of various lengths can be generated, typically up to about 100, 200, 300, 400, or 500kb, but in some cases as long as multiple megabases in regions with significant cloud coverage and abundance of heterozygous variants. Relative phasing of these locally phased blocks can be established using statistical inference using population phased data,such as HapMap or 1000 genomes project data, and/or statistical model based algorithms, for example implementing a hidden Markov model for establishing most likely relative phasing of locally phased variant blocks. Examples of statistical phasing are well known in the art, including the use of "IMPUTE" (HOWIE, et al. A Flexible and Accurate Genotype Imputation Method for the Next

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Generation of Genome-Wide Association Studies. PLoS Genet. 2009 Jun;5(6):e1000529.) or "BEAGLE" (BROWNING, et al. Rapid and Accurate Haplotype Phasing and Missing-Data Inference for Whole-Genome Association Studies By Use of Localized Haplotype Clustering. Am J Hum Genet. 2007 Nov;81(5):1084-97.) software. Statistical phasing is based on the phenomenon of linkage disequlibrium resulting from genomic variants being inherited in large blocks including thousands of variants. Other embodiments include combining phasing approaches described herein with raw whole genome sequencing data, paired end data, or sequencing information from a close relative to establish accurate whole genome variant phasing. Hypermaping can be employed to increase fragment mapping accuracy. Phased genome blocks can be used to establish which variants are collocated on the one of the two chromosomes, whether both copies of a gene are affected by a mutation, or for any other suitable uses known in the art.

Cancer genome sequencing

High degrees of accuracy required by cancer genome sequencing can be achieved using the methods and systems described herein. Typically, inaccurate reference genomes make basecalling challenges when sequencing cancer genomes. Heterogeneous samples and small starting materials, for example a sample obtained by biopsy introduce additional challenges. Further, detection of large scale structural variants and/or losses of heterozygosity is often crucial for cancer genome sequencing, as well as the ability to differentiate between somatic variants and errors in basecalling.

Systems and methods described herein may generate accurate long sequences from complex samples containing 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20 or more varying genomes. Mixed samples of normal, benign, and/or tumor origin may be analyzed, optionally without the need for a normal control. In some embodiments, starting samples as little as 100ng or even as little as hundreds of genome equivalents are utilized to generate accurate long sequences. Systems and methods described herein may allow for detection of large scale structural variants and rearrangements. Phased variant calls may be obtained over long sequences spanning 50, 100, 200, 300, 400, 500, 600, 700, 1000, 1500, 2000, 2500, 3000, 4000, 5000, 10000, or more nucleotides.

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Figure 11 illustrates an exemplary embodiment comprising an algorithm for cancer detection. Accordingly, an initial sequencing quality control round can be followed by demultiplexing the sequencing results into multiple data depositories, such as files, databases, tables, or any other suitable data storage system known in the art. The demultiplexing can be guided by the barcodes that identify the origin of a sequence read, such as a partition. The demultiplexed information can then be analyzed individually from here on.

The demultiplexed sequence information can be aligned to a reference genome and fragment boundaries and/or overlaps can be detected.

Overlapping fragments, such as those that originated from a single partition with two target polynucleotide comprising overlapping sequence segments above a certain length (e.g. over 20, 30, 40, 50, 60, 70, 80, 90, 100 or more bp) may be discarded from the data.

The detection of fragment boundaries and overlaps may allow for calling diploid genome variants. Auxiliary information, such as shotgun sequencing data, may be incorporated in the genome variant analysis. Haplotypes can be locally phased using the genome variant calls. In addition, external data, such as from HapMap, may be combined with local phasing information, for example phasing information covering a range of less than 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1500, 2000, 3000, 4000, or 5000 bp, extending phased regions with external haplotype data over a range of more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100 kb or more.

Haplotypes determined using the methods and systems described herein may be assigned to computational resources, for example computational resources over a network, such as a cloud system. Short variant calls can be corrected, if necessary, using relevant information that is stored in the computational resources. Structural variants can be detected based on the combined information from short variant calls and the information stored in the computational resources. Problematic parts of the genome, such as those with repeat regions, low sequence accuracy, high variant rates, ALU repeats, segmental duplications, or any other relevant problematic parts known in the art, can be reassembled for increased accuracy.

A sample type can be assigned to the sequence information either locally or in a networked computational resource, such as a cloud. In cases where the source of the information is known, for example when the source of the information is from a cancer or normal tissue, the source can be assigned to the sample as part of a sample type. Other sample type examples

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generally include, but are not limited to, tissue type, sample collection method, presence of infection, type of infection, processing method, size of the sample, etc. In cases where a complete or partial comparison genome sequence is available, such as a normal genome in comparison to a cancer genome, the differences between the sample data and the comparison genome sequence can be determined and optionally output.

Metagenomics

Methods and systems described herein are well suited to analyze complex samples with large variations of metagenomic representations. Typically, low frequency genomes are hard to assemble, requiring high computational cost due to need to assemble whole sample. Methods and systems described herein, allow for complexity reduction facilitating the analysis of samples comprising more than 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 100, 200, 300, 400, 500, 1000 or more metagenomic representations. A few, for example about 100-1000 amplifiable molecules can be selected out of the whole pool of DNA, amplified in separated partitions, barcoded, sequenced, and/or analyzed in a partition-specific manner thus reducing computational complexity of the analysis by providing less complex sample within each well. Ability to assemble artificially limited amount of amplifiable sequences together allows for better annotation of DNA samples present in the initial population, because queries against genome databases such as "nt" return results with higher significance as query gets longer. Therefore search sensitivity can be improved using long reads generated by the methods and systems described herein, as compared to shorter reads, such as shotgun short reads.

RNA sequencing

A significant amount of information may be obtained from long-range dependencies between exons in RNA sequences. Methods and systems described herein may generate long reads of RNA that span across multiple exons. Thus, transcripts of 100, 200, 300, 400, 500, 750, 1000, 1500, 2000, 2500, 3000, or more nucleotides may be reconstructed de-novo using the methods and systems described herein.

In some embodiments, RNA sequences may be mapped against a reference transcriptome. The mapping may optionally require less coverage than de-novo assembling the

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transcript, which in turn allows for the detection of less abundant transcripts. Methods and systems of the invention may allow for transcripts that are represented at less than a 1000, 900, 800, 700, 600, 500, 400, 300, 200, 100, 50, 40, 30, 20, 10, 9, 8, 7, 6, 5, 4, 3, or 2 copies in a sample. In some cases, the methods described herein are used to detect and/or quantify gene expression. In some embodiments, the methods described herein provide high discriminative and quantitative analysis of multiples transcripts. The methods described herein can discriminate and quantitate the expression of at least 1, 2, 3, 4, 5, 10, 20, 50, 100, 200, 500, 1,000, 2,000, 5,000, 10,000, 20,000, 50,000, 100,000, different target nucleic acids, for example mRNA or cDNA. In some embodiments, the methods described herein are used to detect and/or quantify gene expression of genes with similar sequences. The methods described herein can discriminate and quantitate the expression of transcripts varying by 1 nt or more than 1, 2, 3, 5, 10, 15, 20, 21, 22, 24, 25, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400 or 500 nt in a target nucleic acid, for example mRNA or cDNA.

Multiplexing

In some instances, the foreign molecules are detected in a multiplexed reaction. For example, at least about 2, at least about 3, at least about 4, at least about 5, at least about 10, at least about 15, at least about 20, at least about 30, at least about 40, at least about 50, at least about 100, at least about 200, at least about 300, at least about 400, at least about 500, at least about 600, at least about 700, at least about 800, at least about 900, or at least about 1000 molecules are detected in a single reaction or a single reaction container. In another example, at least about 2000, at least about 5000, at least about 10000, at least about 15000, at least about 20000, at least about 30000, at least about 40000, at least about 50000, at least about 100000, at least about 200000, at least about 300000, at least about 400000, at least about 500000, at least about 600000, at least about 700000, at least about 800000, at least about 900000, or at least about 1000000 molecules are detected in a single reaction or a single reaction container.

Applications

The methods of the present invention can be used in the analysis of genetic information of selective genomic regions of interest as well as genomic regions which may interact with the

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selective region of interest. Amplification methods as disclosed herein can be used in the devices, kits, and methods known to the art for genetic analysis, such as, but not limited to those found in U.S. Pat. Nos. 6,449,562, 6,287,766, 7,361,468, 7,414,117. 6,225,109, and 6,110,709. In some cases, amplification methods of the present invention can be used to amplify target nucleic acid for DNA hybridization studies to determine the presence or absence of polymorphisms. The polymorphisms, or alleles, can be associated with diseases or conditions such as genetic disease. In other cases the polymorphisms can be associated with susceptibility to diseases or conditions, for example, polymorphisms associated with addiction, degenerative and age related conditions, cancer, and the like. In other cases, the polymorphisms can be associated with beneficial traits such as increased coronary health, or resistance to diseases such as HIV or malaria, or resistance to degenerative diseases such as osteoporosis, Alzheimer's or dementia.

The compositions and methods of the invention can be used for diagnostic, prognostic, therapeutic, patient stratification, drug development, treatment selection, and screening purposes. The present invention provides the advantage that many different target molecules can be analyzed at one time from a single biomolecular sample using the methods of the invention. This allows, for example, for several diagnostic tests to be performed on one sample.

The composition and methods of the invention can be used in genomics. The methods described herein will typically provide an answer rapidly which is very desirable for this application. The methods and composition described herein can be used in the process of finding biomarkers that may be used for diagnostics or prognostics and as indicators of health and disease. The methods and composition described herein can be used to screen for drugs, e.g., drug development, selection of treatment, determination of treatment efficacy and/or identify targets for pharmaceutical development. The ability to test gene expression on screening assays involving drugs is very important because proteins are the final gene product in the body. In some embodiments, the methods and compositions described herein will measure both protein and gene expression simultaneously which will provide the most information regarding the particular screening being performed.

The composition and methods of the invention can be used in gene expression analysis. The methods described herein discriminate between nucleotide sequences. The difference

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between the target nucleotide sequences can be, for example, a single nucleic acid base difference, a nucleic acid deletion, a nucleic acid insertion, or rearrangement. Such sequence differences involving more than one base can also be detected. The process of the present invention is able to detect infectious diseases, genetic diseases, and cancer. It is also useful in environmental monitoring, forensics, and food science. Examples of genetic analyses that can be performed on nucleic acids include e.g., SNP detection, STR detection, RNA expression analysis, promoter methylation, gene expression, virus detection, viral subtyping and drug resistance.

The present methods can be applied to the analysis of biomolecular samples obtained or derived from a patient so as to determine whether a diseased cell type is present in the sample, the stage of the disease, the prognosis for the patient, the ability to the patient to respond to a particular treatment, or the best treatment for the patient. The present methods can also be applied to identify biomarkers for a particular disease.

In some embodiments, the methods described herein are used in the diagnosis of a condition. As used herein the term "diagnose" or "diagnosis" of a condition includes predicting or diagnosing the condition, determining predisposition to the condition, monitoring treatment of the condition, diagnosing a therapeutic response of the disease, and prognosis of the condition, condition progression, and response to particular treatment of the condition. For example, a blood sample can be assayed according to any of the methods described herein to determine the presence and/or quantity of markers of a disease or malignant cell type in the sample, thereby diagnosing or staging the a disease or a cancer.

In some embodiments, the methods and composition described herein are used for the diagnosis and prognosis of a condition.

Numerous immunologic, proliferative and malignant diseases and disorders are especially amenable to the methods described herein. Immunologic diseases and disorders include allergic diseases and disorders, disorders of immune function, and autoimmune diseases and conditions. Allergic diseases and disorders include but are not limited to allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic eczema, atopic dermatitis, and food allergy. Immunodeficiencies include but are not limited to severe combined immunodeficiency (SCID),

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hypereosinophilic syndrome, chronic granulomatous disease, leukocyte adhesion deficiency I and II, hyper IgE syndrome, Chediak Higashi, neutrophilias, neutropenias, aplasias, Agammaglobulinemia, hyper-IgM syndromes, DiGeorge/Velocardial-facial syndromes and Interferon gamma-TH1 pathway defects. Autoimmune and immune dysregulation disorders include but are not limited to rheumatoid arthritis, diabetes, systemic lupus erythematosus, Graves' disease, Graves ophthalmopathy, Crohn's disease, multiple sclerosis, psoriasis, systemic sclerosis, goiter and struma lymphomatosa (Hashimoto's thyroiditis, lymphadenoid goiter), alopecia aerata, autoimmune myocarditis, lichen sclerosis, autoimmune uveitis, Addison's disease, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritis nodosa, and inflammatory bowel disease, allograft rejection and tissue destructive from allergic reactions to infectious microorganisms or to environmental antigens.

Proliferative diseases and disorders that may be evaluated by the methods of the invention include, but are not limited to, hemangiomatosis in newborns; secondary progressive multiple sclerosis; chronic progressive myelodegenerative disease; neurofibromatosis; ganglioneuromatosis; keloid formation; Paget's Disease of the bone; fibrocystic disease (e.g., of the breast or uterus); sarcoidosis: Peronies and Duputren's fibrosis, cirrhosis, atherosclerosis and vascular restenosis.

Malignant diseases and disorders that may be evaluated by the methods of the invention include both hematologic malignancies and solid tumors.

Hematologic malignancies are especially amenable to the methods of the invention when the sample is a blood sample, because such malignancies involve changes in blood-borne cells. Such malignancies include non-Hodgkin's lymphoma, Hodgkin's lymphoma, non-B cell lymphomas, and other lymphomas, acute or chronic leukemias, polycythemias, thrombocythemias, multiple myeloma, myelodysplastic disorders, myeloproliferative disorders, myelofibroses, atypical immune lymphoproliferations and plasma cell disorders.

Plasma cell disorders that may be evaluated by the methods of the invention include multiple myeloma, amyloidosis and Waldenstrom's macroglobulinemia.

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Example of solid tumors include, but are not limited to, colon cancer, breast cancer, lung cancer, prostate cancer, brain tumors, central nervous system tumors, bladder tumors, melanomas, liver cancer, osteosarcoma and other bone cancers, testicular and ovarian carcinomas, head and neck tumors, and cervical neoplasms.

Genetic diseases can also be detected by the process of the present invention. This can be carried out by prenatal or post-natal screening for chromosomal and genetic aberrations or for genetic diseases. Examples of detectable genetic diseases include: 21 hydroxylase deficiency, cystic fibrosis, Fragile X Syndrome, Turner Syndrome, Duchenne Muscular Dystrophy, Down Syndrome or other trisomies, heart disease, single gene diseases, HLA typing, phenylketonuria, sickle cell anemia, Tay-Sachs Disease, thalassemia, Klinefelter Syndrome, Huntington Disease, autoimmune diseases, lipidosis, obesity defects, hemophilia, inborn errors of metabolism, and diabetes.

The methods described herein can be used to diagnose pathogen infections, for example infections by intracellular bacteria and viruses, by determining the presence and/or quantity of markers of bacterium or virus, respectively, in the sample.

A wide variety of infectious diseases can be detected by the process of the present invention. Typically, these are caused by bacterial, viral, parasite, and fungal infectious agents. The resistance of various infectious agents to drugs can also be determined using the present invention.

Bacterial infectious agents which can be detected by the present invention include Escherichia coli, Salmonella, Shigella, KlESBiella, Pseudomonas, Listeria monocytogenes, Mycobacterium tuberculosis, Mycobacterium aviumintracellulare, Yersinia, Francisella, Pasteurella, Brucella, Clostridia, Bordetella pertussis, Bacteroides, Staphylococcus aureus, Streptococcus pneumonia, B-Hemolytic strep., Corynebacteria, Legionella, Mycoplasma, Ureaplasma, Chlamydia, Neisseria gonorrhea, Neisseria meningitides, Hemophilus influenza, Enterococcus faecalis, Proteus vulgaris, Proteus mirabilis, Helicobacter pylori, Treponema palladium, Borrelia burgdorferi, Borrelia recurrentis, Rickettsial pathogens, Nocardia, and Acitnomycetes.

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Fungal infectious agents which can be detected by the present invention include Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Paracoccidioides brasiliensis, Candida albicans, Aspergillus fumigautus, Phycomycetes (Rhizopus), Sporothrix schenckii, Chromomycosis, and Maduromycosis.

Viral infectious agents which can be detected by the present invention include human immunodeficiency virus, human T-cell lymphocytotrophic virus, hepatitis viruses (e.g., Hepatitis B Virus and Hepatitis C Virus), Epstein-Barr Virus, cytomegalovirus, human papillomaviruses, orthomyxo viruses, paramyxo viruses, adenoviruses, corona viruses, rhabdo viruses, polio viruses, toga viruses, bunya viruses, arena viruses, rubella viruses, and reo viruses.

Parasitic agents which can be detected by the present invention include Plasmodium falciparum, Plasmodium malaria, Plasmodium vivax, Plasmodium ovale, Onchoverva volvulus, Leishmania, Trypanosoma spp., Schistosoma spp., Entamoeba histolytica, Cryptosporidum, Giardia spp., Trichimonas spp., Balatidium coli, Wuchereria bancrofti, Toxoplasma spp., Enterobius vermicularis, Ascaris lumbricoides, Trichuris trichiura, Dracunculus medinesis, trematodes, Diphyllobothrium latum, Taenia spp., Pneumocystis carinii, and Necator americanis.

The present invention is also useful for detection of drug resistance by infectious agents. For example, vancomycin-resistant Enterococcus faecium, methicillin-resistant Staphylococcus aureus, penicillin-resistant Streptococcus pneumoniae, multi-drug resistant Mycobacterium tuberculosis, and AZT-resistant human immunodeficiency virus can all be identified with the present invention

Thus, the target molecules detected using the compositions and methods of the invention can be either patient markers (such as a cancer marker) or markers of infection with a foreign agent, such as bacterial or viral markers.

The compositions and methods of the invention can be used to identify and/or quantify a target molecule whose abundance is indicative of a biological state or disease condition, for example, blood markers that are upregulated or downregulated as a result of a disease state.

In some embodiments, the methods and compositions of the present invention can be used for cytokine expression. The low sensitivity of the methods described herein would be

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helpful for early detection of cytokines, e.g., as biomarkers of a condition, diagnosis or prognosis of a disease such as cancer, and the identification of subclinical conditions.

Sample

The different samples from which the target polynucleotides are derived can comprise multiple samples from the same individual, samples from different individuals, or combinations thereof. In some embodiments, a sample comprises a plurality of polynucleotides from a single individual. In some embodiments, a sample comprises a plurality of polynucleotides from two or more individuals. An individual is any organism or portion thereof from which target polynucleotides can be derived, non-limiting examples of which include plants, animals, fungi, protists, monerans, viruses, mitochondria, and chloroplasts. Sample polynucleotides can be isolated from a subject, such as a cell sample, tissue sample, or organ sample derived therefrom, including, for example, cultured cell lines, biopsy, blood sample, or fluid sample containing a cell. The subject may be an animal, including but not limited to, an animal such as a cow, a pig, a mouse, a rat, a chicken, a cat, a dog, etc., and is usually a mammal, such as a human. Samples can also be artificially derived, such as by chemical synthesis. In some embodiments, the samples comprise DNA. In some embodiments, the samples comprise genomic DNA. In some embodiments, the samples comprise mitochondrial DNA, chloroplast DNA, plasmid DNA, bacterial artificial chromosomes, yeast artificial chromosomes, oligonucleotide tags, or combinations thereof. In some embodiments, the samples comprise DNA generated by primer extension reactions using any suitable combination of primers and a DNA polymerase, including but not limited to polymerase chain reaction (PCR), reverse transcription, and combinations thereof. Where the template for the primer extension reaction is RNA, the product of reverse transcription is referred to as complementary DNA (cDNA). Primers useful in primer extension reactions can comprise sequences specific to one or more targets, random sequences, partially random sequences, and combinations thereof. Reaction conditions suitable for primer extension reactions are known in the art. In general, sample polynucleotides comprise any polynucleotide present in a sample, which may or may not include target polynucleotides.

Methods for the extraction and purification of nucleic acids are well known in the art. For example, nucleic acids can be purified by organic extraction with phenol, phenol/chloroform/isoamyl alcohol, or similar formulations, including TRIzol and TriReagent.

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Other non-limiting examples of extraction techniques include: (1) organic extraction followed by ethanol precipitation, e.g., using a phenol/chloroform organic reagent (Ausubel et al., 1993), with or without the use of an automated nucleic acid extractor, e.g., the Model 341 DNA Extractor available from Applied Biosystems (Foster City, Calif.); (2) stationary phase adsorption methods (U.S. Pat. No. 5,234,809; Walsh et al., 1991); and (3) salt-induced nucleic acid precipitation methods (Miller et al., (1988), such precipitation methods being typically referred to as "salting-out" methods. Another example of nucleic acid isolation and/or purification includes the use of magnetic particles to which nucleic acids can specifically or non-specifically bind, followed by isolation of the beads using a magnet, and washing and eluting the nucleic acids from the beads (see e.g. U.S. Pat. No. 5,705,628). In some embodiments, the above isolation methods may be preceded by an enzyme digestion step to help eliminate unwanted protein from the sample, e.g., digestion with proteinase K, or other like proteases. See, e.g., U.S. Pat. No. 7,001,724. If desired, RNase inhibitors may be added to the lysis buffer. For certain cell or sample types, it may be desirable to add a protein denaturation/digestion step to the protocol. Purification methods may be directed to isolate DNA, RNA, or both. When both DNA and RNA are isolated together during or subsequent to an extraction procedure, further steps may be employed to purify one or both separately from the other. Sub-fractions of extracted nucleic acids can also be generated, for example, purification by size, sequence, or other physical or chemical characteristic. In addition to an initial nucleic isolation step, purification of nucleic acids can be performed after any step in the methods of the invention, such as to remove excess or unwanted reagents, reactants, or products.

In some embodiments, sample polynucleotides are fragmented into a population of fragmented DNA molecules of one or more specific size range(s). In some embodiments, fragments are generated from at least about 1, 10, 100, 1000, 10000, 100000, 300000, 500000, or more genome-equivalents of starting DNA. Fragmentation may be accomplished by methods known in the art, including chemical, enzymatic, and mechanical fragmentation. In some embodiments, the fragments have an average length from about 10 to about 10,000, 20,000, 30,000, 40,000, 50,000 or more nucleotides. In some embodiments, the fragments have an average length from about 50 to about 2,000 nucleotides. In some embodiments, the fragments have an average length from about 100-50,000, 200-2,500, 10-1,000, 10-800, 10-500, 50-500,

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50-250, 50-150 nucleotides, or any range bounded by any of these values (e.g. about 200-500). In some embodiments, the fragments have an average length less than 500 nucleotides, such as less than 400 nucleotides, less than 300 nucleotides, less than 200 nucleotides, or less than 150 nucleotides. In some embodiments, the fragmentation is accomplished mechanically comprising subjection sample polynucleotides to acoustic sonication. In some embodiments, the fragmentation comprises treating the sample polynucleotides with one or more enzymes under conditions suitable for the one or more enzymes to generate double-stranded nucleic acid breaks. Examples of enzymes useful in the generation of polynucleotide fragments include sequence specific and non-sequence specific nucleases. Non-limiting examples of nucleases include DNase I, Fragmentase, restriction endonucleases, variants thereof, and combinations thereof. For example, digestion with DNase I can induce random double-stranded breaks in DNA in the absence of Mg^{++} and in the presence of Mn^{++}. In some embodiments, fragmentation comprises treating the sample polynucleotides with one or more restriction endonucleases. Fragmentation can produce fragments having 5′ overhangs, 3′ overhangs, blunt ends, or a combination thereof. In some embodiments, such as when fragmentation comprises the use of one or more restriction endonucleases, cleavage of sample polynucleotides leaves overhangs having a predictable sequence. In some embodiments, the method includes the step of size selecting the fragments via standard methods such as column purification or isolation from an agarose gel.

n some embodiments, the 5′ and/or 3′ end nucleotide sequences of fragmented DNA are not modified prior to ligation with one or more adapter oligonucleotides. For example, fragmentation by a restriction endonuclease can be used to leave a predictable overhang, followed by ligation with one or more adapter oligonucleotides comprising an overhang complementary to the predictable overhang on a DNA fragment. In another example, cleavage by an enzyme that leaves a predictable blunt end can be followed by ligation of blunt-ended DNA fragments to adapter oligonucleotides comprising a blunt end. In some embodiments, the fragmented DNA molecules are blunt-end polished (or "end repaired") to produce DNA fragments having blunt ends, prior to being joined to adapters. The blunt-end polishing step may be accomplished by incubation with a suitable enzyme, such as a DNA polymerase that has both 3′ to 5′ exonuclease activity and 5′ to 3′ polymerase activity, for example T4 polymerase. In some embodiments, end repair is followed by an addition of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12,

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13, 14, 15, 16, 17, 18, 19, 20 or more nucleotides, such as one or more adenine, one or more thymine, one or more guanine, or one or more cytosine, to produce an overhang. DNA fragments having an overhang can be joined to one or more adapter oligonucleotides having a complementary overhang, such as in a ligation reaction. For example, a single adenine can be added to the 3′ ends of end repaired DNA fragments using a template independent polymerase, followed by ligation to one or more adapters each having a thymine at a 3′ end. In some embodiments, adapter oligonucleotides can be joined to blunt end double-stranded DNA fragment molecules which have been modified by extension of the 3′ end with one or more nucleotides followed by 5′ phosphorylation. In some cases, extension of the 3′ end may be performed with a polymerase such as for example Klenow polymerase or any of the suitable polymerases provided herein, or by use of a terminal deoxynucleotide transferase, in the presence of one or more dNTPs in a suitable buffer containing magnesium. In some embodiments, target polynucleotides having blunt ends are joined to one or more adapters comprising a blunt end. Phosphorylation of 5′ ends of DNA fragment molecules may be performed for example with T4 polynucleotide kinase in a suitable buffer containing ATP and magnesium. The fragmented DNA molecules may optionally be treated to dephosphorylate 5′ ends or 3′ ends, for example, by using enzymes known in the art, such as phosphatases.

In some embodiments, each of the plurality of independent samples comprises at least about 1 pg, 10 pg, 100 pg, 1 ng, 10 ng, 20 ng, 30 ng, 40 ng, 50 ng, 75 ng, 100 ng, 150 ng, 200 ng, 250 ng, 300 ng, 400 ng, 500 ng, 1 μg, 1.5 μg, 2 μg, or more of nucleic acid material. In some embodiments, each of the plurality of independent samples comprises less than about 1 pg, 10 pg, 100 pg, 1 ng, 10 ng, 20 ng, 30 ng, 40 ng, 50 ng, 75 ng, 100 ng, 150 ng, 200 ng, 250 ng, 300 ng, 400 ng, 500 ng, 1 μg, 1.5 μg, 2 μg, or more of nucleic acid.

Kits

Any of the compositions described herein may be comprised in a kit. In a non-limiting example the kit, in suitable container means, comprises: equipment and reagents for DNA fragmentation, an end repair enzyme, adapter ligation enzymes, DNA adapter oligonucleotides,

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equipment and/or reagents for size selection, and/or qPCR standards. In another non-limiting example the kit, in suitable container means, comprises PCR enzymes and plastics. In a yet further non-limiting example the kit, in suitable container means, comprises a holey plate with fragmentation enzyme, a plate, for example an elution plate, with barcoding oligos, and/or a plate, for example an elution plate, optionally preloaded with PCR enzyme.

The kit can further contain enzymes and/or reagents useful for ligation, cleavage and or amplification. The kit can contain a DNA-polymerase. The kit can contain reagents for amplification. The kit can further optionally contain reagents for sequencing, for example, reagents useful for next-generation massively parallel sequencing methods.

The containers of the kits can generally include at least one vial, test tube, flask, bottle, syringe or other containers, into which a component may be placed, and preferably, suitably aliquoted. Where there is more than one component in the kit, the kit also can generally contain a second, third or other additional container into which the additional components can be separately placed. However, various combinations of components can be comprised in a container.

When the components of the kit are provided in one or more liquid solutions, the liquid solution can be an aqueous solution. However, the components of the kit can be provided as dried powder(s). When reagents and/or components are provided as a dry powder, the powder can be reconstituted by the addition of a suitable solvent.

A kit can include instructions for employing the kit components as well the use of any other reagent not included in the kit. Instructions can include variations that can be implemented.

In one aspect, the invention provides kits containing any one or more of the elements disclosed in the above methods and compositions. In some embodiments, a kit comprises a composition of the invention, in one or more containers. In some embodiments, the invention provides kits comprising adapters, primers, and/or other oligonucleotides described herein. In some embodiments, the kit further comprises one or more of: (a) a DNA ligase, (b) a DNA-dependent DNA polymerase, (c) an RNA-dependent DNA polymerase, (d) random primers, (e) primers comprising at least 4 thymidines at the 3' end, (f) a DNA endonuclease, (g) a DNA-

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dependent DNA polymerase, (h) one or more primers, each primer having one of a plurality of selected sequences, (i) a DNA kinase, (j) a DNA exonuclease, (k) magnetic beads, (l) an RNA ligase, and (m) one or more buffers suitable for one or more of the elements contained in said kit. The adapters, primers, other oligonucleotides, and reagents can be, without limitation, any of those described above. Elements of the kit can further be provided, without limitation, in any of the amounts and/or combinations (such as in the same kit or same container) described above. The kits may further comprise additional agents, such as those described above, for use according to the methods of the invention. The kit elements can be provided in any suitable container, including but not limited to plates, test tubes, vials, flasks, bottles, ampules, syringes, or the like. The agents can be provided in a form that may be directly used in the methods of the invention, or in a form that requires preparation prior to use, such as in the reconstitution of lyophilized agents. Agents may be provided in aliquots for single-use or as stocks from which multiple uses, such as in a number of reaction, may be obtained.

Computer Systems

The computer system 500 illustrated in Figure 12 may be understood as a logical apparatus that can read instructions from media 511 and/or a network port 505, which can optionally be connected to server 509 having fixed media 512. The system, such as shown in Figure 12 can include a CPU 501, disk drives 503, optional input devices such as keyboard 515 and/or mouse 516 and optional monitor 507. Data communication can be achieved through the indicated communication medium to a server at a local or a remote location. The communication medium can include any means of transmitting and/or receiving data. For example, the communication medium can be a network connection, a wireless connection or an internet connection. Such a connection can provide for communication over the World Wide Web. It is envisioned that data relating to the present disclosure can be transmitted over such networks or connections for reception and/or review by a party 522 as illustrated in Figure 12.

Figure 13 is a block diagram illustrating a first example architecture of a computer system 100 that can be used in connection with example embodiments of the present invention. As depicted in Figure 13, the example computer system can include a processor 102 for processing instructions. Non-limiting examples of processors include: Intel Xeon™ processor, AMD Opteron™ processor, Samsung 32-bit RISC ARM 1176JZ(F)-S v1.0™ processor, ARM

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Cortex-A8 Samsung S5PC100™ processor, ARM Cortex-A8 Apple A4™ processor, Marvell PXA 930™ processor, or a functionally-equivalent processor. Multiple threads of execution can be used for parallel processing. In some embodiments, multiple processors or processors with multiple cores can also be used, whether in a single computer system, in a cluster, or distributed across systems over a network comprising a plurality of computers, cell phones, and/or personal data assistant devices.

As illustrated in Figure 13, a high speed cache 104 can be connected to, or incorporated in, the processor 102 to provide a high speed memory for instructions or data that have been recently, or are frequently, used by processor 102. The processor 102 is connected to a north bridge 106 by a processor bus 108. The north bridge 106 is connected to random access memory (RAM) 110 by a memory bus 112 and manages access to the RAM 110 by the processor 102. The north bridge 106 is also connected to a south bridge 114 by a chipset bus 116. The south bridge 114 is, in turn, connected to a peripheral bus 118. The peripheral bus can be, for example, PCI, PCI-X, PCI Express, or other peripheral bus. The north bridge and south bridge are often referred to as a processor chipset and manage data transfer between the processor, RAM, and peripheral components on the peripheral bus 118. In some alternative architectures, the functionality of the north bridge can be incorporated into the processor instead of using a separate north bridge chip.

In some embodiments, system 100 can include an accelerator card 122 attached to the peripheral bus 118. The accelerator can include field programmable gate arrays (FPGAs) or other hardware for accelerating certain processing. For example, an accelerator can be used for adaptive data restructuring or to evaluate algebraic expressions used in extended set processing.

Software and data are stored in external storage 124 and can be loaded into RAM 110 and/or cache 104 for use by the processor. The system 100 includes an operating system for managing system resources; non-limiting examples of operating systems include: Linux, Windows™, MACOS™, BlackBerry OS™, iOS™, and other functionally-equivalent operating systems, as well as application software running on top of the operating system for managing data storage and optimization in accordance with example embodiments of the present invention.

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In this example, system 100 also includes network interface cards (NICs) 120 and 121 connected to the peripheral bus for providing network interfaces to external storage, such as Network Attached Storage (NAS) and other computer systems that can be used for distributed parallel processing.

Figure 14 is a diagram showing a network 200 with a plurality of computer systems 202a, and 202b, a plurality of cell phones and personal data assistants 202c, and Network Attached Storage (NAS) 204a, and 204b. In example embodiments, systems 202a, 202b, and 202c can manage data storage and optimize data access for data stored in Network Attached Storage (NAS) 204a and 204b. A mathematical model can be used for the data and be evaluated using distributed parallel processing across computer systems 202a, and 202b, and cell phone and personal data assistant systems 202c. Computer systems 202a, and 202b, and cell phone and personal data assistant systems 202c can also provide parallel processing for adaptive data restructuring of the data stored in Network Attached Storage (NAS) 204a and 204b. Figure 14 illustrates an example only, and a wide variety of other computer architectures and systems can be used in conjunction with the various embodiments of the present invention. For example, a blade server can be used to provide parallel processing. Processor blades can be connected through a back plane to provide parallel processing. Storage can also be connected to the back plane or as Network Attached Storage (NAS) through a separate network interface.

In some example embodiments, processors can maintain separate memory spaces and transmit data through network interfaces, back plane or other connectors for parallel processing by other processors. In other embodiments, some or all of the processors can use a shared virtual address memory space.

Figure 15 is a block diagram of a multiprocessor computer system 300 using a shared virtual address memory space in accordance with an example embodiment. The system includes a plurality of processors 302a-f that can access a shared memory subsystem 304. The system incorporates a plurality of programmable hardware memory algorithm processors (MAPs) 306a-f in the memory subsystem 304. Each MAP 306a-f can comprise a memory 308a-f and one or more field programmable gate arrays (FPGAs) 310a-f. The MAP provides a configurable functional unit and particular algorithms or portions of algorithms can be provided to the FPGAs

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310a-f for processing in close coordination with a respective processor. For example, the MAPs can be used to evaluate algebraic expressions regarding the data model and to perform adaptive data restructuring in example embodiments. In this example, each MAP is globally accessible by all of the processors for these purposes. In one configuration, each MAP can use Direct Memory Access (DMA) to access an associated memory 308a-f, allowing it to execute tasks independently of, and asynchronously from, the respective microprocessor 302a-f. In this configuration, a MAP can feed results directly to another MAP for pipelining and parallel execution of algorithms.

The above computer architectures and systems are examples only, and a wide variety of other computer, cell phone, and personal data assistant architectures and systems can be used in connection with example embodiments, including systems using any combination of general processors, co-processors, FPGAs and other programmable logic devices, system on chips (SOCs), application specific integrated circuits (ASICs), and other processing and logic elements. In some embodiments, all or part of the computer system can be implemented in software or hardware. Any variety of data storage media can be used in connection with example embodiments, including random access memory, hard drives, flash memory, tape drives, disk arrays, Network Attached Storage (NAS) and other local or distributed data storage devices and systems.

In example embodiments, the computer system can be implemented using software modules executing on any of the above or other computer architectures and systems. In other embodiments, the functions of the system can be implemented partially or completely in firmware, programmable logic devices such as field programmable gate arrays (FPGAs) as referenced in Figure 15, system on chips (SOCs), application specific integrated circuits (ASICs), or other processing and logic elements. For example, the Set Processor and Optimizer can be implemented with hardware acceleration through the use of a hardware accelerator card, such as accelerator card 122 illustrated in Figure 13.

Incorporation by Reference

References and citations to other documents, such as patents, patent applications, patent

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publications, journals, books, papers, web contents, have been made throughout this disclosure. All such documents are hereby incorporated herein by reference in their entirety for all purposes.

Equivalents

The invention may be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein.

EXAMPLES

Example 1: Genome assembly from short sequence reads

An in vitro protocol was developed that allows amplification sequencing and reassembly of intermediate sized genomics fragments. In brief, genomic DNA was sheared to appropriate fragment size, amplification adapters were ligated at the ends of fragments, and the library was quantitated using qPCR to establish the number of amplifiable DNA fragments. The library was amplified library using adapter-specific primers with PCR after diluting the library to a necessary concentration. Amplification was carried out in independent wells of a PCR plate such that each well had an independent amplified population of molecules. The average number of molecules within each well was kept around 500-1000 to reduce complexity of unique DNA sequences, which is important to aid sequence assembly downstream. The resulting pool of amplified molecules were fragmented into a sequencing library using Nextera DNA transposase, and sequencing adapters with barcodes unique to each well were incorporated through limited cycle PCR. The library was then sequenced. After sequencing, reads were separated according to the barcodes and original long fragments were assembled using developed assembly algorithms described herein.

Methods of the invention allowed highly parallel preparation and sequencing of a large number of individual samples prepared from an artificially limited population of DNA molecules. The resulting complexity bottleneck was important for successful reassembly of the long DNA fragments.

To calibrate performance of the method, it was first applied it to sequencing of human genomic DNA. DNA was sheared to 4-8kb, and a 5-7kb gel cut was used as starting material for

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sample preparation. The Library was quantitated using qPCR relative to a set of previously sequenced standards and dilution was chosen to have a mean number of molecules around 1000. In this protocol, 192 barcodes were used, corresponding to wells of two 96 well plates. Barcodes were chosen such that to guarantee that all barcodes were at least two errors away from each other, and all reads that did not match exact barcode sequences were discarded. After sequencing, reads were aligned to a human genome reference, and it was established that an average number of distinct fragments was close to 1000. Fragment length distribution was found to be smaller than the initial gel cut, which can be explained by the fact that last few hundred base pairs from each fragment were underrepresented in the data due to the library construction method. Median coverage per fragment was around 20x which was sufficient to allow de-novo assembly of intermediate sized fragments (Figure 2).

Consensus sequences were assembled as described above. After assembly, a distribution of contigs with median size (N50) of approximately 3.5kb was obtained. Complete reconstruction of full fragments was not possible for all intermediate sized fragments due to high repeat content of the human genome and variation of coverage due to sampling statistics; however, low frequency repeats were resolved using methods of the invention because it is unlikely that they will appear in multiple wells (Figure 3).

Due to artificial dilution and amplification of limited amount of molecules, most of the fragments within each partitioned portion were a result of amplification of a fragment originating from a disjoint set of locations on the genome (otherwise overlaps would have been detected by coverage based analysis, or detecting heterozygous variants inconsistent with single molecule amplification, or by analysis of end markers embedded in the amplification adapters). This allowed haplotype-resolved variant calling to be performed by detecting variants using a pipeline that assumes haploid genome and "stitching together" overlapping fragments that share the same variants to obtain longer stretches of phased variants. This can be combined with haplotyping chips and bioinformatics approaches to extend continuous stretches of phased genome.

Methods of the invention were used to detect novel sequences by comparative analysis of assembled intermediate sized fragments (Fig 4).

Example 2: Sample DNA preparation

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Genomic DNA was prepared using DNAeasy kit and sheared with HydroShear instrument to obtain DNA with size range around 10kb. Sample was run on 0.8% e-gel to perform initial size selection to select band 7-10kb band. Sample was analyzed using Agilent Bioanalyzer to confirm size distribution. DNA was treated with NEB end repair kit to obtain blunt end 5' phosphorylated ends.

Example 3: Repair ends

A New England Biolabs end repair module was used to make blunt ends as follows. In 100uL volume mix: 10uL of 10X Neb next End repair reaction buffer, 5uL of NEB Next End repair enzyme mix, 50uL of eluted sample, and 35uL of water. The mixture is incubated for 30 minutes at 20°C and then purified on a Qiagen column. Elusion was performed in 30ul water.

Example 4: Ligate Amplification Adaptors

A kit commercially available from 454 Life Sciences was used to ligate adapters onto the fragmented nucleic acid. The two sequence primers below were used:

Primer A1: 5'-CCATCTCATCCCTGCGTGTCTCCGACTCAG-3'

3'-TCTCCGACTCAG-5'

Primer B: 5'-/5BioTEG/CCTATCCCCTGTGTGCCTTGGCAGTCTCAG-3'

3'-TGGCAGTCTCAG-5'

Ligation was accomplished as follows. A mix of DNA 10 ul (450ng); 2x ligation Buffer 20ul; Adapter mix 5ul; and Ligase 5ul was incubated at 25°C for 15 minutes.

Example 5: DNA purification

Ampure beads purification was performed after ligation. The ratio of DNA to beads was 1:1.5 (Human DNA 40ul:60ul beads). The DNA and beads were gently vortexed by tapping on tube and incubated for 10 minutes. The tubes were then placed on a magnetic rack for 3 minutes and the supernatant was discarded. Two washed were performed with 70% ethanol without removing tubes from the rack. Most of the ethanol was removed and caps were removed from the tubes to allow for air drying until completely dry (approximately 5 minutes). Elution was performed in 25 µl of water. Incubation was for a few minutes and the supernatant was collected.

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Example 6: Fill-in reaction and size selection

A mixture of DNA 20ul; 10x fill in buffer 2.5ul; dNTP mix 1ul; fill in polymerase 1.5ul was prepared and incubated for 20 minutes at 37°C. 20 µL was transferred to the agarose gel and size selection was performed. Samples were cut from Qiagen gel and nucleic acid fragments eluted in 30ul water.

Example 7: Quantitate library using qPCR

To quantitate, the sample library was compared to a reference library of known concentration, using LongAmp polymerase, and the same primer concentration that will be used for the amplification reaction. A mixture of 1.25uL of 20x EvaGreen dye, 0.5uL of Rox reference dye in 25uL reaction volume was prepared. The qPCR was conducted according to the same thermocycling protocol as the used from the PCR reaction, see Table 2.

Example 8: PCR amplification of partitioned nucleic acids

The PCR reaction mixture is shown in Table 1 below.

Table 1

	1rnx	220rnx
LONGAMP-V2-LEFT (100µm)	0.1µl	20µl
LONGAMP-V2-RIGHT (100µm)	0.1µl	20µl
DNA	x (500 molecules)	x (110k molecules)
NEB LongAmp (M0287L)	12.5µl	2750µl
Water	12.05µl	2673µl

LONGAMP-V2-LEFT 5'- CCA TCT CAT CCC TGC GTG TCT CCG -3'

LONGAMP-V2-RIGHT 5'- CCT ATC CCC TGT GTG CCT TGG CAG T -3'

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The PCR reaction was conducted as follows. Two 96 half skirt plates were placed on ice to allow them to cool. The PCR cycler was set at 94°C for preheating. To a 15mL tube, was added water, both primers, and calculated amount of the sample. This mixture was vortexed rigorously, and placed on ice to cool down. 2x Enzyme master mix was added and the mixture was vortexed rigorously. 25mL was transferred to a sterile container. Using an 8-channel pipette, the mixture was dispensed across all wells of both plates. The plates were covered with transparent PCR film, quickly spun, placed on the thermocycler, and the PCR reaction was conducted as shown in Table 2 below:

Table 2

Step	Temperature	Time
1	94	0:30
2	94	0:15
3	65	8:00
4	Cycle to step 2 24 times	
5	65	8:00
6	4	hold

Example 9: DNA purification

A Zymo ZR-96 DNA clean and concentration (Zymogen D4024) kit was used for DNA purification. The two Zymo plates were assembled and the membrane plate was put on top of the collection plate. After the PCR reaction was finished 100uL of the binding buffer was dispensed into each well and the PCR reaction contents were mixed with DNA binding buffer and transfer it to a Zymo plate. The plates were spun at 2200g (or more) for 5 minutes, discarding the flow-through. 300uL of the wash buffer was added to each well. The plates were spun again at 2200g (or more) for 5 minutes, discarding the flow-through. 300uL of the wash buffer was added to each well. The plates were spun again at 2200g (or more) for 5 minutes.

The membrane plate was transferred to an elution plate and the collection plate was discarded. 12uL of water was added to the middle of each membrane. The plates were spun at 2200g (or more) for 5 minutes, use slower ramp-up speed (4 instead of 9).

Example 10: Fragmentation

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The amplified nucleic acid is then fragmented. Each reaction had: 4uL of DNA from the previous step eluted in water; 1uL of 5x high molecular weight buffer, and 4nL of nextera enzyme Illumina compatible 250uL of high molecular weight buffer (HMW) and 10uL of Nextera were combined in a 2mL tube with enzyme. The mixture was vortexed, spun, and placed on ice. 4uL from elution plates was transferred to new PCR plates directly to the bottom without touching the walls. 1uL of the buffer-enzyme mixture was transferred to the walls of the 96 well plates, which were then covered with transparent PCR film. A quick spin down was performed to start the reaction, and the plates were vortexed while holding a rubber seal on the top to prevent cross-contamination between wells, followed by a second quick spin. The plates were placed on a cycler with a constant temperature of 55°C for about 5 minutes. The plates were removed from the cycler and DNA binding buffer was added to each well. The purification was repeated as described above and elution plates were used to which 1uL of 25X PCR primer mix designed to incorporate a custom set of bar code sequences according to the manufacturer recommendations was added.

Example 11: PCR reaction

Two plates were placed on ice and 12.5uL of 2x Phusion GC polymerase master mix (NEB M0532L) was transfer to the plates. All of the volume eluted after the fragmentation reaction was transferred to the wells. The plates contain: 1uL of 25x PCR primer mix that was added to elution plates; 11.5uL of DNA eluted in water after Nextera step; and 12.5uL of 2x Phusion polymerase. The plates were covered with transparent PCR film, vortexed, and spun. The plates were then placed on a cycler and thermocycled as shown in Table 3.

Table 3

Step	Temperature	Time
1	72	3:00
2	95	0:30
3	95	0:10
4	62	0:30
5	72	3:00
6	Cycle to 4 for 8 more times	
7	4	hold

Example 12: DNA purification

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The amplified DNA was purified using the Qiagen 96-well plate vacuum protocol, which is commercially available from Qiagen. 80 uL of PM (DNA binding buffer for Qiagen 96WP purification kit) was added to each well. Well contents were mixed and the volume from all 192 wells was transferred to 25ml tray. The contents of the tray were transferred to 50mL tubes and vortexed. The contents were then transferred to 16 wells of 96 well plate purification system and placed on vacuum manifold. The vacuum is turned on and left running until the liquid is gone. 900uL of PE buffer was added to each well, and the vacuum again was turned on until the liquid was gone. 900uL of PE buffer was added again to each well and the vacuum again was turned on for 10 minutes. 60uL of TE was added to the center of each well and let sit for 2 minutes, and the vacuum again was turned on for 5 minutes. All contents were transferred to a single 2mL tube.

Example 13: Size selection

The nucleic acid was then size selected using Egel Syber safe (2% agarose) gels. The gels were pre-run gel for 2 minutes. 8 middle lanes of the gels were loaded with 16 uL of the purified sample from last step, the next two lanes were filled with clean water, 16uL of 30ng/uL ladder was added to the nearby wells. The gels were run for 30 minutes, opened, and the band from 500-700bp was cut from the gels. The DNA was purified using two Qiaquick columns and eluted in 35uL of TE.

The purified DNA is then run again. Another 2% sybr safe gel was pre-run for 2 minutes. 4 lanes with purified sample from the first gel purification were loaded, water was loaded in nearby wells and two ladder wells. Gels were run for 30 minutes, opened, and the band from 500-700bp was cut. The DNA was purified using two Qiaquick columns and eluted in 35uL of TE.

Example 14: Quantitation

Quantitation (i.e., estimating number of molecules that can form clusters on Illumina flowcell) was performed with qPCR relative to a know standard previously characterized by direct DNA sequencing, using Agilent bioanalyzer, or using Fluidigm digital PCR to get absolute library quantitation.

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Example 15: Bioinformatic pipeline

After reads were obtained from sequencing instrument, they were subjected to a number of quality checks. First, sequences similar to the Nextera insertion sequences were detected and removed from ends of the reads. This situation may happen if distance between two read primers is less than read length, for example due to imperfect final gel purification. Second, quality trimming was then performed to remove ends of the reads that has quality less than a certain threshold, in this protocol, less than 15. Third, overlaps were detected between paired reads, if detected reads were combined in one single read and stored in a separate single read pool.

Reads were then split by bar code by matching indexing reads to a set of 192 7bp bar codes. Bar codes were designed such that they were at least two sequencing errors away from each other which makes miscalls very unlikely. High quality reads resulting from this process were then mapped to a genome reference in order to perform haplotype-resolved variant calling and obtain basic quality statistics.

Another pipeline used high quality reads for de-novo fragment assembly. Reads with certain bar codes were first pre-processed to correct low frequency kmers that were a result of sequencing errors. Resulting read pools were assembled in contigs, paired end read information was then used to combine contigs in scaffolds and partially mapped reads were then used to fill gaps in scaffolds. Resulting scaffolds were then assembled into bigger scaffolds using de-novo assemblers designed to work with Sanger data to produce draft genome assembly.

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What is claimed is:

1. A method for relating sequence components in a target polynucleotide, the method comprising:
    (a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length, and wherein the known nucleotide sequence is capable of serving as an amplification target;
    (b) partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 99.999%;
    (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments;
    (d) obtaining partial or complete sequence information from at least a subset of the fragments; and
    (e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides.
2. A method for relating sequence components in a target polynucleotide, the method comprising:
    (a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length of greater than 30 bp, and wherein the known nucleotide sequence is capable of serving as an amplification target;
    (b) partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 100%;

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(c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments;

(d) obtaining partial or complete sequence information from at least a subset of the fragments; and

(e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides.

3. The method as in one of claims 1-2, further comprising subjecting at least one partition to exponential nucleic acid amplification using the known nucleotide sequence as an amplification target thereby amplifying the one or more target polynucleotides into amplicons such that at least a fraction of the sequence segments originating from the at least one or more target polynucleotides or the amplicons that are exponentially amplified in the at least one partition is estimated to be present as a single copy prior to exponential nucleic acid amplification among the one or more target polynucleotides that get exponentially amplified in the at least one partition with a likelihood that is less than 99.999%.
4. The method as in one of claims 1-2, wherein the at least one sample comprises a first target polynucleotide and a second target polynucleotide each adjacent to a first known nucleotide sequence and a second known nucleotide sequence at at least one end, wherein the first known nucleotide sequence is not the same as the second known nucleotide sequence.
5. The method of claims 1, wherein the sequence segment length is greater than about 30bp.
6. The method as in one of claims 1-2, wherein the sequence segment length is greater than about 50bp.
7. The method as in one of claims 1-2, wherein the sequence segment length is less than about 100bp.
8. The method as in one of claims 1-2, wherein the fraction is greater than 10%.
9. The method as in one of claims 1-2, wherein the fraction is greater than 20%.
10. The method as in one of claims 1-2, wherein the fraction is greater than 50%.
11. The method as in one of claims 1-2, wherein the fraction is 95%.
12. The method as in one of claims 1-2, wherein the likelihood is greater than 80%.

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13. The method as in one of claims 1-2, wherein the likelihood is 99%.
14. The method as in one of claims 1-2, wherein upon partitioning at least one sequence segment is present in multiple copies in the at least one partition.
15. The method as in one of claims 1-2, wherein the method further comprises amplifying the target polynucleotide prior to subjecting the partition to polynucleotide fragmentation.
16. The method of claim 15, wherein the method further comprises exponentially amplifying the target polynucleotide prior to subjecting the partition to polynucleotide fragmentation.
17. The method as in one of claims 1-2, wherein the target polynucleotide is adjacent to a known nucleotide sequence at both ends.
18. The method as in one of claims 1-2, wherein the known sequence is introduced onto the target polynucleotide by ligating an adaptor oligonucleotide.
19. The method as in one of claims 1-2, wherein, on average, the fragments are longer than 10 bp.
20. The method as in one of claims 1-2, wherein on average, the fragments are shorter than 2000 bp.
21. The method as in one of claims 1-2, wherein on average, the fragments are shorter than 1000 bp.
22. The method as in one of claims 1-2, wherein on average, the fragments are longer than 250 bp.
23. The method as in one of claims 1-2, wherein on average, the one or more target polynucleotides are longer than 5000 bp.
24. The method as in one of claims 1-2, wherein on average, the one or more target polynucleotides are longer than 10000 bp.
25. The method as in one of claims 1-2, wherein the fragments within a partition are labeled with one or more partition specific barcodes.
26. The method of claim 25, wherein the barcodes are nucleic acid sequences.
27. The method of claim 25, wherein the barcodes are greater than 3 nucleotides long.
28. The method of claim 25, wherein the barcodes are greater than 5 nucleotides long.

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29. The method of claim 25, wherein the one or more partition specific barcodes comprise 2 barcodes that are each greater than 2 nucleotides long.
30. The method of claim 29, wherein all two partition specific barcodes comprise at least two differences in the nucleic acid sequence.
31. The method as in one of claim 1-2, wherein the sequence information comprises sequence reads obtained by sequencing.
32. The method as in one of claims 1-2, wherein the sequence information comprises an accuracy of greater than 99%.
33. The method as in one of claims 1-2, wherein the sequence information comprises an accuracy of greater than 95%.
34. The method as in one of claims 1-2, wherein the sequence information comprises an accuracy of greater than 90%.
35. The method as in one of claims 1-2, wherein the sequence information comprises an accuracy of greater than 80%.
36. The method as in one of claims 1-2, wherein the sequence information comprises an average accuracy of greater than 99%.
37. The method as in one of claims 1-2, wherein the sequence information comprises an average accuracy of greater than 95%.
38. The method as in one of claims 1-2, wherein the sequence information comprises an average accuracy of greater than 90%.
39. The method as in one of claims 1-2, wherein the sequence information comprises an average accuracy of greater than 80%.
40. The method of claim 31, wherein the sequence reads comprise an accuracy of greater than 99.98%.
41. The method of claim 31, wherein the sequence information spans more than 50 bp.
42. The method of claim 31, wherein the sequence information spans more than 100 bp.
43. The method of claim 31, wherein the sequence information spans more than 200 bp.
44. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 1 month.
45. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 2 weeks.

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46. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 1 week.
47. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 1 day.
48. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 3 hours.
49. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 1 hour.
50. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 30 minutes.
51. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 10 minutes.
52. The method as in one of claims 1-2, wherein all sequence information is obtained in less than 5 minutes.
53. The method as in one of claims 1-2, wherein the relating step comprises an average accuracy of at least 95%.
54. The method as in one of claims 1-2, wherein the relating step comprises an average accuracy of at least 99%.
55. The method as in one of claims 1-2, wherein the target polynucleotide within the sample is flagged if one or more of its sequence segments are substantially similar to one or more sequence segments of a second target polynucleotide partitioned into the same partition.
56. The method as in one of claims 1-2, further comprising a sequence coverage of greater than 20 fold.
57. The method as in one of claims 1-2, further comprising an average sequence coverage of less than 500 fold.
58. The method of claim 31, wherein the sequencing comprises sequencing by synthesis.
59. The method of claim 31, wherein the sequencing comprises ion semiconductor sequencing.
60. The method of claim 31, wherein the sequencing comprises single molecule real time sequencing.

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61. The method of claim 31, wherein the sequencing comprises nanopore sequencing.
62. The method of claim 31, wherein the sequencing comprises sequencing by electron microscopy.
63. The method as in one of claims 1-2, wherein the target polynucleotide originates from genomic DNA.
64. The method of claim 63, wherein the genomic DNA originates from a polyploid genome.
65. The method as in one of claims 1-2, wherein the target polypeptide comprises a portion of a major histocompatibility complex gene.
66. The method as in one of claims 1-2, wherein the target polypeptide originates from fetal DNA.
67. The method of claim 31, wherein the sequencing comprises obtaining paired end reads.
68. A method for relating sequence components in a target polynucleotide, the method comprising:
    (a) providing at least one sample comprising one or more target polynucleotides wherein each target polynucleotide comprises one or more sequence segments with a sequence length;
    (b) partitioning the sample into a finite plurality of partitions such that at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 99.999%;
    (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments;
    (d) obtaining partial or complete sequence information from the fragments; and
    (e) relating sequence information from a plurality of fragments into the target polynucleotides.
69. The method of claim 68, wherein a fraction of said one or more target polynucleotides in the sample are each attached to one or more labels.

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70. The method of claims 69, wherein said label is nucleic acid binding proteins, optical labels, nucleotide analogs, or oligonucleotides.

71. A method for relating sequence components in a target polynucleotide, the method comprising:

(a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length;

(b) partitioning the sample into a finite plurality of partitions and subjecting at least one partition to exponential nucleic acid amplification thereby amplifying the one or more target polynucleotides into amplicons such that at least a fraction of the sequence segments originating from the at least one or more target polynucleotides or the amplicons that are exponentially amplified in the at least one partition is estimated to be present as a single copy prior to exponential nucleic acid amplification among the one or more target polynucleotides that get exponentially amplified in the at least one partition with a likelihood that is less than 99.999%;

(c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments;

(d) obtaining partial or complete sequence information from at least a subset of the fragments; and

(e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides.

72. A method for relating sequence components in a target polynucleotide, the method comprising:

(a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length of greater than 30 bp;

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(b) partitioning the sample into a finite plurality of partitions and subjecting at least one partition to exponential nucleic acid amplification thereby amplifying the one or more target polynucleotides into amplicons such that at least a fraction of the sequence segments originating from the at least one or more target polynucleotides or the amplicons that are exponentially amplified in the at least one partition is estimated to be present as a single copy prior to exponential nucleic acid amplification among the one or more target polynucleotides that get exponentially amplified in the at least one partition with a likelihood that is less than 100%;

(c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments;

(d) obtaining partial or complete sequence information from at least a subset of the fragments; and

(e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides.

73. A kit for relating sequence components in the one or more target polynucleotides as in one of claims 1-2, comprising

(a) one or more enzymes capable of repairing at least one end of polynucleotides;

(b) one or more ligases capable of ligating an oligonucleotide sequence to the one or more target polynucleotides;

(c) one or more known nucleotide sequences capable of serving as an amplification target;

(d) a system capable of selecting a subset of the one or more target polynucleotides of a desired length; and

(e) one or more polymerases capable of polynucleotide synthesis.

74. The kit of claim 73, further comprising one or more restriction endonucleases.

75. A kit for relating sequence components in a target polynucleotide, comprising

(a) a device comprising a substrate with one or more reaction volumes comprising one or more restriction endonucleases capable of polynucleotide fragmentation;

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(b) a device comprising a substrate with one or more reaction volumescomprising one or more oligonucleotides with a known sequence; and

(c) a device comprising a substrate with one or more reaction volumes comprising one or more polymerases capable of polynucleotide synthesis.

76. The method as in one of claims 1-2, further comprising utilizing computing resources that are delivered over a network to improve detection of sequence variants and detection average accuracy.

77. The method as in one of claims 1-2, wherein the one or more target polynucleotides originate from a single molecule, and wherein the related sequence information links two or more positions on the single molecule.

78. The method of claim 77, wherein the two or more positions on the single molecule are separated by more than 5000 bp.

79. The method of claim 77, wherein the two or more positions on the single molecule are separated by more than 10000 bp.

80. The method as in one of claims 1-2, wherein the one or more target polynucleotides comprise a first target polynucleotide and a second polynucleotide and the related sequence information to the first target polynucleotide and the related sequence information to the second target polynucleotide are linked.

81. The method as in one of claims 1-2, further comprising detecting a genomic structural variation.

82. The method as in one of claims 1-2, wherein the one or more target polynucleotides originate from one or more tissue samples, wherein relating sequence information comprises detecting a plurality of sequence variants in the one or more tissue samples, and wherein the plurality of sequence variants from one or more tissue sample are compared.

83. The method as in one of claims 1-2, further comprising providing a diagnosis based on the related sequence information.

84. The method of claim 83, wherein the diagnosis is directed to a disease selected from the group consisting of allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic eczema, atopic dermatitis, food allergy, severe combined immunodeficiency (SCID), hypereosinophilic syndrome, chronic granulomatous disease, leukocyte adhesion

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deficiency I and II, hyper IgE syndrome, Chediak Higashi, neutrophilias, neutropenias, aplasias, Agammaglobulinemia, hyper-IgM syndromes, DiGeorge/Velocardial-facial syndromes and Interferon gamma-TIH pathway defects, rheumatoid arthritis, diabetes, systemic lupus erythematosus, Graves' disease, Graves ophthalmopathy, Crohn's disease, multiple sclerosis, psoriasis, systemic sclerosis, goiter and struma lymphomatosa (Hashimoto's thyroiditis, lymphadenoid goiter), alopecia aerata, autoimmune myocarditis, lichen sclerosis, autoimmune uveitis, Addison's disease, atrophic gastritis, myasthenia gravis, idiopathic thrombocytopenic purpura, hemolytic anemia, primary biliary cirrhosis, Wegener's granulomatosis, polyarteritis nodosa, and inflammatory bowel disease, allograft rejection and tissue destructive from allergic reactions to infectious microorganisms or to environmental antigens, hemangiomatosis in newborns, secondary progressive multiple sclerosis, chronic progressive myelodegenerative disease, neurofibromatosis, ganglioneuromatosis, keloid formation, Paget's Disease of the bone, fibrocystic disease (e.g., of the breast or uterus), sarcoidosis, Peronies and Duputren's fibrosis, cirrhosis, atherosclerosis and vascular restenosis, hematologic malignancies and solid tumors, 21 hydroxylase deficiency, cystic fibrosis, Fragile X Syndrome, Turner Syndrome, Duchenne Muscular Dystrophy, Down Syndrome or other trisomies, heart disease, single gene diseases, HLA typing, phenylketonuria, sickle cell anemia, Tay-Sachs Disease, thalassemia, Klinefelter Syndrome, Huntington Disease, autoimmune diseases, lipidosis, obesity defects, hemophilia, inborn errors of metabolism, and diabetes.

85. The method as in one of claims 1-2, wherein the one or more target polynucleotides comprise at least a first target polynucleotide adjacent to a first known nucleotide sequence at at least one end and a second target polynucleotide adjacent to a second known nucleotide sequence at at least one end, wherein the first known nucleotide sequence is not the same as the second known nucleotide sequence.

86. The method of claim 85, wherein the first target polynucleotide further comprises a third known nucleotide sequence at at least one end, wherein the second target polynucleotide further comprises a fourth known nucleotide sequence at at least one end, wherein the third known nucleotide sequence is dependent on the first known

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nucleotide sequence and wherein the fourth known nucleotide sequence is dependent on the second known nucleotide sequence.

87. The method of claim 86, wherein relating sequence information from the plurality of fragments into the first target polynucleotide comprises linking the first and the third known nucleotide sequences.
88. The method of claim 87, wherein the first and third known nucleotide sequences are different from the second and fourth known nucleotide sequences.
89. The method as in one of claims 1-2, further comprising identifying the presence of a pathogen in the at least one sample.
90. The method of claim 89, wherein the pathogen is selected from the group consisting of a bacterial agent, a virus, a parasite, and a fungus.
91. The method of claim 90, wherein the bacterial agent is selected from the group consisting of Escherichia coli, Salmonella, Shigella, KlESBiella, Pseudomonas, Listeria monocytogenes, Mycobacterium tuberculosis, Mycobacterium aviumintracellulare, Yersinia, Francisella, Pasteurella, Brucella, Clostridia, Bordetella pertussis, Bacteroides, Staphylococcus aureus, Streptococcus pneumonia, B-Hemolytic strep., Corynebacteria, Legionella, Mycoplasma, Ureaplasma, Chlamydia, Neisseria gonorrhea, Neisseria meningitides, Hemophilus influenza, Enterococcus faecalis, Proteus vulgaris, Proteus mirabilis, Helicobacter pylori, Treponema palladium, Borrelia burgdorferi, Borrelia recurrentis, Rickettsial pathogens, Nocardia, and Acitnomycetes.
92. The method of claim 90, wherein the fungus is selected from the group consisting of Cryptococcus neoformans, Blastomyces dermatitidis, Histoplasma capsulatum, Coccidioides immitis, Paracoccidioides brasiliensis, Candida albicans, Aspergillus fumigautus, Phycomycetes (Rhizopus), Sporothrix schenckii, Chromomycosis, and Maduromycosis.
93. The method of claim 90, wherein the virus is selected from the group consisting of human immunodeficiency virus, human T-cell lymphocytotrophic virus, hepatitis viruses (e.g., Hepatitis B Virus and Hepatitis C Virus), Epstein-Barr Virus, cytomegalovirus, human papillomaviruses, orthomyxo viruses, paramyxo viruses,

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adenoviruses, corona viruses, rhabdo viruses, polio viruses, toga viruses, bunya viruses, arena viruses, rubella viruses, and reo viruses.

94. The method of claim 90, wherein the parasite is selected from the group consisting of Plasmodium falciparum, Plasmodium malaria, Plasmodium vivax, Plasmodium ovale, Onchoverva volvulus, Leishmania, Trypanosoma spp., Schistosoma spp., Entamoeba histolytica, Cryptosporidum, Giardia spp., Trichimonas spp., Balatidium coli, Wuchereria bancrofti, Toxoplasma spp., Enterobius vermicularis, Ascaris lumbricoides, Trichuris trichiura, Dracunculus medinesis, trematodes, Diphyllobothrium latum, Taenia spp., Pneumocystis carinii, and Necator americanis.
95. The method of claim 89, wherein the pathogen comprises a drug resistant pathogen.
96. The method of claim 95, wherein the drug resistant pathogen is selected from the group consisting of vancomycin-resistant Enterococcus faecium, methicillin-resistant Staphylococcus aureus, penicillin-resistant Streptococcus pneumoniae, multi-drug resistant Mycobacterium tuberculosis, and AZT-resistant human immunodeficiency virus.
97. A method of forming a linear nucleic acid molecule comprising a target polynucleotide with an adaptor oligonucleotide at each end, the method comprising the steps of:
    (a) providing a target polynucleotide and an intermediate polynucleotide, wherein the intermediate polynucleotide comprises at least two adaptor oligonucleotides;
    (b) forming a circular polynucleotide construct by combining the target polynucleotide with the intermediate polynucleotide at each end;
    (c) cleaving the circular polynucleotide construct within the intermediate polynucleotide to form a linearized molecule.
98. The method of claim 97, wherein the target polynucleotide is subjected to a size selection technique for a particular sized polynucleotide at about 50, 100, 250, 500, 1000, 2500, 5000, or 10,000 nucleotides.
99. The method of claim 97, wherein the target polynucleotide is created by fragmentation of a large double stranded polynucleotide by mechanical shearing, chemical or enzymatic treatment.

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100. The method of claim 97, wherein the target polynucleotide is created by a polymerase and nucleotide triphosphates.

101. The method as in one of claims 99-100, wherein the target polynucleotide is subjected to melting temperature thereby producing a single stranded target polynucleotide.

102. The method of claim 97, wherein target polynucleotide comprises a sticky end that pairs sufficiently complementary with the intermediate polynucleotide.

103. The method of claim 97, wherein the target polynucleotide comprises a blunt end.

104. The method of claim 103, wherein the blunt end is generated by fragmentation and enzymatic end repair.

105. The method of claim 104, wherein the enzymatic end repair comprises a polymerase and one or more nucleotide triphosphates.

106. The method of claim 97, wherein the target polynucleotide comprises a poly-N-tail.

107. The method of claim 106, wherein the poly-N-tail comprises one or more adenine, thymine, guanine or cytosine nucleotide bases at either its 3' or 5'end that pair sufficiently complementary with the intermediate polynucleotide.

108. The method of claim 97, wherein in step (a) the target polynucleotide and the intermediate polynucleotide are present in a ratio of about 1:1, 1:2, 1:3, 1:4, 1:6, 1:8, 1:10 or 1:20.

109. The method of claim 97, wherein in step (b) the target polynucleotide and the intermediate polynucleotide are ligated in a ratio of 1:1.

110. The method of claim 97, wherein the adaptor oligonucleotide is single or double stranded.

111. The method of claim 97, the circular polynucleotide construct is single or double stranded.

112. The method of claim 97, wherein the adaptor oligonucleotides at each end of the target polynucleotide are substantially the same.

113. The method of claim 97, wherein the adaptor oligonucleotides at each end of the target polynucleotide are different.

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114. The method of claim 113, wherein at least 3 bases of the adaptor oligonucleotides at each end of the target polynucleotide are different.

115. The method of claim 113, wherein at least 4 bases of the adaptor oligonucleotides at each end of the target polynucleotide are different.

116. The method of claim 97, further comprising more than one adaptor oligonucleotides at each end.

117. The method of claim 97, wherein the adaptor oligonucleotide comprises one or more identification elements.

118. The method of claim 117, wherein at least one of the one or more identification elements comprises a unique identifying tag.

119. The method of claim 117, wherein at least one of the one or more identification elements comprises a multiple cloning site.

120. The method of claim 117, wherein at least one of the one or more identification elements comprises a universal priming site.

121. The method of claim 117, wherein at least one of the one or more identification elements comprises a recognition site for a polymerase.

122. The method of claim 117, wherein at least one of the one or more identification elements comprises a nick in the adaptor oligonucelotide.

123. The method of claim 117, wherein at least one of the one or more identification elements comprises a molecular binding site.

124. The method of claim 117, wherein at least one of the one or more identification elements comprises a recognition site for a topoisomerase enzyme and wherein the topoisomerase is capable of attaching to the recognition site a 3' end of the recognition site.

125. The method of claim 117, comprising a combination of the one or more identification elements from claims 118-124 in any order.

126. A method of claim 97, wherein in step (c) the intermediate polynucleotide is cleaved using a restriction endonuclease.

127. The method of claim 97, wherein in step (b) ligation of blunt or sticky ends comprises a ligase.

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128. The method of claim 97, wherein cleaving the circular polynucleotide construct comprises adenine-thymine or guanine-cytosine complementary base pairing.

129. The method of claim 97, wherein forming a circular polynucleotide comprises using a topoisomerase enzyme.

130. The method of claim 97, further comprising an additional recovery step employing affinity capture to a molecular binding site in an adaptor oligonucleotide.

131. The method of claim 130, wherein the affinity capture is employed after step (c).

132. A composition capable of creating a linear nucleic acid molecule comprising a target polynucleotide with an adaptor oligonucleotide at each end for the identification and isolation of a target polynucleotide, the composition comprising:

(a) the target polynucleotide;

(b) an intermediate polynucleotide comprising at least two adaptor oligonucleotides;

wherein the intermediate polynucleotide further comprises at least one or more elements that allow for circularization, linearization, identification, amplification or isolation.

133. The composition of claim 132, wherein the elements are selected from the group consisting of:

(a) a unique identifying tag;

(b) a multiple cloning site;

(c) a universal priming site;

(d) a recognition site for a polymerase;

(e) a molecular binding site; and

(f) a topoisomerase enzyme covalently attached at 3' end to its recognition site.

134. The composition of claim 133, wherein the composition comprises the intermediate polynucleotide and the target polynucleotide in a ratio of about 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 8:1, 10:1, or 20:1.

135. The composition as in one of claims 132-134 wherein said target polynucleotide is rendered into a circular molecule.

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136. The composition of claim 135, wherein the circular molecule further comprises the intermediate polynucleotide.

137. A kit comprising the composition as in one of claims 132-136 capable of creating the linear nucleic acid molecule comprising the target polynucleotide with an adaptor oligonucleotide at each end, comprising one or more components selected from the group consisting of one or more polymerases, one or more ligases, one or more restriction endonucleases, one or more primers complementary to a universal priming site, one or more molecular binding molecules that recognize a molecular binding site, one or more topoisomerases, one or more single nucleotide triphosphates and one or more terminal transferases.

138. The kit of claim 137, further comprising one or more class II transposons.

139. The kit as in one of claims 137-138 further comprising a sequencing adaptor, a sequencing primer, or a barcode adaptor.

140. The method of claim 106, wherein the poly-N-tail is at a 3' end of the target polynucleotide.

141. The method of claim 106, wherein the intermediate polynucleotide is sufficiently complementary to the poly-N-tail.

142. The method of claim 117, wherein the one or more identification elements allow for identification or isolation of the target polynucleotide.

143. The method of claim 124, wherein the attaching comprises forming a covalent bond.

144. A method for obtaining a sequence, the method comprising:
determining an amount of amplifiable nucleic acid present in a sample;
partitioning the nucleic acid based upon results of the determining step such that each partitioned portion comprises, on average, a subset of unique sequences;
sequencing the nucleic acid to obtain sequence reads; and
obtaining a sequence from the reads.

145. The method according to claim 144, wherein prior to the determining step, the method further comprises fragmenting the nucleic acid.

146. The method as in one of claims 144-145, further comprising attaching a set of unique marker identifier to ends of each fragment.

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147. The method according to claim 146, wherein the unique marker identifiers comprise bar code sequences that are part of adapter sequences.

148. The method according to claim 147, wherein the bar code sequences are the same.

149. The method according to claim 147, wherein the bar code sequences are different.

150. The method as in one of claims 144-146, further comprising attaching labels to the nucleic acids in each partitioned portion.

151. The method according to claim 150, wherein the labels are bar code sequences.

152. The method according to claim 150, wherein prior to the attaching labels step, the method further comprises amplifying the nucleic acids in each partitioned portion.

153. The method according to claim 152, wherein after the amplifying step, the method further comprising fragmenting the amplified nucleic acids in each partitioned portion.

154. The method according to claim 153, wherein fragmenting comprises restriction digesting.

155. The method according to claim 153, wherein fragmenting comprises mechanically fragmenting.

156. The method according to claim 153, wherein fragmenting comprises using an in vitro translocation enzyme.

157. The method according to claim 144, wherein partitioning comprises dispensing the sample into different wells of a microwell plate.

158. The method according to claim 144, wherein partitioning comprises segmenting the sample into droplets.

159. The method according to claim 144, wherein partitioning is performed under microfluidic control.

160. The method according to claim 144, wherein sequencing is sequencing-by-synthesis.

161. The method according to claim 144, wherein sequencing is single molecule sequencing-by-synthesis.

162. The method according to claim 160, wherein the sequence is a consensus sequence.

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163. The method according to claim 144, wherein the sequence is a haplotype sequence.

164. A method for obtaining a sequence, the method comprising:

obtaining nucleic acid;

fragmenting the nucleic acid;

determining an amount of amplifiable nucleic acid present in a sample;

partitioning the fragmented nucleic acids based upon results of the determining step;

amplifying the partitioned nucleic acids;

attaching bar codes to the amplified nucleic acid;

sequencing the nucleic acid to obtain bar coded sequence reads; and

obtaining a sequence from the reads.

165. The method according to claim 164, wherein each partitioned portion comprises, on average, a unique subset of nucleic acids.

166. The method according to claim 164, further comprising attaching marker identifiers to ends of the fragments.

167. The method according to claim 164, wherein fragmenting comprises restriction digesting.

168. The method according to claim 164, wherein fragmenting comprises mechanically fragmenting.

169. The method according to claim 164, wherein fragmenting comprises using an in vitro translocation enzyme.

170. The method according to claim 164, wherein partitioning comprises dispensing the sample into different wells of a microwell plate.

171. The method according to claim 164, wherein partitioning comprises segmenting the sample into droplets.

172. The method according to claim 164, wherein partitioning is performed under microfluidic control.

173. The method according to claim 164, wherein sequencing is sequencing-by-synthesis.

174. The method according to claim 173, wherein sequencing is single molecule sequencing-by-synthesis.

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175. The method according to claim 164, wherein the sequence is a consensus sequence.

176. The method according to claim 164, wherein the sequence is a haplotype sequence.

177. A system for reagent dispensing, the system comprising:

a first vessel having a flow through hole on a bottom portion of the vessel; and

a second vessel;

wherein the system is configured such that the first vessel is situated above the second vessel such that the second vessel is capable of receiving a reagent from the first vessel.

178. The system according to claim 177, wherein the first and second vessels are multiwell plates.

179. The system according to claim 177, wherein the multiwell plates are 96 or 384 well plates.

180. The system according to claim 177, wherein the first vessel further comprises a cover.

181. The system according to claim 177, further comprising a centrifuge.

182. The system according to claims 177 or 181, further comprising a permeable membrane, wherein the membrane is situated between the first and second vessels.

183. The system according to claim 182, wherein force generated by the centrifuge causes a reagent in the first vessel to pass through the membrane and into the second vessel.

184. A method for dispensing reagents, the method comprising:

providing a system comprising a first vessel having a flow through hole on a bottom portion of the vessel; a second vessel; wherein the system is configured such that the first vessel is situated above the second vessel such that the second vessel is capable of receiving a reagent from the first vessel;

dispensing a reagent into the first vessel; and

applying centrifugal force to the system to cause the reagent to pass into the second vessel.

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185. The method according to claim 184, wherein prior to the providing step, the method further comprises dispensing a sample into the second vessel.

186. The method according to claim 184, wherein the first and second vessels are multiwell plates.

187. The method according to claim 186, wherein the multiwell plates are 96 or 384 well plates.

188. The method according to claim 184, wherein the first vessel further comprises a cover.

189. The method according to claim 184, wherein the centrifugal force is generated by a centrifuge.

190. The method according to claim 184, further comprising a permeable membrane, wherein the membrane is situated between the first and second vessels.

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Figure 1

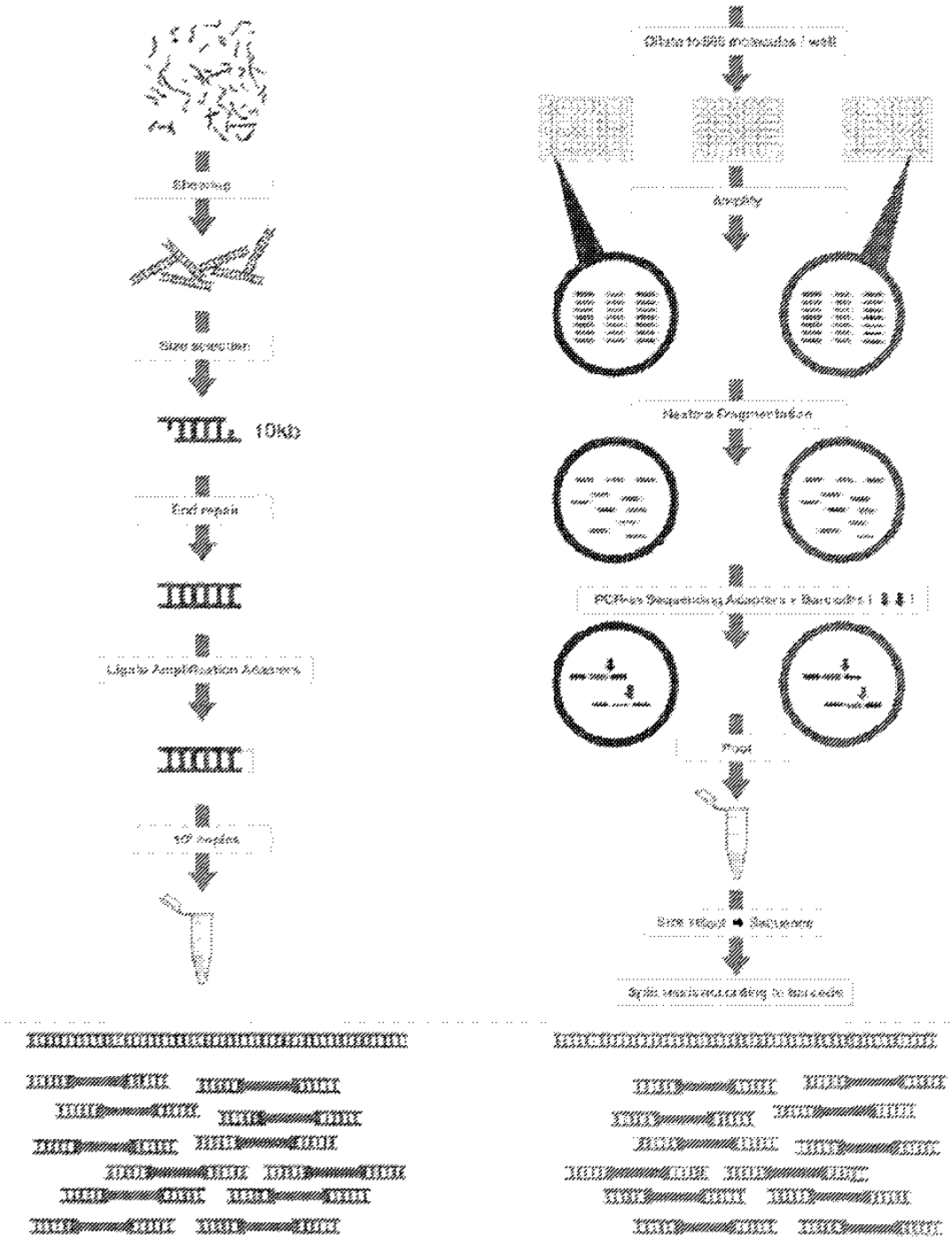

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Figure 2

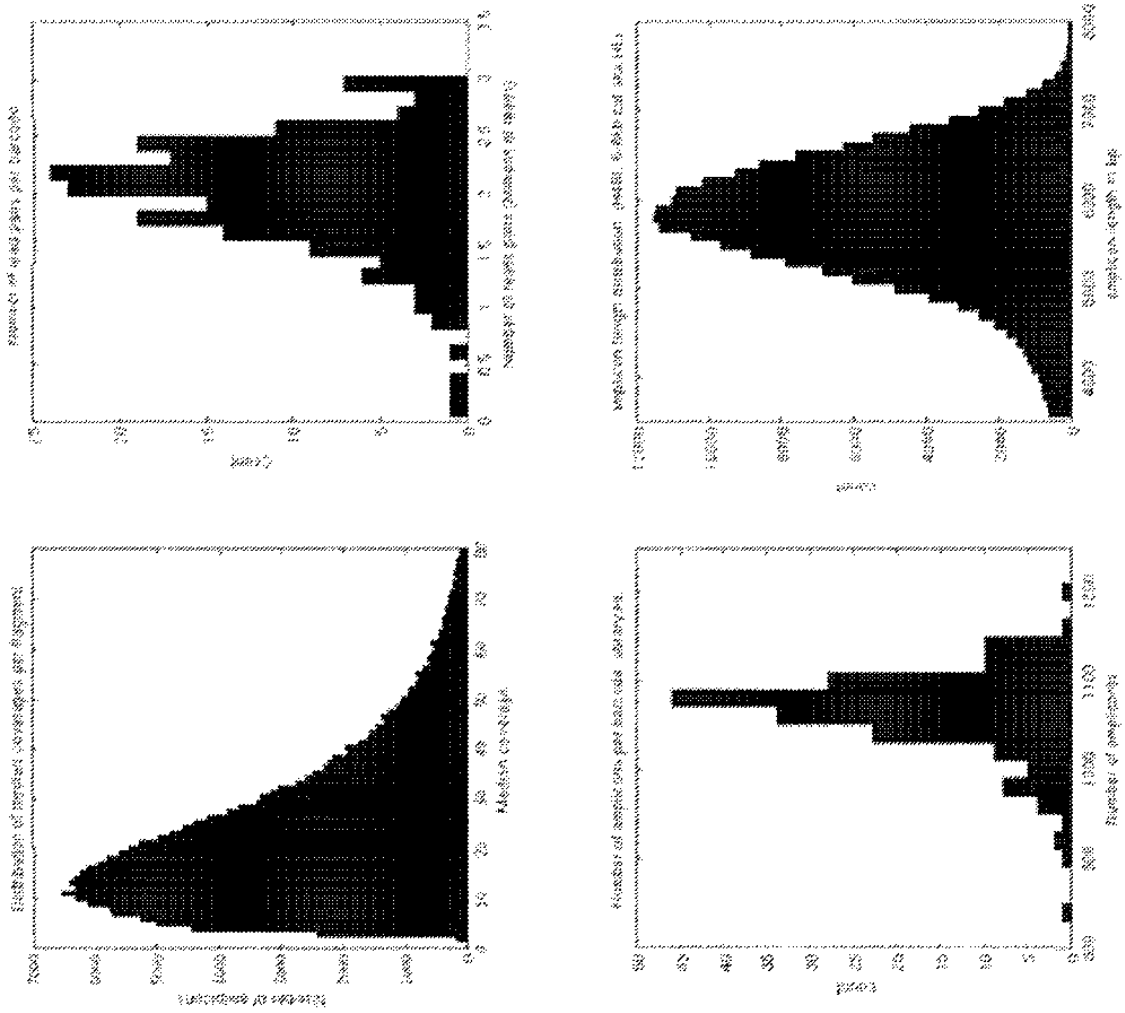

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Figure 3

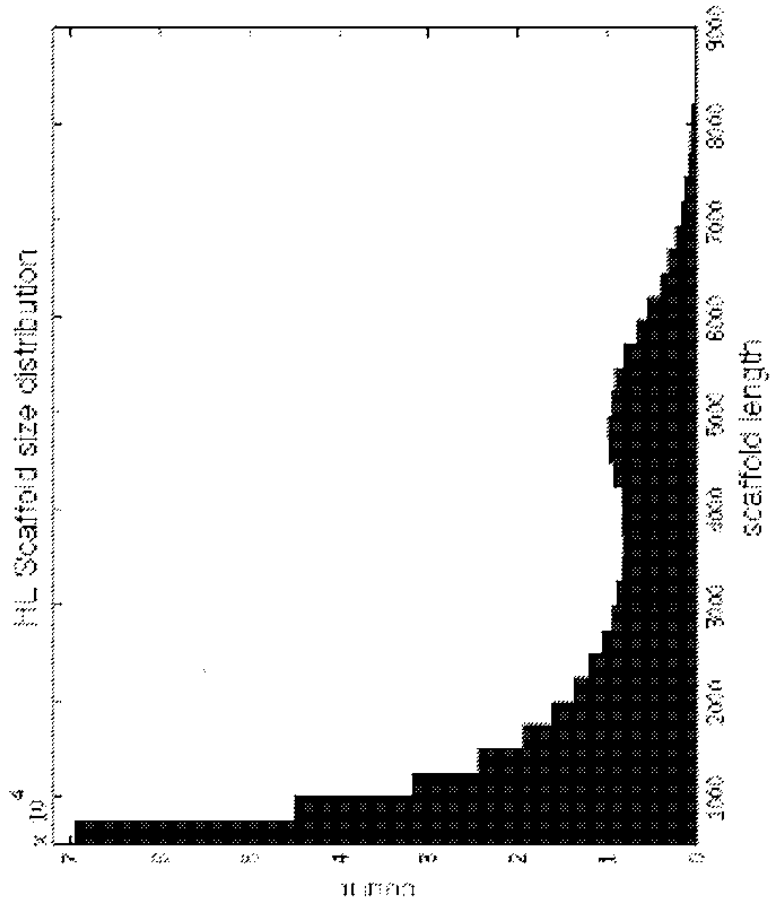

Figure 4

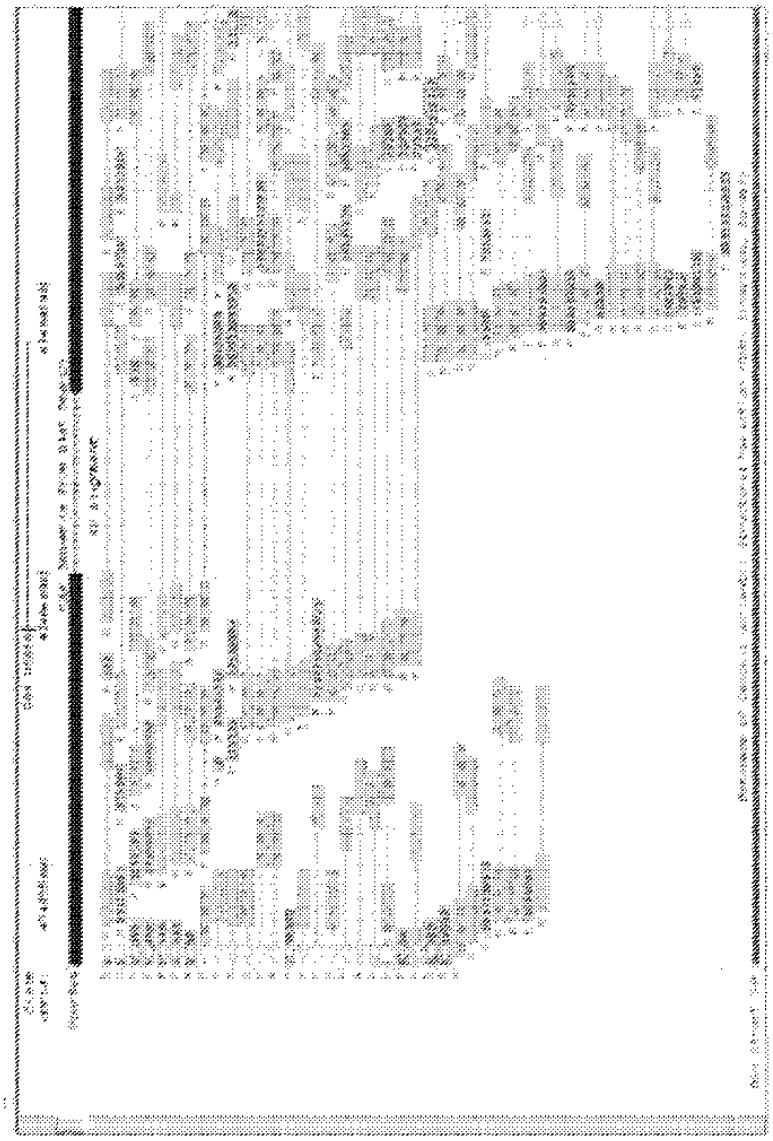

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Figure 5A

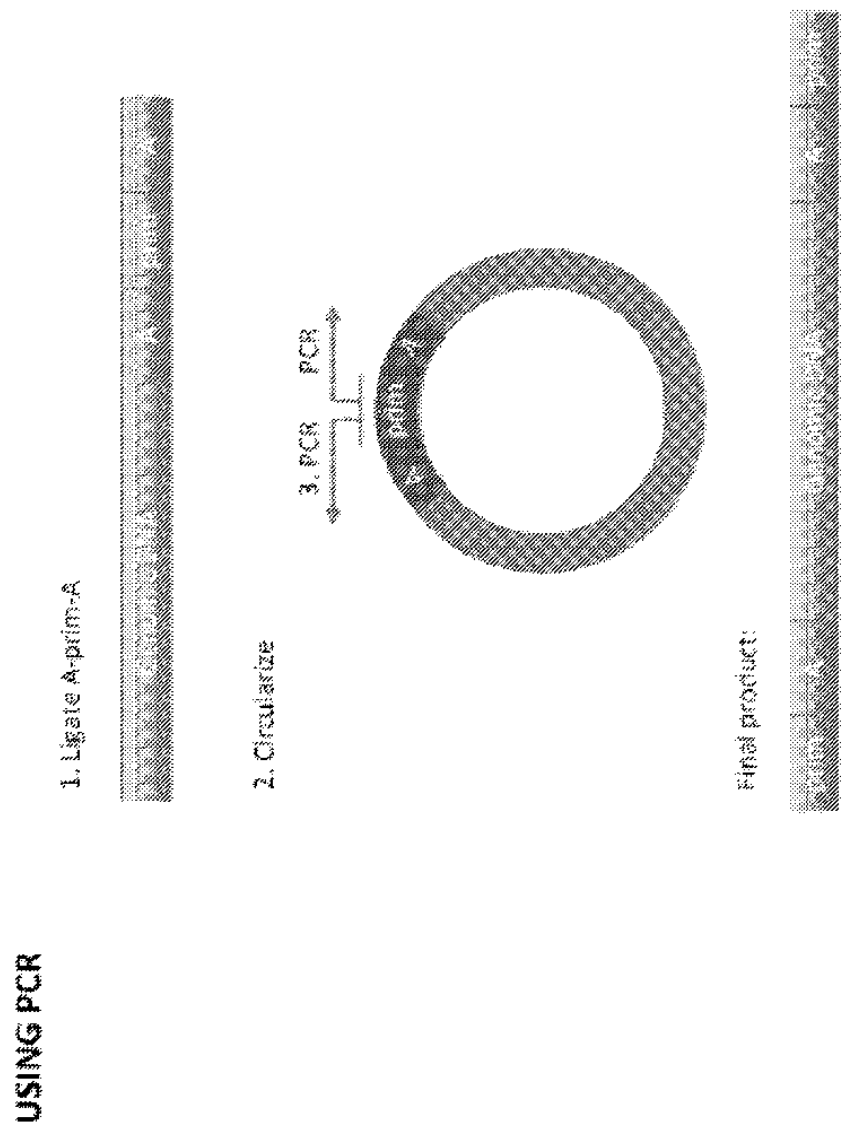
USING PCR
1. Ligate A-prim-A
2. Circularize
3. PCR
PCR
Final product:

Figure 5B

USING RESTRICTION ENZYMES
3. Ligate A-rest-A
2. Circularize
3. Cut with restriction enzyme
Final product:

Figure 6

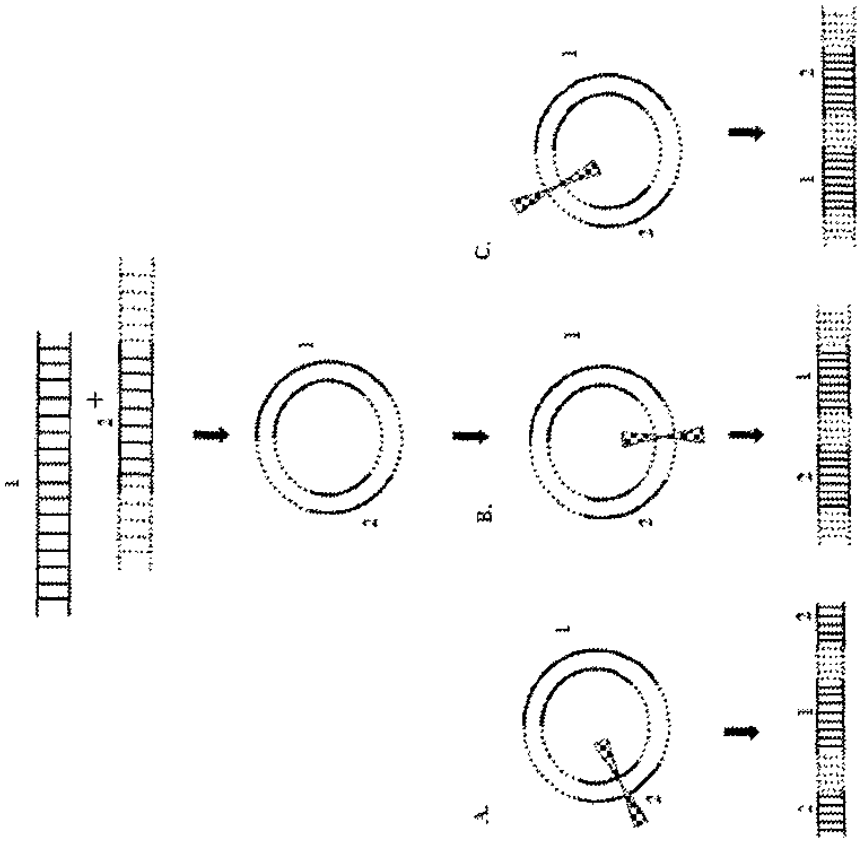

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Figure 7

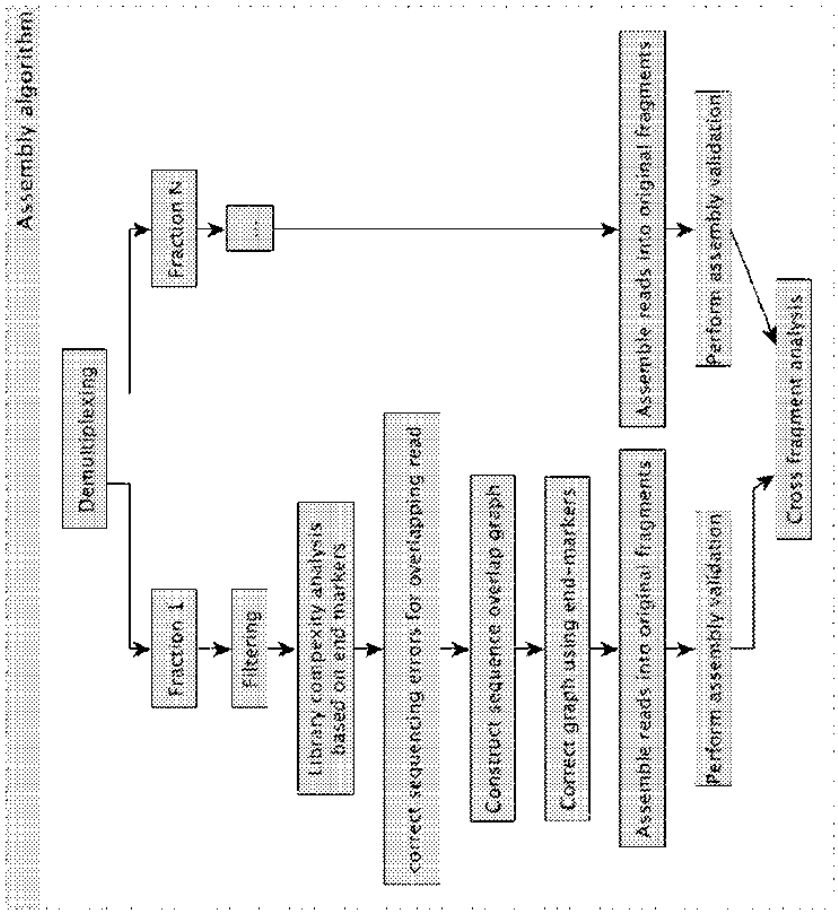
Assembly algorithm
Demultiplexing
Fraction 1
Fraction N
Filtering
Library complexity analysis based on end markers
correct sequencing errors for overlapping read
Construct sequence overlap graph
Correct graph using end-markers
Assemble reads into original fragments
Perform assembly validation
Assemble reads into original fragments
Perform assembly validation
Cross fragment analysis

Figure 8

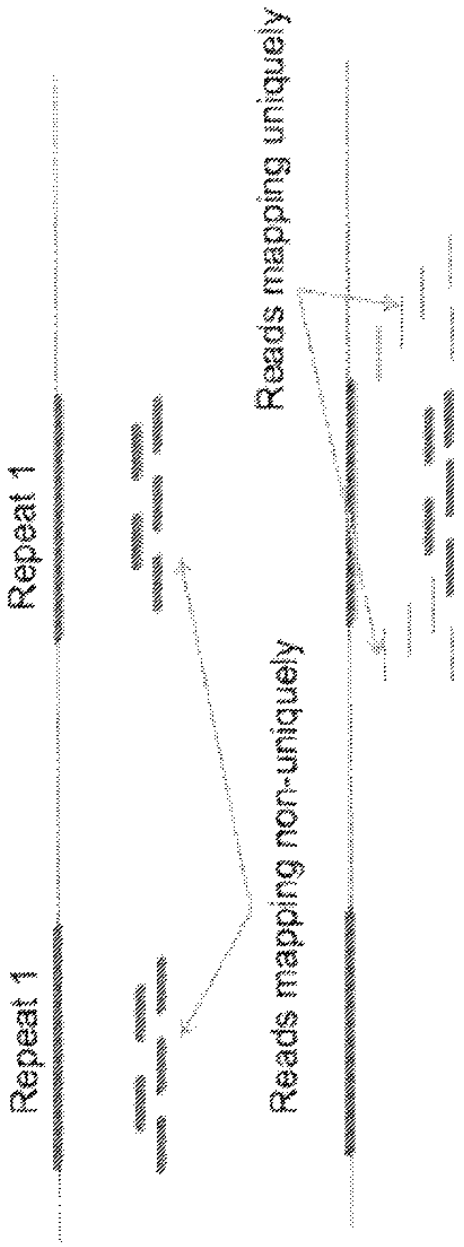

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Figure 9

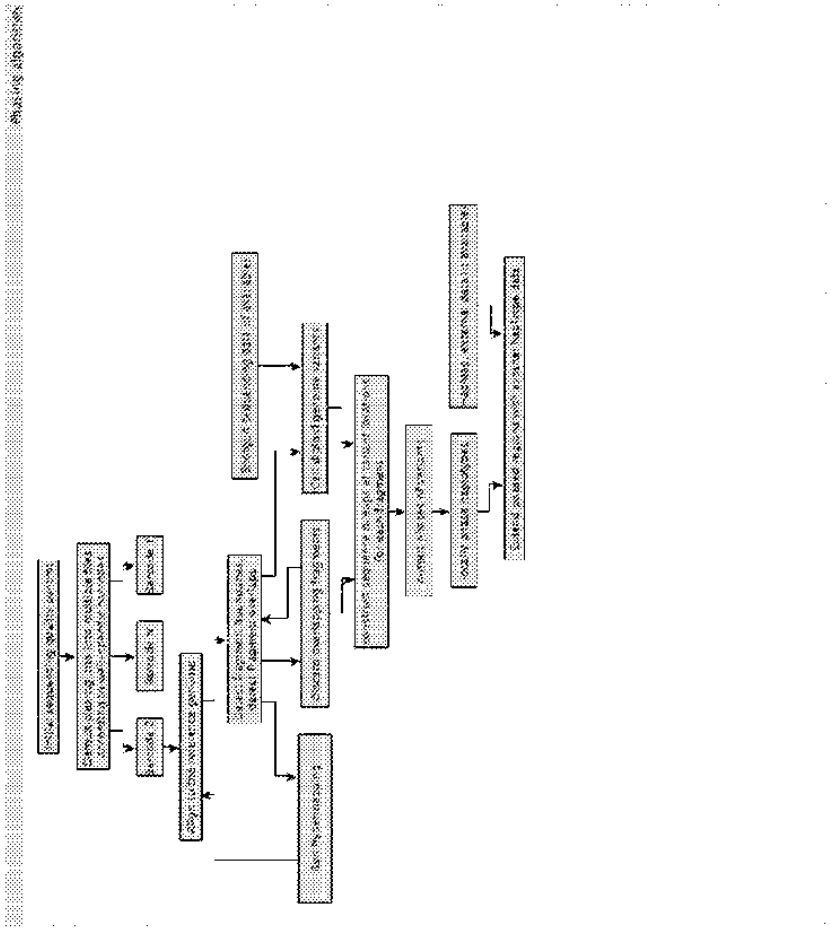

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Figure 10

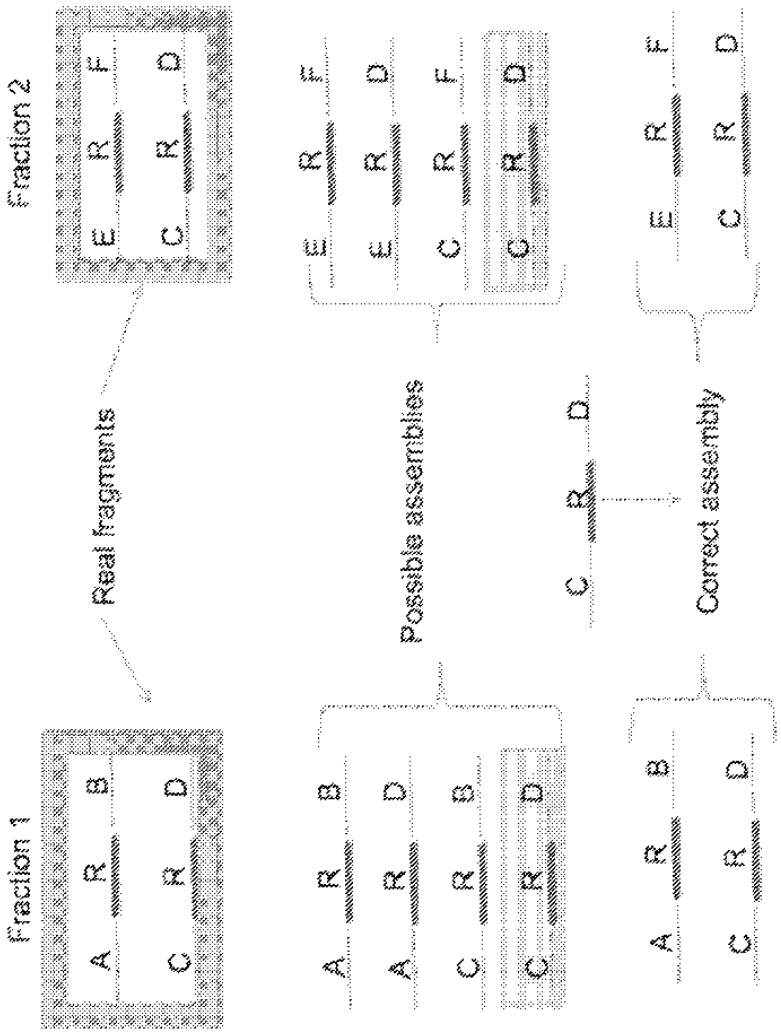

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Figure 11

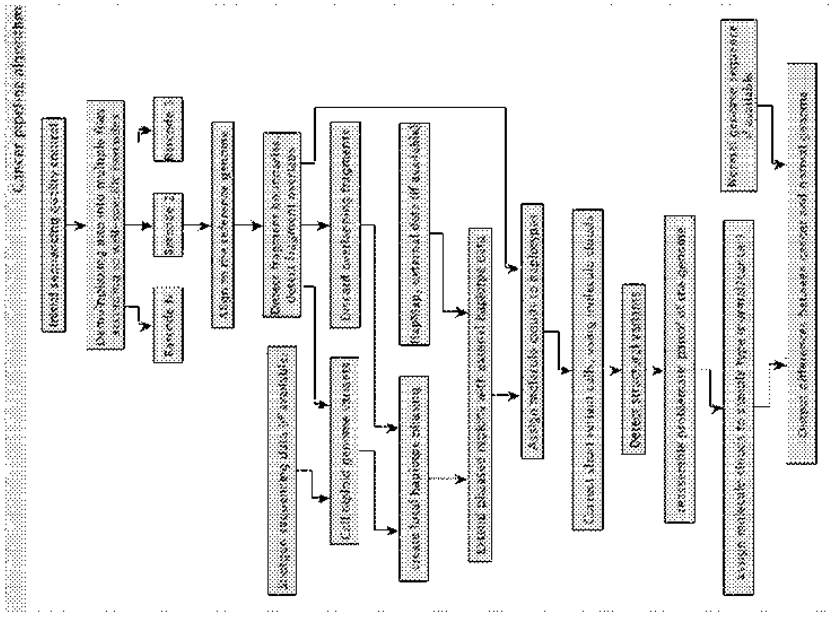

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Figure 12

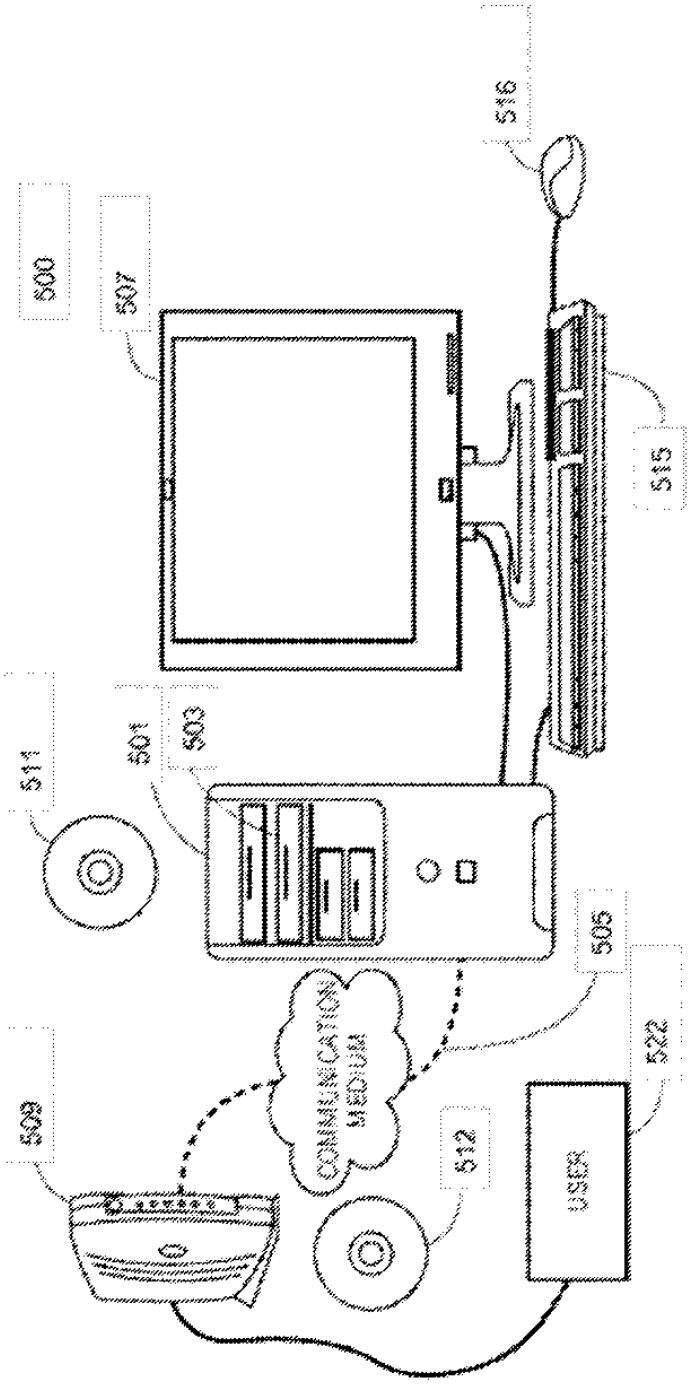
516
500
507
515
511
501
503
505
522
509
COMMUNICATION MEDIUM
512
USER

Figure 13

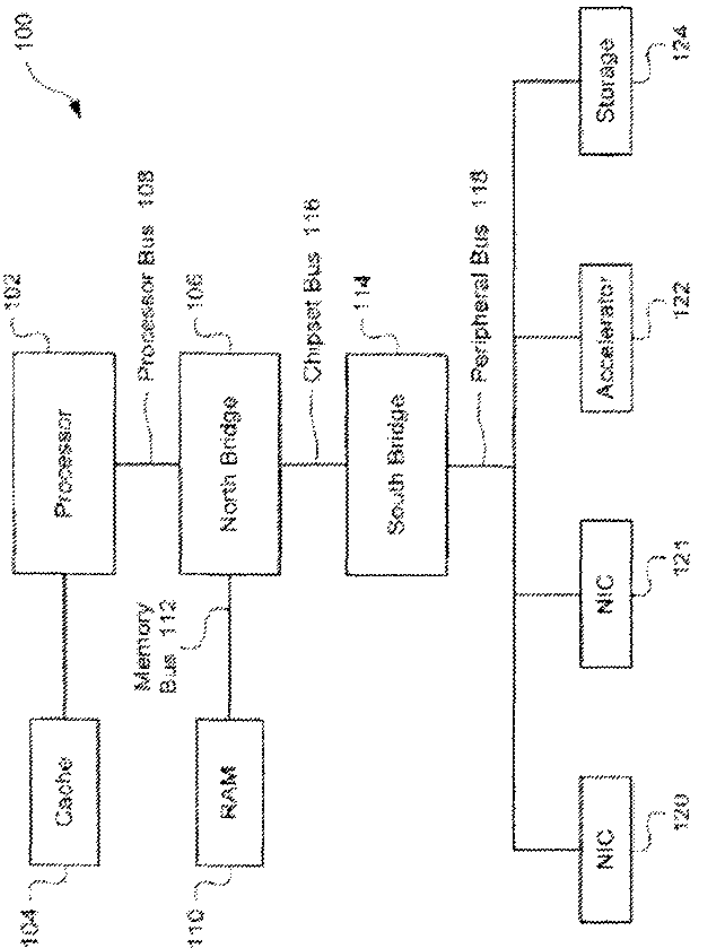
100
102
Processor
Processor Bus 108
106
North Bridge
Chipset Bus 116
114
South Bridge
Peripheral Bus 118
Storage
124
Accelerator
122
NIC
121
NIC
120
Cache
104
Memory Bus 112
RAM
110

Figure 14

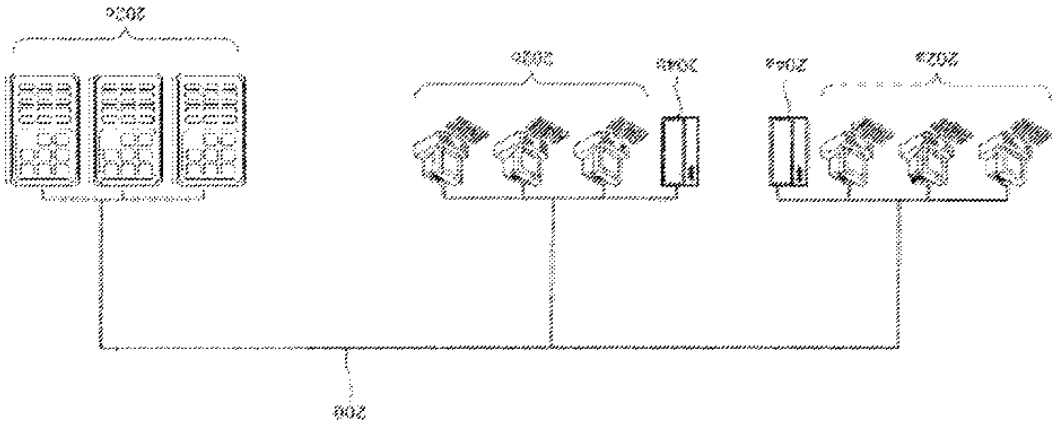

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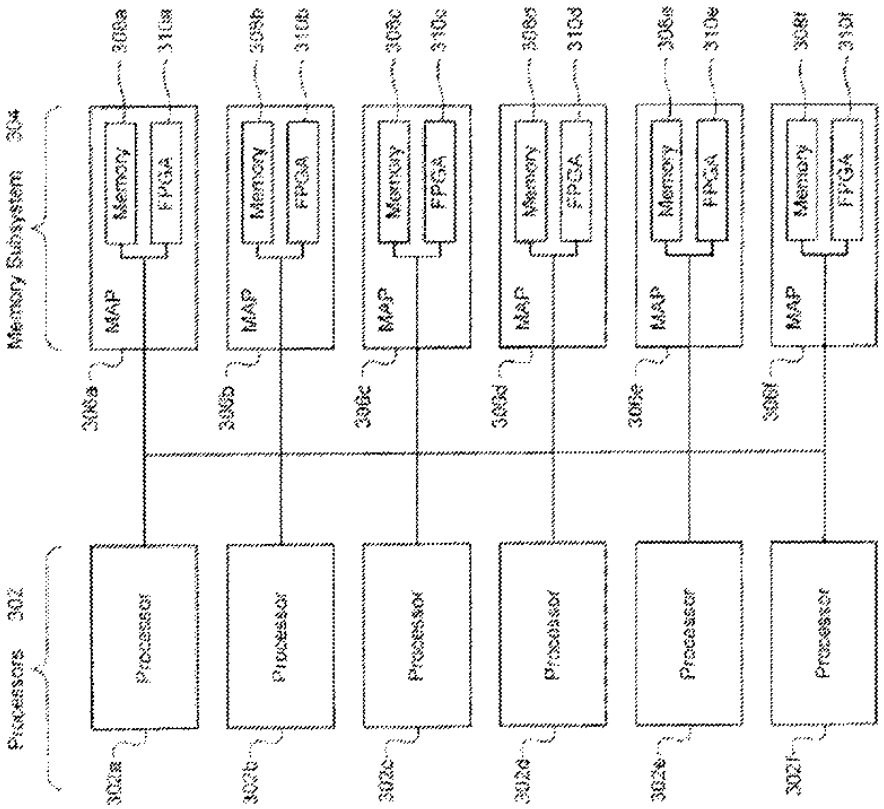
Figure 15



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/54461

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2013.01)
USPC - 435/6.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - C12Q 1/68 (2013.01)
USPC - 435/6.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/6.11, 435/6.12

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; PubWEST(USPT, PGPB, EPAB, JPAB); Google Scholar
Search terms: partition, dilution, nucleic acid, nucleotide, polynucleotide, DNA, RNA, sequence, known, PCR, amplify, sequencing, fragment, fragmentation, copy, primer, polymerase, barcode, adaptor, adapter, ion semiconductor, real time, nanopore, electron microsco

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	WO 2010/148039 A2 (DRMANAC et al.) 23 December 2010 (23.12.2010) para [0038], [0046], [0050], [0055]-[0056], [0060], [0064], [0066], [0083], [0090], [0102], [0117], [0122], [0124], [0128], [0130]-[0132], [0153], [0168], [0198], [0207]-[0209], [0213], [0215], [0221], [0223], [0248], [0261], [0268]-[0269], [0271]-[0272], [0283], [0288],[0366], [0375], [0400], [0423],[0447]	1-58, 60, 63-64, 66-67, 73-74, 76-83, 85-90 --- 59, 61, 62, 65, 84, 91-96
X	US 2006/0281082 A1 (ZHU) 14 December 2006 (14.12.2006) para [0021], [0024]-[0027], [0089], [0107]-[0108], [0110]	1, 2
Y	US 2011/0201507 A1 (RAVA et al.) 18 August 2011 (18.08.2011) para [0128], [0135], [0137], [0138]	59, 61, 62
Y	US 2003/0170652 A1 (INOKO et al.) 11 September 2003 (11.09.2003) para [0044]	65, 84
Y	US 2003/0082535 A1 (LEUSHNER et al.) 1 May 2003 (01.05.2003) para [0020]-[0021]	91-96

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 January 2013 (14.01.2013)	04 FEB 2013
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/54461

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 125, 137-139, 150-156
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I: Claims 1-67, 73-74, and 76-96, drawn to a generic method for relating sequence components in a target polynucleotide, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length, and partitions wherein at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 99.999 and drawn to a generic method for relating sequence components in a target polynucleotide, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length of greater than 30 bp, and partitions wherein at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 100%.

---please see continuation on extra sheet---

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-67, 73-74, 76-96

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

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Continuation of: Box No. III Observations where unity of invention is lacking

Group II: Claims 68-70, drawn to a variation on the generic method for relating sequence components in a target polynucleotide, wherein the sample need not comprise one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end

Group III: Claims 71 and 72, drawn to a variation on the generic method for relating sequence components in a target polynucleotide, wherein a sample partition is further subjected to exponential nucleic acid amplification, and wherein partition is estimated to be present as a single copy prior to exponential nucleic acid amplification among the one or more target polynucleotides that get exponentially amplified in the at least one partition with a likelihood that is less than 99.999% and drawn to a variation on the generic method for relating sequence components in a target polynucleotide, wherein a sample partition is further subjected to exponential nucleic acid amplification, and wherein partition is estimated to be present as a single copy prior to exponential nucleic acid amplification among the one or more target polynucleotides that get exponentially amplified in the at least one partition with a likelihood that is less than 100%

Group IV: Claims 75, drawn to a kit

Group V: Claims 97-124, 126-136, 140-143, drawn to a method and composition for forming a linear nucleic acid molecule

Group VI: Claims 144-149, 157-176, drawn to a method for obtaining a sequence comprising use of bar codes

Group VII: Claims 177-190, drawn to systems and methods for dispensing reagents

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The shared technical feature of the inventions listed as Groups I-III is the generic method for relating sequence components in a target polynucleotide, the method comprising: (a) providing at least one sample comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end, wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length, and wherein the known nucleotide sequence is capable of serving as an amplification target; (b) partitioning the sample into a finite plurality of partitions; (c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments; (d) obtaining partial or complete sequence information from at least a subset of the fragments; and (e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides. The shared technical feature of the inventions listed as Groups I, II and III are partitions wherein at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 99.999%. The shared technical feature of the inventions listed as Groups I and III is a target polynucleotide comprising one or more sequence segments with a sequence segment length of greater than 30 bp, and partitions wherein at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 100%.

These shared technical features of Groups I-III fail to provide a contribution over the prior art, as evidenced by US 2006/0281082 A to Zhu. Zhu teaches method for relating sequence components in a target polynucleotide, the method comprising:
(a) providing at least one sample (para [0024]-[0027]) comprising one or more target polynucleotides each adjacent to a known nucleotide sequence at at least one end (para [0088] - "Where desired, one or more pairs of "adaptor" oligonucleotides [i.e. known nucleotide sequence] may be used to bridge the cloning ends of the DNA fragments of interest [i.e. target polynucleotide]"), wherein each target polynucleotide comprises one or more sequence segments with a sequence segment length of greater than 30 bp (para [0022] - "fragments with a size range of 100-2000 bps"), and wherein the known nucleotide sequence is capable of serving as an amplification target (para [0089] - "PCR amplification may optionally be used to enrich the fragments of interest and increase the amount of DNA by using the adaptor sequence [i.e. known nucleotide sequence] as PCR primer");
(b) partitioning the sample into a finite plurality of partitions (para [0108] - "When it is desirable to assay an individual for the polymorphisms in the set, nucleic acid is isolated from that individual, and it can be partitioned with the same methods that were used to isolate the original set of polymorphisms"; para [0110] - " isolate an appropriate partition") such that at least a fraction of the sequence segments in at least one partition is estimated to be present as a single copy in the at least one partition with a likelihood that is less than 100% and less than 99.999% (para [0021] - "Thus the method provides a reproducible method of reducing the complexity of the sample. . . a partition with at least 10, 100, or 1000-fold reduced complexity compared to the sample nucleic acid can be generated");
(c) subjecting the partition to polynucleotide fragmentation thereby generating a set of fragments (para [0110] - "restriction-digest the sample");
(d) obtaining partial or complete sequence information from at least a subset of the fragments (para [0108] -"the present invention can facilitate efficient genotyping"; para [0110] - "For example, if one wishes to genotype a new sample for 10,000, or 1000 or 100 SNPs isolated from a specific partition, one could restriction-digest the sample; isolate an appropriate partition; and amplify by PCR using primers complementary to a generic linker. The resulting amplification products could be hybridized to an appropriate 'genotyping array'"); and
(e) relating sequence information from a plurality of fragments into a subset of the one or more target polynucleotides (para [0107] - "Thus the invention also provides for a method for making a genotyping microchip for use in assaying a limited population of polymorphisms within a sample"). In the absence of a contribution over the prior art, the shared technical features are not shared special technical features.

The special technical feature of the invention listed as Group IV is the method step of subjecting at least one partition to exponential nucleic acid amplification which is not shared by the other Groups. Nevertheless, this special technical feature fails to provide a contribution over Zhu, which teaches subjecting at least one partition to exponential nucleic acid amplification (para [0110] - "isolate an appropriate partition; and amplify by PCR using primers"). In the absence of a contribution over the prior art, the shared technical feature is not a shared special technical feature.

---please see continuation on next extra sheet---

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US 12/54461

Continuation of: Previous extra sheet (Box No. III Observations where unity of invention is lacking)

The shared technical feature of the inventions listed as Groups I-III and VI is the method steps of partitioning, fragmenting, amplifying, and sequencing a nucleic acid from a sample. As previously discussed, this shared technical feature fails to provide a contribution over Zhu (para [0110] - "For example, if one wishes to genotype a new sample for 10,000, or 1000 or 100 SNPs isolated from a specific partition, one could restriction-digest the sample; isolate an appropriate partition; and amplify by PCR using primers complementary to a generic linker. The resulting amplification products could be hybridized to an appropriate 'genotyping array'").

Further, the special technical feature of the inventions listed as Group IV is a kit. This special technical feature is not shared by the inventions of Groups I-III, V, and VI. The special technical feature of the inventions listed as Group V is the method steps and composition for forming a linear nucleic acid molecule. This special technical feature is not shared by the inventions of Groups I-IV, VI and VII. The special technical feature of the inventions listed as Group VI is the method steps for obtaining a sequence comprising use of bar codes. This special technical feature is not shared by the inventions of Groups I-V and VII. The special technical feature of the inventions listed as Group VII is the system and method for dispensing reagents. This special technical feature is not shared by the inventions of Groups I-VI.

Unity of invention exists only when the same or corresponding technical feature is shared by the claimed inventions. Without a shared special technical feature, the inventions of Groups I-VII lack unity with one another.

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Electronic Acknowledgement Receipt

EFS ID:	15785074
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	15-MAY-2013
Filing Date:	
Time Stamp:	18:40:55
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Non Patent Literature	BOULANGER-Massively-Parallel.pdf	1061907 27e05e6e170c9f4050eb6ff25f765d60501ae767	no	10

Warnings:

Information:

2	Non Patent Literature	CASBON_Reflex.pdf	213805 7 f85ba0ccc52 fda5dcae15b0dcc4a0aa12c48 e0f4	no	6
Warnings:					
Information:					
3	Non Patent Literature	FAN-Whole-genome.pdf	1038138 bedd1ecc7d3bc6864788106 12ac7 25c8ce9 7e012	no	9
Warnings:					
Information:					
4	Non Patent Literature	HIATT-Paralle.pdf	1954126 20804cc65e7aeb3 700a 1886940ad9f7 40b 74e9	no	13
Warnings:					
Information:					
5	Non Patent Literature	KAPER-Whole-genome_halotyping.pdf	436410 ea9e1acafaalcc 39e8694bf9d4b1d8aa2630 7 6e09	no	6
Warnings:					
Information:					
6	Non Patent Literature	KIRKNESS-Sequencing_of_isolated.pdf	1690559 0443990b2 85cd7e98e6eeb7d9fa4c1581e 94da7	no	21
Warnings:					
Information:					
7	Non Patent Literature	KITZMAN-HAPLOTYPE-RESOLVED.pdf	1056721 a38a2ab7d7ed1fee13888e3007 8678fb8411 516e	no	11
Warnings:					
Information:					
8	Non Patent Literature	Kozarewa-96-PLEX.pdf	160619 12201b2b1e4fe6beaa7f7a3d2aac0a02de0 0d03	no	20
Warnings:					
Information:					
9	Non Patent Literature	KOZAREWA-AMPLIFICATION-FREE.pdf	2398839 8fdc138a69d1484f8c1 1b6bde 6a65d1f99 9e01	no	12
Warnings:					
Information:					
10	Non Patent Literature	KWOK-Single_Molecule.pdf	331402 c6fbb7704a5efe52a 70886affcab18625 1e86	no	8
Warnings:					
Information:					

11	Non Patent Literature	LUNDIN-Hierarchical_Taggingpdf.pdf	1755841 a71de4c92d48b1e45c80b0ccf0fcaa239ca80bd171	no	7
Warnings:					
Information:					
12	Non Patent Literature	OYOLA_Optimizing.pdf	1094148 0322e65c799204a8493d89ae454165d0f9b6a49	no	12
Warnings:					
Information:					
13	Non Patent Literature	REISNER-Single_Molecule.pdf	3171050 31f798a9b801be23e1a9611d1be6e6e896e8c96	no	6
Warnings:					
Information:					
14	Non Patent Literature	TURNER_High-throughput.pdf	885295 144953b61227aeee901e181a972bcd681ec9a1b	no	13
Warnings:					
Information:					
15	Non Patent Literature	TURNER-Assaying.pdf	2529051 2f5ce2ba9fb06bd724efb865d1034f566cd4447	no	17
Warnings:					
Information:					
16	Non Patent Literature	VANNIEUWERBURGH.pdf	5102955 be8ba4e2a43ccc01c3419299cb66618300146012da	no	8
Warnings:					
Information:					
17	Non Patent Literature	XIAO-Determination.pdf	494875 3e91e190e4ec7b5d8da2a166e10d978986e4bd6e770	no	9
Warnings:					
Information:					
18	Information Disclosure Statement (IDS) Form (SB08)	CGLC-020CON2-IDS_SB08.pdf	614026 1afe8875e4836ce9a4b74f1828887e941901367cd3	no	6
Warnings:					
Information:					
19	Foreign Reference	WO2001090418A1.pdf	6288987 e4a4ce2e1495ac1486d989ffb27e8194f2ee46fa55a	no	49
Warnings:					
Information:					

20	Foreign Reference	WO2004065617A2.pdf	5064044 [illegible]	no	33
Warnings:					
Information:					
21	Foreign Reference	WO2013036929A1.pdf	15559329 [illegible]	no	130
Warnings:					
Information:					
		Total Files Size (in bytes):	52902127		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/859,450	04/09/2013	2852	730	CGLC-020CON2	13	1

CONFIRMATION NO. 9317

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

FILING RECEIPT

OC00000006128606 3

Date Mailed: 05/23/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

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Applicant(s)

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Assignment For Published Patent Application

Population Genetics Technologies Ltd, Cambridge, UNITED KINGDOM

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/622,872 09/19/2012
which is a CON of 13/387,343 02/15/2012 PAT 8298767
which is a 371 of PCT/IB2010/002243 08/13/2010
which claims benefit of 61/288,792 12/21/2009
and claims benefit of 61/235,595 08/20/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 05/16/2013

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The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/859,450**

Projected Publication Date: 08/29/2013

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **
Title

Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

Preliminary Class

396

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 13/859,450

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k) (l), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	13 minus 20 =	*	x 40 =	0.00	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	1 minus 3 =	*	x 210 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	730		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE(S)	SMALL ENTITY ADDITIONAL FEE(S)	OR	OTHER THAN SMALL ENTITY RATE(S)	OTHER THAN SMALL ENTITY ADDITIONAL FEE(S)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE(S)	ADDITIONAL FEE(S)	OR	RATE(S)	ADDITIONAL FEE(S)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
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I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 93726

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned below the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

■ The address associated with Customer Number: 93726

OR

☐	Firm or Individual Name		
	Address		
	City	State	Zip
	Country		
	Telephone	Email	

Assignee Name and Address: Population Genetics Technologies Ltd
Babraham Research Campus
Cambridge, United Kingdom CB22 3AT

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	Mel Kronick	Date	09/25/2012
Name	Mel Kronick, Ph.D.	Telephone	(650) 269-0445
Title	Director		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Acknowledgement Receipt	
EFS ID:	16282817
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	15-JUL-2013
Filing Date:	09-APR-2013
Time Stamp:	16:23:50
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73.	CGLC-020CON2-373c_Statement.pdf	30341 [illegible]	no	2
Warnings:					
Information:					

2	Power of Attorney	CGLC-Population_Genetics_Technologies_Ltd.pdf	1460141 c50fabd5174a8857ee4641a8f4ff9010e5dc3bd8	no	1

Warnings:	
Information:	
Total Files Size (in bytes):	1490482

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/96 (08-12)
Approved for use through 01/31/2013. OMB 0651-0031
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)

Applicant/Patent Owner: **Population Genetics Technologies Ltd**

Application No./Patent No.: **13/859,450** Filed/Issue Date: **April 9, 2013**

Titled: **Compositions and Methods for Intramolecular Nucleic Acid Rearrangement**

Population Genetics Technologies LTD, a **Corporation**
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (chose **one** of options 1, 2, 3, 4 below):

1. ☒ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.* bankruptcy, probate), or an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2, or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel **030434**, Frame **0434**, or for which a copy thereof is attached.

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

   The document was recorded in the United States Patent and Trademark Office at

   Reel _____, Frame _____, or for which a copy thereof is attached.

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450**.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/AIA/96 (08-12)
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U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
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STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

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4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/James S. Keddie, Reg. No. 48,920/	July 15, 2013
Signature	Date
James S. Keddie, Ph.D.	48,920
Printed or Typed Name	Title or Registration Number

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	13859450
	Filing Date	2013-04-09
	First Named Inventor	Sydney Brenner, Ely
	Art Unit	1634
	Examiner Name	Bhat, Narayan Kameshwar
	Attorney Docket Number	CGLC-020CON2

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1					
If you wish to add additional U.S. Patent citation information please click the Add button.						Add

U.S.PATENT APPLICATION PUBLICATIONS						Remove
Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20120316074		2012-12-13	SAXONOV	
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FOREIGN PATENT DOCUMENTS								Remove
Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐
If you wish to add additional Foreign Patent Document citation information please click the Add button								Add

NON-PATENT LITERATURE DOCUMENTS			Remove
Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13859450
	Filing Date	2013-04-09
	First Named Inventor	Sydney Brenner, Ely
	Art Unit	1634
	Examiner Name	Bhat, Narayan Kameshwar
	Attorney Docket Number	CGLC-020CON2

	1	SCHWARTZ; et al., "Capturing native long-range contiguity by in situ library construction and optical sequencing", PNAS (Nov. 2012), 109(46):18749-18754.	☐
	2	WANG; et al., "Self-Formed Adaptor PCR: a Simple and Efficient Method for Chromosome Walking", Applied and Environmental Microbiology (Aug. 2007), 73(15):5048-5051.	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00324

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13859450
	Filing Date	2013-04-09
	First Named Inventor	Sydney Brenner, Ely
	Art Unit	1634
	Examiner Name	Bhat, Narayan Kameshwar
	Attorney Docket Number	CGLC-020CON2

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/James S. Keddie, Reg. No. 48,920/	Date (YYYY-MM-DD)	2013-07-18
Name/Print	James S. Keddie	Registration Number	48,920

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00325

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Page 00326

Electronic Acknowledgement Receipt

EFS ID:	16352545
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie/Sarah Zizzo
Filer Authorized By:	James Samuel Keddie
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	18-JUL-2013
Filing Date:	09-APR-2013
Time Stamp:	16:31:29
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	updated_IDS_7-18-13.pdf	612446 [illegible]	no	4

Warnings:

Information:

2	Non Patent Literature	Schwartz_CapturingLong-RangeContiguity_PNAS-2012-Schwartz-18749-54.pdf	1481364 59e91184ac95f846f89225642f8025ddbbdd2f	no	6
Warnings:					
Information:					
3	Non Patent Literature	ApplEnvironMicrobiol_2007_Wang.pdf	197594 04b59cc860180744b5ba78f41b2f44c3c54a0f7b	no	4
Warnings:					
Information:					
		Total Files Size (in bytes):	2291404		

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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
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<u>New International Application Filed with the USPTO as a Receiving Office</u>
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P.O. Box 1450
Alexandria, VA 22313-1450
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JUL 18 2013
OFFICE OF PETITIONS

EPA-BOZICEVIC FIELD & FRANCIS LLP
1900 UNIVERSITY AVE
SUITE 200
EAST PALO ALTO CA 94303

In re Application of
SYDNEY BRENNER et al
Application No. 13/859,450
Filed: April 9, 2013
Attorney Docket No. CGLC-020CON2

DECISION ON PETITION
TO MAKE SPECIAL UNDER
37 CFR 1.102(c)(1)

This is a decision on the petition under 37 CFR 1.102(c)(1), filed April 9, 2013, to make the above-identified application special based on applicant's age as set forth in M.P.E.P. § 708.02, Section IV.

The petition is **GRANTED**.

A grantable petition to make an application special under 37 CFR 1.102(c)(1) and MPEP § 708.02, Section IV: Applicant's Age must be accompanied by evidence showing that at least one of the applicants is 65 years of age, or more, such as a birth certificate or a statement by applicant. No fee is required.

The instant petition includes a signed statement from an attorney or agent registered to practice before the Patent and Trademark Office (37 CFR 1.34). Accordingly, the above-identified application has been accorded "special" status.

Telephone inquiries concerning this decision should be directed to the undersigned at 571-272-0602.

All other inquiries concerning either the examination or status of the application should be directed to the Technology Center.

The application is being forwarded to the Technology Center 1600, Art Unit 1634 for action on the merits commensurate with this decision.

Thurman K. Page
Supervisory Petitions Examiner
Office of Petitions

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2

CONFIRMATION NO. 9317

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

POA ACCEPTANCE LETTER

OC00000002667713

Date Mailed: 07/23/2013

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 07/15/2013.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

/ttkim/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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SUBMITTED ELECTRONICALLY

SUPPLEMENTAL AMENDMENT and INTERVIEW SUMMARY		
	Attorney Docket No.	CGLC-020CON2
	Confirmation No.	9317
	First Named Inventor	Sydney Brenner
	Application Number	13/859,450
	Filing Date	April 9, 2013
	Group Art Unit	2852
	Examiner Name	TBD
Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Title: "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"	

Sir:

This communication is filed in follow-up to telephonic interviews with Exr. Bhat held on July 24, 2013, and July 26, 2013. The amendment was requested by Exr. Bhat.

AMENDMENTS TO THE CLAIMS

Please amend the claims as shown below. A complete listing of the claims, including their current status identifiers, is set forth below.

1-20 (Canceled)

21. (Currently amended) A composition comprising a mixture of:

a) a first plurality of **segments** ~~fragments that have been amplified from different parts~~ of a single nucleic acid molecule of a **contiguous region** ~~locus~~ in genomic DNA, wherein each of said first plurality of **segments** ~~fragments~~ is appended to a first multiplex identifier (MID) sequence; and

b) a second plurality of **segments** ~~fragments that have been amplified from different parts~~ of another nucleic acid molecule of said **contiguous region** ~~locus~~, wherein each of said second plurality of **segments** ~~fragments~~ is appended to a second MID sequence and said first MID sequence and said second MID **sequence** are different,

wherein all of the segments in said composition have a multiplex identifier that uniquely identifies an individual nucleic acid molecule of said contiguous region from which said segments originate.

22. (Previously presented) The composition of claim 21, wherein said genomic DNA is mammalian genomic DNA.

23. (Previously presented) The composition of claim 22, wherein said mammalian genomic DNA is human genomic DNA.

24. (Currently amended) The composition of claim 21, wherein said **segments** ~~fragments~~ are in the range of 100 to 5,000 bp in length.

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25. (Currently amended) The composition of claim 21, wherein said **segments** ~~fragments~~ are 400 bp or less in length.

26. (Currently amended) The composition of claim 21, wherein:

the different ~~parts~~ **segments** of said single nucleic acid molecule are distributed along said single nucleic acid molecule; and

the different ~~parts~~ **segments** of said another nucleic acid molecule are distributed along said another nucleic acid molecule.

27. (Currently amended) The composition of claim 26, wherein:

the different ~~parts~~ **segments** of said single nucleic acid molecule are distributed along said single nucleic acid molecule at intervals in the range of 250 bp to 5kb; and

the different ~~parts~~ **segments** of said another nucleic acid molecule are distributed along said another nucleic acid molecule at intervals in the range of 250 bp to 5kb.

28. (Currently amended) The composition of claim 21, wherein:

substantially all ~~parts~~ of said single nucleic acid molecule of said locus **is** ~~are~~ represented in said first plurality of **segments** ~~fragments~~; and

substantially all ~~parts~~ of said another nucleic acid molecule of said locus **is** ~~are~~ represented in said first plurality of **segments** ~~fragments~~.

29. (Previously presented) The composition of claim 21, wherein said locus is up to 30kb in length.

30. (Previously presented) The composition of claim 21, wherein said genomic DNA is genomic DNA from a virus or bacteria.

31. (Currently amended) The composition of claim 21, further pluralities of **segments** ~~fragments~~ that have each been amplified from different parts of a further molecule of said

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locus, wherein each of said further plurality of **segments** ~~fragments~~ is appended to a unique MID sequence that identifies the molecule from which they were amplified.

32. (Currently amended) A method comprising:

sequencing said first plurality of **segments** ~~fragments~~ and said a second plurality of **segments** ~~fragments~~ of a composition of claim 21 to provide a plurality of sequences;

wherein each sequence comprises: (i) the nucleotide sequence of at least a portion of said locus and (ii) an associated MID sequence.

33. (Previously presented) The method of claim 32, further comprising defining a linkage relationship between said sequences using the MID sequence that is associated with each of the sequences, wherein sequences that comprise the first MID sequence are linked and sequences that comprise the second MID sequence are linked.

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REMARKS

Formal Matters

Claims 21-33 are pending.

Claims 21, 24, 25, 26, 27, 28, 31 and 32 are amended. In claim 21, the word "fragments" has been replaced by the word "segments" for clarity, as proposed by the Examiner in the interview. In claims 26 and 27 the word "parts" has also been replaced by the word "segments" for clarity. Support for the wherein clause, which is inherent to the method described in Fig. 5, is found at, e.g., lines 17-29 of page 29, particularly in the following sentence "Any sequences that then result from the reflex process on that particular molecule ... will thus be labeled with the same unique MID tag", where "the same unique MID tag" refers to the unique ID tag added to the "individual nucleic acid molecules" described in the previous sentence. Claims 24, 25, 26, 27, 28, 31 and 32 were amended to be consistent with the amendments to claim 21. No new matter is added.

Interview Summary

Exr. Bhat is thanked for productive telephonic interviews with the undersigned and Mel Kronick on July 24, 2013, and July 26, 2013.

During the interview Exr. Bhat suggested replacing the word "fragments" with the word "segments" for clarity. During the interview, the Examiner also requested that the Applicants provide a brief summary of how the claims are distinguished from six references. Applicants' brief comments on the five references – as presented during the interview - are set forth below.

US20070020640 – does not provide *segments* of a region, where each of the segments has the same MID sequence; also doesn't provide composition in which all of the segments have a multiplex identifier that uniquely identifies the individual molecule of said contiguous region from which said segments originate

US20100113296 - does not provide composition in which all of the segments have a multiplex identifier that *uniquely identifies* the individual molecule of said contiguous region from which said segments originate

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US 2010/0086914 – does not provide composition in which all of the segments have a multiplex identifier that *uniquely identifies* the individual molecule of said contiguous region from which said segments originate

US 7,544,473 – does not provide *segments* of a region, where each of the segments has the same MID sequence; also doesn't provide composition in which all of the segments have a multiplex identifier that uniquely identifies the individual molecule of said contiguous region from which said segments originate

US 8,101,346 - does not provide composition in which all of the segments have a multiplex identifier that *uniquely identifies* the individual molecule of said contiguous region from which said segments originate; not clear if it really provides *segments* of a region, where each of the segments has the same MID sequence

The Examiner indicated that the amendment shown above would likely distinguish the claims from the five references for the reasons outlined in the Applicants' brief comments.

The "wherein" clause shown above was discussed. The Applicants were requested to file a supplemental amendment so that the wherein clause could be entered. The Examiner suggested that, in order to compact prosecution, the Applicants briefly discussed the utility of the claimed method..

Comments

As discussed during the interview, the claimed composition is useful for haplotyping. In one illustrative example, the composition can be used to determine whether two specific mutations are linked in the same nucleic acid molecule in a sample. As the Examiner knows, each diploid cell contains one set of maternally-inherited chromosomes and one set of paternally-inherited chromosomes. Conventional methods (e.g., in the methods described in the references cited above as well as other "shotgun sequencing" methods) may identify the same two mutations, but it is not possible to tell from the sequence data alone whether the mutations are linked (i.e., on the same molecule). Specifically, in some cases, one of the mutations may be at a particular locus in a maternal chromosome (e.g., maternal chromosome 1), and the other of the mutations may be at the same locus in a paternal chromosome (e.g., paternal chromosome 1). Such mutations are *unlinked*. In other cases, both of the mutations may at the

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same locus in either the maternal chromosome or the paternal chromosome. In this case, the mutations are *linked*. Such information cannot be obtained using traditional sequencing methods. This same ability to establish linkage can also be used in analyzing mutations in a viral genome, e.g., like that of HIV, where one wants to determine if mutations in two (or more) different positions of a viral genome are from the same virus particle or from two (or more) different virus particles (each with its own single nucleic acid genome) since such linkage could provide knowledge about what therapeutic interventions might be of value.

In the claimed composition, the multiplex identifier uniquely identifies an individual nucleic acid molecule from which the segments originate. As such, by sequencing the segments and obtaining the multiplex identifier, any mutation found in a segment can be mapped to an individual starting molecule. This concept, which can be referred to as defining a "linkage relationship" between sequences, is described in the application on page 30, lines 3-5 and page 30 lines 12-15.

The Examiner is invited to telephone the undersigned at (650) 833 7723 if he has any further questions.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CGLC-020CON2.

Respectfully submitted,

Date: July 29, 2013

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie, Ph.D.
Registration No. 48,920

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Page 00337

Electronic Acknowledgement Receipt

EFS ID:	16438911
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	29-JUL-2013
Filing Date:	09-APR-2013
Time Stamp:	17:39:09
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		CGLC-020CON2-Suppl_Amend.pdf	48008 b08177fa84cb1f98c8ed8397afc3182134afc2e3	yes	7

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	4
	Applicant Arguments/Remarks Made in an Amendment	5	7
Warnings:			
Information:			
	Total Files Size (in bytes):	48008	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014 OMB 0651-0032
U.S. Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 13/859,450	Filing Date 04/09/2013	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)		
	07/29/2013	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	* 13	Minus	** 20	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 1	Minus	***3	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	0

		(Column 1)		(Column 2)	(Column 3)		
		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/Tina J. Barden/

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2	9317

95726 7590 08/02/2013
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

EXAMINER	
BHAT, NARAYAN KAMESHWAR	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
08/02/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com
zuehlke@bozpat.com

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Applicant-Initiated Interview Summary	**Application No.**	**Applicant(s)**	
	13/859,450	BRENNER ET AL.	
	Examiner	**Art Unit**	
	NARAYAN BHAT	1634	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Examiner: Bhat*. (3)_____.

(2) *Representatives: Mr. Keddie and Mr. MelKronick*. (4)_____.

Date of Interview: *26 July 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *21*.

Identification of prior art discussed: *Cited in the 892 form*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/Narayan K. Bhat/ Examiner, Art Unit 1634	

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Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: The representative Mr. Keddie contacted the Examiner on June 19, 2013 to inquire the status of instant '450 application that is made special due to age of the inventor. The Examiner informed that said application has not been docketed and will get in touch with the representative upon it's docketing to the Examiner. The Examiner contacted the representative on July 22, 2013 to inform the representative that the '450 application has been docketed and has to be moved quickly. The Examiner also informed that the subject matter of claim 21 would be obvious over the references that have been listed in 892 form and sent to the representative electronically on the same day. The representative informed that the references will be reviewed and amend claims if needed and requested a formal interview on July 26, 2013.

The representative e-mailed the amendments to claim 21 and brief remarks regarding each references sent electronically, for discussion purpose only prior to the interview. During the interview Mr. Keddie discussed the novelty of the claimed invention including single nucleic acid molecule requirement and further explained that claim 21 as amended would be novel over the art of the record. The Examiner agreed that amendments are novel over the cited arts and suggested to file a formal reply along with the discussed and agreed claim amendments along with support for the amendments and remarks for further considerations. The Examiner also emphasized that the amendments would require further search and other considerations.

Notice of References Cited	Application/Control No. 13/859,450	Applicant(s)/Patent Under Reexamination BRENNER ET AL.	
	Examiner NARAYAN BHAT	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-7,544,473	06-2009	Brenner, Sydney	435/6.12
*	B	US-8,101,346	01-2012	Takahama, Shinichiro	435/6.12
*	C	US-2007/0020640	01-2007	McCloskey et al.	435/006
*	D	US-2010/0086914	04-2010	BENTLEY et al.	435/6
*	E	US-2010/0113296	05-2010	Myerson, Joel	506/9
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00345

Filed Electronically August 6, 2013

REQUEST FOR CORRECTED FILING RECEIPT Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	CGLC-020CON2
	Applicant	Brenner, Sydney
	Serial Number	13/859,450
	Filing Date	April 9, 2013
	Group Art Unit	2852
	Examiner Name	
	Title: *"Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"*	

Sir:

A filing receipt for the above-identified patent application has been issued by the U.S. Patent and Trademark Office (copy attached) and has been found to contain error.

Please update the Filing Receipt with the correct residence information for the following inventors:

Sydney Brenner, Ely, United Kingdom; Gi Mikawa, **Great Shelford,** United Kingdom; Robert Osborne, **Great Chesterford,** United Kingdom; Andrew Slatter, London, United Kingdom.

If for any reason a fee is found to be necessary, the Commissioner is authorized to charge such fee to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: August 6, 2013

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie, Reg. No. 48,920

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/859,450	04/09/2013	2852	730	CGLC-020CON2	13	1

CONFIRMATION NO. 9317

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

FILING RECEIPT

OC00000006128606 3

Date Mailed: 05/23/2013

RECEIVED
By mtaa at 8:58 am, May 23, 2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

SYDNEY BRENNER, ELy, UNITED KINGDOM;
GI MIKAWA, ~~Cambridge, UNITED KINGDOM;~~ Great Shelford, UNITED KINGDOM;
ROBERT OSBORNE, ~~Essex, UNITED KINGDOM;~~ Great Chesterford, UNITED KINGDOM;
ANDREW SLATTER, London, UNITED KINGDOM;

Applicant(s)

Population Genetics Technologies Ltd, Cambridge, UNITED KINGDOM

Assignment For Published Patent Application

Population Genetics Technologies Ltd, Cambridge, UNITED KINGDOM

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 13/622,872 09/19/2012
which is a CON of 13/387,343 02/15/2012 PAT 8298767
which is a 371 of PCT/IB2010/002243 08/13/2010
which claims benefit of 61/288,792 12/21/2009
and claims benefit of 61/235,595 08/20/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 05/16/2013

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00347

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/859,450**

Projected Publication Date: 08/29/2013

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **
Title

Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

Preliminary Class

396

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4158).

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Page 00348

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

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SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	SYDNEY		BRENNER	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	ELy	Country of Residence i	GB

Mailing Address of Inventor:

Address 1	3 Barton Square		
Address 2			
City	Ely	**State/Province**	Cambridgeshire
Postal Code	CB7 4PJ	**Country** i	GB

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	GI		MIKAWA	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	~~Cambridge~~ Great Shelford	Country of Residence i	GB

Mailing Address of Inventor:

Address 1	104 High Street		
Address 2	GT Abington		
City	~~Cambridge~~ Great Shelford	**State/Province**	Cambridgeshire
Postal Code	CB1 6A3	**Country** i	GB

Inventor 3 Remove

Legal Name

PTO/AIA/14 (08-12)
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SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Prefix	Given Name	Middle Name	Family Name	Suffix
	ROBERT		OSBORNE	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	~~Essex~~ Great Chesterford	Country of Residence i	GB

Mailing Address of Inventor:

Address 1	38 Pilgrim Close
Address 2	~~Great Chesterford~~

City	~~Essex~~ Great Chesterford	State/Province	Essex
Postal Code	CB10 1QG	**Country** i	GB

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	ANDREW		SLATTER	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	London	Country of Residence i	GB

Mailing Address of Inventor:

Address 1	65a Huddleston Road
Address 2	

City	London	State/Province	GB
Postal Code	N7 0AE	**Country** i	GB

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	93726		
Email Address	docket@bozpat.com	Add Email	Remove Email

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Application Information:

Title of the Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement		
Attorney Docket Number	CGLC-020CON2	**Small Entity Status Claimed** ☒	
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	13	**Suggested Figure for Publication (if any)**	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for thr Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	93726		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	13622872	2012-09-19
Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13622872	Continuation of	13387343	2012-02-15
Prior Application Status	Pending	Remove	

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SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13387343	a 371 of international	PCT/IB2010/002243	2010-08-13
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
IB2010002243	non provisional of	61288792	2009-12-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
IB2010002243	non provisional of	61235595	2009-08-20

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Priority Claimed
			◉ Yes ○ No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Authorization to Permit Access:

☒ Authorization to Permit Access to the Instant Application by the Participating Offices

If checked, the undersigned hereby grants the USPTO authority to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the World Intellectual Property Office (WIPO), and any other intellectual property offices in which a foreign application claiming priority to the instant patent application is filed access to the instant patent application. See 37 CFR 1.14(c) and (h). This box should not be checked if the applicant does not wish the EPO, JPO, KIPO, WIPO, or other intellectual property office in which a foreign application claiming priority to the instant patent application is filed to have access to the instant patent application.

In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

In accordance with 37 CFR 1.14(c), access may be provided to information concerning the date of filing this Authorization.

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SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

◉ Assignee	○ Legal Representative under 35 U.S.C. 117
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Assignee is an Organization check here. ☒

Organization Name	Population Genetics Technologies Ltd

Mailing Address Information:

Address 1	Babraham Research Campus		
Address 2			
City	Cambridge	**State/Province**	
Country	GB	Postal Code	CB22 3AT
Phone Number		Fax Number	
Email Address	docket@bozpat.com		

Additional Applicant Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications

Signature	/James S. Keddie, Ph.D., Reg. No. 48,920/			Date (YYYY-MM-DD)	2013-08-06
First Name	James S.	Last Name	Keddie	Registration Number	48920

Additional Signature may be generated within this form by selecting the Add button.

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00354

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SUPPLEMENTAL **Application Data Sheet 37 CFR 1.76**	Attorney Docket Number	CGLC-020CON2
	Application Number	
Title of Invention	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00355

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00356

Electronic Acknowledgement Receipt

EFS ID:	16512541
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	06-AUG-2013
Filing Date:	09-APR-2013
Time Stamp:	18:18:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	CGLC-020CON2_Req_Corr_FR.pdf	21950 [illegible]	no	1

Warnings:

Information:

2	Request for Corrected Filing Receipt	CGLC-020CON2_Corrected-FR.pdf	454631 [redacted]	no	3
Warnings:					
Information:					
3	Request for Corrected Filing Receipt	CGLC-020CON2-Suppl_ADS.pdf	589982 [redacted]	no	7
Warnings:					
Information:					
			Total Files Size (in bytes):	1066563	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

SUBMITTED ELECTRONICALLY

INTERVIEW SUMMARY		
	Attorney Docket No.	CGLC-020CON2
	Confirmation No.	9317
	First Named Inventor	Sydney Brenner
	Application Number	13/859,450
	Filing Date	April 9, 2013
	Group Art Unit	2852
Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Bhat
	Title: "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"	

Interview Summary

Exr. Bhat is thanked for a productive telephonic interview with the undersigned on August 7, 2013.

Potentially clarifying claim amendments and a possible rejection were discussed. During the interview, Exr. Bhat requested clarification of why the claims are not rendered obvious by Laird et al (Proc. Natl. Acad. Sci. 2004 101: 204-209). The undersigned explained that, among other things, the Laird reference does not disclose producing multiple different segments of a genomic region. The undersigned also explained that Laird is only interested in analyzing a single segment and does a single PCR reaction. As such, Laird has no interest in producing multiple different segments of a genomic region and provides no way for producing the same. Exr. Bhat indicated amending the claim 21 to say "a first plurality of different segments" would render this potential rejection moot. Exr. Bhat agreed that "different" segments can be overlapping or non-overlapping.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number CGLC-020CON2.

Respectfully submitted,

Date: August 7, 2013

By: /James S. Keddie, Reg. No.48,920/
James S. Keddie, Ph.D.
Registration No. 48,920

Electronic Acknowledgement Receipt

EFS ID:	16528798
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	Compositions and Methods for Intramolecular Nucleic Acid Rearrangement
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	07-AUG-2013
Filing Date:	09-APR-2013
Time Stamp:	18:29:51
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant summary of interview with examiner	CGLC-020CON2-Interview_Summary.pdf	17213 0d4595106f4a3ad070bda9b32cf891012d26d5aa	no	1

Warnings:

Information:

Total Files Size (in bytes):	17213

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
13/859,450	04/09/2013	1634	730	CGLC-020CON2	13	1

CONFIRMATION NO. 9317

CORRECTED FILING RECEIPT

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

Date Mailed: 08/15/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

SYDNEY BRENNER, ELy, UNITED KINGDOM;
GI MIKAWA, Great Shelford, UNITED KINGDOM;
ROBERT OSBORNE, Great Chesterford, UNITED KINGDOM;
ANDREW SLATTER, London, UNITED KINGDOM;

Applicant(s)

Population Genetics Technologies Ltd, Cambridge, UNITED KINGDOM

Assignment For Published Patent Application

Population Genetics Technologies Ltd, Cambridge, UNITED KINGDOM

Power of Attorney: The patent practitioners associated with Customer Number 93726

Domestic Priority data as claimed by applicant

This application is a CON of 13/622,872 09/19/2012
which is a CON of 13/387,343 02/15/2012 PAT 8298767
which is a 371 of PCT/IB2010/002243 08/13/2010
which claims benefit of 61/288,792 12/21/2009
and claims benefit of 61/235,595 08/20/2009

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access - A proper **Authorization to Permit Access to Application by Participating Offices** (PTO/SB/39 or its equivalent) has been received by the USPTO.

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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If Required, Foreign Filing License Granted: 05/16/2013

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 13/859,450**

Projected Publication Date: 08/29/2013

Non-Publication Request: No

Early Publication Request: No
** SMALL ENTITY **
Title

Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

Preliminary Class

435

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00363

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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Alexandria, Virginia 22313-1450
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NOTICE OF ALLOWANCE AND FEE(S) DUE

93726 7590 08/23/2013

EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

EXAMINER	
BHAT, NARAYAN KAMESHWAR	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/23/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2	9317

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/25/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 02/11)

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

93726 7590 08/23/2013
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission
I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2	9317

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/25/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
BHAT, NARAYAN KAMESHWAR	1634	435-091100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
- ☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
- ☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively, 1
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed. 2 3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent): ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
- ☐ Issue Fee
- ☐ Publication Fee (No small entity discount permitted)
- ☐ Advance Order - # of Copies

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
- ☐ A check is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number (enclose an extra copy of this form).

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10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00366

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature	Date
Typed or printed name	Registration No.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Page 00367

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2	9317

93726 7590 08/23/2013

EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

EXAMINER	
BHAT, NARAYAN KAMESHWAR	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 08/23/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 0 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 0 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

PTOL-85 (Rev. 02/11)

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
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Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 13/859,450	Applicant(s) BRENNER ET AL.	
	Examiner NARAYAN BHAT	Art Unit 1634	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *7/29/13*.

   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are *21-31*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.

   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☒ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date See Continuation Sheet
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☒ Interview Summary (PTO-413), Paper No./Mail Date *7/30/13* .
5. ☒ Examiner's Amendment/Comment
6. ☒ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/Narayan K. Bhat/
Examiner, Art Unit 1634

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Continuation of Attachment(s) 2. Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date: 4/9/13, 5/15/13 & 7/18/13.

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
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NOTICE OF ALLOWANCE

1. This office action is in response to the papers filed on April 9, 2013 and July 29, 2013. Instant application is a continuation of 13622872, filed 09/19/2012, which is a continuation of 13387343, filed 02/15/2012, now U.S. Patent 8,298,767. Claims 21-33 are pending in this application.

Interview Summary

2. Following the interview between the Examiner and the representatives Mr. Keddie and Mr. MelKronick on July 26, 2013, Applicant filed supplemental amendments on July 29, 2013 to overcome the potential rejections over the arts of the record. Following the search for the limitations of amended claim 21, the Examiner contacted the representative Mr. Keddie on multiple dates and the interview summaries are listed below.

July 30, 2013: Discussed the amended claims of July 29, 2013. Alternative recitations for "another nucleic acid molecule", "individual nucleic acid molecule" in claim 21, "wherein" clause limitations in claims 21 and 31, "further molecule" in claim 31 and antecedent basis for "said" locus in claims 28, 29 and 31 were discussed. The representative agreed to further amend said claims and send them electronically for further review and discussion. The amended claims were sent to the Examiner electronically on the same day.

August 7, 2013: Discussed the amended claims of July 30, 2013. The specific claim languages were discussed to overcome the potential rejection of said amended

claims over Laird (PNAS, 2004, cited in the IDS of 4/9/13) in view of McKloskey et al (cited in the previous interview). Also, the Examiner suggested the need for further clarification for the "wherein" clause of claims 21 and 31. The representative agreed to further amend said claims and send them electronically for further review and discussion. The amended claims were sent to the Examiner electronically on the same day.

The representative also discussed that a plurality of "different" segments of the nucleic acid molecule encompasses overlapping or non-overlapping segments of the nucleic acid molecule. The Examiner concurred with the interpretation of a plurality of "different" segments of the nucleic acid molecule can be overlapping or non-overlapping.

August 8, 2013: Discussed the amended claims of August 7, 2013. The specific claim languages were discussed to further clarify the "wherein" clause of claim 21 to be consistent with the invention as illustrated in Fig. 5 of the instant specification. The Examiner suggested reciting "further molecule" of claim 31 as "third molecule" to be consistent with the previous recitation of first and second nucleic acid molecules in claim 21. An agreement was reached regarding the claim languages of pending claims to overcome the rejection over art of the record including the cited references in the filed IDS and over the concepts of appending nested PCR fragments or amplified PCR fragments for multiplex genotyping with multiplex identifier sequence.

The Examiner informed the representative that claims 32 and 33 are drawn to a method whereas claims 21-31 are drawn to a composition. If the composition of claims

21-31 is found allowable and if claims 32 and 33 include all the limitations of allowed composition, they can also be allowed. The representative informed that if the composition claims of 21-31 are allowable, the Applicant would like to cancel claims 32 and 33 and pursue them separately.

The claim amendments with the discussed and agreed phrases were sent to the Examiner electronically on August 8, 2013, with authorization to cancel claims 32 and 33 via Examiner's amendments if the composition of claims 21-31 is found allowable.

Claim Status

3. Upon entry of claims of August 8, 2013 via Examiner's amendments, claims 21 and 24-31 are amended. Claims 32 and 33 are cancelled. The claim amendments have been reviewed and entered. No new matter has been introduced by the Claim amendments. The support for the claims of April 9, 2013 in the specification as identified by the Applicant is acknowledged by the Examiner.

Information Disclosure Statement

4. The information disclosure statement (IDS) submitted on April 9, 2013, May 15, 2013 and July 18, 2013 is being considered by the examiner. ***All the references cited in the said IDSs have been considered by the Examiner.*** It is noted that the date of publication of the NPL reference # 2 of Casbon (***post art***) filed in the IDS of May 15, 2013 has been updated.

It is also noted that the bulk of the cited references in the said IDSs or in the field of molecular tagging prior to the filing date of the instant application discloses tagging of sample or a nucleic acid of interest with an identifier in the form of barcode, or multiplex identifier or zipcode or tagging sequences to track it in further analysis.

However, it is in the Examiner's opinion it would not have been obvious to a person of ordinary skill in the art to modify the references of the record or references related to nested PCR, amplified DNA fragments for multiplex genotyping to arrive at the claimed composition requiring a contiguous region in genomic DNA further comprising a plurality of nucleic acid molecules, wherein, in said composition, all of the segments of each of the nucleic acid molecules of the contiguous region comprises a unique MID sequence that uniquely identifies each of the nucleic acid molecules.

Specification, Abstract, Drawings, Continuing Data and Oath/Declaration

5. The specification, abstract, drawings and Oath/Declaration field on April 9, 2013 have been reviewed and entered. The specification, abstract, drawings and Oath/Declaration are compliant. The initialed BIB data sheet has been made of the record.

Potential Rejections

6. The copending applications by the inventors of the instant application and the prosecution of the copending application resulting in the issuance of the patents have

been reviewed for the ODP rejection. It is in the Examiner's opinion that the instant pending claims have different scope than the claims of the allowed patents or claims of copending application going through the prosecution in view of the art of the record.

7. It is also in the Examiner's opinion that the instant pending claims have overcome potential objections, rejections under 35 USC 112 first and second paragraphs, under 35 USC 102 and 103(a) rejection. As discussed in sections 2 and 4, instant pending claims are novel over the art of the record.

EXAMINER'S AMENDMENT

8. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given electronically by Applicant's representative Mr. Keddie on August 8, 2013.

Please replace the claim listing of July 29, 2013 with the following claim listing.

1-20 (Canceled)

21. (Currently amended) A composition comprising a mixture of:

a) a first plurality of **different** segments of a ~~single~~ **first** nucleic acid molecule of a contiguous region in genomic DNA, **wherein said contiguous region in genomic DNA is represented by a plurality of nucleic acid molecules, and** wherein each of said first plurality of segments is appended to a first multiplex identifier (MID) sequence; and

b) a second plurality of **different** segments of ~~another~~ **a second** nucleic acid molecule of said contiguous region, wherein each of said second plurality of segments is appended to a second MID sequence and said first MID sequence and said second MID sequence are different,

wherein**, in said composition,** all of the segments **of each of the nucleic acid molecules of the contiguous region comprises a unique MID sequence that uniquely identifies each of the nucleic acid molecules** ~~in said composition have a multiplex identifier that uniquely identifies a an individual nucleic acid molecule of said contiguous region from which said segments originate~~.

22. (Previously presented) The composition of claim 21, wherein said genomic DNA is mammalian genomic DNA.

23. (Previously presented) The composition of claim 22, wherein said mammalian genomic DNA is human genomic DNA.

24. (Currently amended) The composition of claim 21, wherein **the** ~~said~~ segments **of a) and b)** are in the range of 100 to 5,000 bp in length.

25. (Currently amended) The composition of claim 21, wherein **the** ~~said~~ segments **of a) and b)** are 400 bp or less in length.

26. (Currently amended) The composition of claim 21, wherein:

the different segments of said ~~single~~ **first** nucleic acid molecule are distributed along said ~~single~~ **first** nucleic acid molecule; and

the different segments of said ~~another~~ **second** nucleic acid molecule are distributed along said **second** ~~another~~ nucleic acid molecule.

27. (Currently amended) The composition of claim 26, wherein:

the different segments of said ~~single~~ **first** nucleic acid molecule are distributed along said ~~single~~ **first** nucleic acid molecule at intervals in the range of 250 bp to 5kb; and

the different segments of said ~~another~~ **second** nucleic acid molecule are distributed along said ~~another~~ **second** nucleic acid molecule at intervals in the range of 250 bp to 5kb.

28. (Currently amended) The composition of claim 21, wherein:

substantially all of said ~~single~~ **first** nucleic acid molecule of said **contiguous region** ~~locus~~ is represented in said first plurality of segments; and

substantially all of said **second** ~~another~~ nucleic acid molecule of said **contiguous region** ~~locus~~ is represented in said ~~first~~ **second** plurality of segments.

29. (Currently amended) The composition of claim 21, wherein said **contiguous region** ~~locus~~ is up to 30kb in length.

30. (Currently amended) The composition of claim 21, wherein said genomic DNA is genomic DNA from a virus or ~~bacteria~~ **a bacterium**.

31. (Currently amended) The composition of claim 21, further **comprising a third plurality of different segments of a third nucleic acid molecule of said contiguous region, wherein each of said third plurality of segments is appended to a third MID sequence and said third MID sequence is different to said first and second MID sequences** ~~pluralities of segments that have each been amplified from different parts of a further molecule of said locus, wherein each of said further plurality of segments is appended to a unique MID sequence that identifies the molecule from which they were amplified~~.

32. (Canceled)

33. (Canceled)

9. Claims 21-31 has been renumbered as 1-11.

REASONS FOR ALLOWANCE

10. The following is an examiner's statement of reasons for allowance:

New art cited: Braverman et al (WO2008150432) discloses an identifier element for identifying an origin of a template nucleic acid molecule that comprises a nucleic acid element comprising a sequence composition, which is similar to the arts cited in the interview summary filed by the Examiner and mailed on August 2, 2013. The arguments filed by the Applicant on July 29, 2013 have been fully considered (Remarks, pgs. 5-7) and are persuasive. In the Examiner's opinion, the composition of allowed claims is novel over the art of the record as discussed in section 4.

Post art: Casbon et al (cited in the IDS filed May 15, 2013). ***The post art of Casbon*** (at least one inventor in common) published in the peer reviewed Nucleic Acids Research discloses a technique for appending daughter amplicons of a long contiguous nucleic acid sequence with a multiplex identifier sequence (Fig. 1 and Abstract), which is similar to the limitations of section 'a' of instant claim 21.

Since appending daughter amplicons of the long contiguous nucleic acid sequence with the multiplex identifier sequence (i.e., the limitations of section 'a' of

instant claim 21) has been reviewed by the experts in the field and found to be novel to be published in the peer-reviewed journal, the composition of the instant claim 21 requiring the contiguous region in genomic DNA further comprising a plurality of nucleic acid molecules, wherein, in said composition, all of the segments of each of the nucleic acid molecules of the contiguous region comprises a unique MID sequence that uniquely identifies each of the nucleic acid molecules is novel as also viewed by the experts in the nucleic acid field.

For these reasons the composition of instant pending claims is novel over the art of the record.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Conclusion

11. Claims 21-31 are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

Examiner-Initiated Interview Summary	Application No. 13/859,450	Applicant(s) BRENNER ET AL.	
	Examiner NARAYAN BHAT	Art Unit 1634	

All participants (applicant, applicant's representative, PTO personnel):

(1) *Examiner: Bhat*. (3)_____.

(2) *Representative: Mr. Keddie*. (4)_____.

Date of Interview: *30 July 2013*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *21,28,29 and 31*.

Identification of prior art discussed: *None*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

See Continuation Sheet.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/Narayan K. Bhat/ Examiner, Art Unit 1634	

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Continuation of Substance of Interview including description of the general nature of what was agreed to if an agreement was reached, or any other comments: Following the interview between the Examiner and the representatives Mr. Keddie and Mr. MelKronick on July 26, 2013, Applicant filed supplemental amendments on July 29, 2013 to overcome the potential rejections over the arts of the record. Following the search for the limitations of amended claim 21, the Examiner contacted the representative Mr. Keddie on multiple dates and the interview summaries are listed below.

July 30, 2013: Discussed the amended claims of July 29, 2013. Alternative recitations for "another nucleic acid molecule", "individual nucleic acid molecule" in claim 21, "wherein" clause limitations in claims 21 and 31, "further molecule" in claim 31 and antecedent basis for "said" locus in claims 28, 29 and 31 were discussed. The representative agreed to further amend said claims and send them electronically for further review and discussion. The amended claims were sent to the Examiner electronically on the same day.

August 7, 2013: Discussed the amended claims of July 30, 2013. The specific claim languages were discussed to overcome the potential rejection of said amended claims over Laird (PNAS, 2004, cited in the IDS of 4/9/13) in view of McKloskey et al (cited in the previous interview). Also, the Examiner suggested the need for further clarification for the "wherein" clause of claims 21 and 31. The representative agreed to further amend said claims and send them electronically for further review and discussion. The amended claims were sent to the Examiner electronically on the same day. The representative also discussed that a plurality of "different" segments of the nucleic acid molecule encompasses overlapping or non-overlapping segments of the nucleic acid molecule. The Examiner concurred with the interpretation of a plurality of "different" segments of the nucleic acid molecule can be overlapping or non-overlapping.

August 8, 2013: Discussed the amended claims of August 7, 2013. The specific claim languages were discussed to further clarify the "wherein" clause of claim 21 to be consistent with the invention as illustrated in Fig. 5 of the instant specification. The Examiner suggested reciting "further molecule" of claim 31 as "third molecule" to be consistent with the previous recitation of first and second nucleic acid molecules in claim 21. An agreement was reached regarding the claim languages of pending claims to overcome the rejection over art of the record including the cited references in the filed IDS and over the concepts of appending nested PCR fragments or amplified PCR fragments for multiplex genotyping with multiplex identifier sequence.
The Examiner informed the representative that claims 32 and 33 are drawn to a method whereas claims 21-31 are drawn to a composition. If the composition of claims 21-31 is found allowable and if claims 32 and 33 include all the limitations of allowed composition, they can also be allowed. The representative informed that if the composition claims of 21-31 are allowable, the Applicant would like to cancel claims 32 and 33 and pursue them separately.
The claim amendments with the discussed and agreed phrases were sent to the Examiner electronically on August 8, 2013, with authorization to cancel claims 32 and 33 via Examiner's amendments if the composition of claims 21-31 is found allowable.

Notice of References Cited	Application/Control No. 13/859,450	Applicant(s)/Patent Under Reexamination BRENNER ET AL.	
	Examiner NARAYAN BHAT	Art Unit 1634	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
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	D	US-			
	E	US-			
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	I	US-			
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	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N	WO 2008150432	12-2008	US	Braverman et al	
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
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*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13859450
Filing Date	2013-04-09
First Named Inventor	Sydney Brenner, Ely
Art Unit	1634
Examiner Name	Bhat, Narayan Kameshwar
Attorney Docket Number	CGLC-020CON2

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	1	20120316074		2012-12-13	SAXONOV	

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	13859450
	Filing Date	2013-04-09
	First Named Inventor	Sydney Brenner, Ely
	Art Unit	1634
	Examiner Name	Bhat, Narayan Kameshwar
	Attorney Docket Number	CGLC-020CON2

13859450 - GAU: 1634

	1	SCHWARTZ; et al., "Capturing native long-range contiguity by in situ library construction and optical sequencing", PNAS (Nov. 2012), 109(46):18749-18754.	☐
	2	WANG; et al., "Self-Formed Adaptor PCR: a Simple and Efficient Method for Chromosome Walking", Applied and Environmental Microbiology (Aug. 2007), 73(15):5048-5051.	☐

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EXAMINER SIGNATURE

Examiner Signature	/Narayan Bhat/	Date Considered	08/09/2013

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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"multiplex identifier" "plurality" "fragments"

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System and method for identification of individual samples from a multiplex mixture
MS Bayrak-Toydemir, JF Tavtigian, M Bekritsky - WO Patent App. PCT/..., 2008 - google.com
... unique identifier (UID) element which is sometimes also referred to as a **multiplex identifier** (MID), with ... from a single nucleic acid template molecule or a population of a **plurality** of substantially ... selection methods known in the art to selectively isolate nucleic acid **fragments** of the ...
Cite

System and method for improved processing of nucleic acids for production of sequencable libraries
T Adam, MS Bayrak-Toydemir, M Bekritsky - US Patent App. 12/..., 2008 - google.com
... using methods and unique adaptor elements to produce libraries of **fragments** amenable for ... which may be a T nucleotide species, or comprises a **plurality** a bases. ... compatible with those disclosed above, the complementary region comprises a **multiplex identifier** element, which ...
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System and method for improved processing of nucleic acids for production of sequencable libraries
M Bekritsky, MS Bayrak-Toydemir, JM Rothstein... - WO Patent App. PCT..., 2009 - google.com
... using methods and unique adaptor elements to produce libraries of **fragments** amenable for ... which may be a T nucleotide species, or comprises a **plurality** a bases. ... compatible with those disclosed above, the complementary region comprises a **multiplex identifier** element, which ...
Cite

System and method for improved processing of nucleic acids for production of sequencable libraries
DC Bolduc, JR Bowers, MJ Rothstein... - US Patent App. 12/..., 2008 - Google Patents
... acids using methods and unique adaptor elements to produce libraries of **fragments** amenable for ... an enriched population of single stranded molecules amplifying a **plurality** of members ... member that comprises a sequence com- position for the **multiplex identifier** element; and ...
All 2 versions Cite

Best Abstracts
A Amir, L Dorsogna, M van Loenen, M Keyser - 2008 - Wiley Online Library
Page 1. Abstracts for Oral Presentation Best Abstracts O1 Alloreactivity of virus specific memory T-cells is common Avital Amir, Lloyd Dorsogna, Marleen van Loenen, Michel Kester, Ilias Doxiadis, Dave Roelen, Frederick Falkenburg ...
Cite

System and method for detection of hiv integrase variants
BB Seaton, JEP Sullivan - WO Patent App. PCT/..., 2008 - google.com
... may exist on either strand and include a single base position or a **plurality** of base ... size selection methods known in the art to selectively isolate nucleic acid **fragments** of the ... methods, quality control elements, unique identifiers (also referred to as a **multiplex identifier** or "MID ...
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System and method for detection of hiv tropism variants
BB Seaton, JEP Sullivan - WO Patent App. PCT/..., 2008 - google.com
... may exist on either strand and include a single base position or a **plurality** of base ... size selection methods known in the art to selectively isolate nucleic acid **fragments** of the ... methods, quality control elements, unique identifiers (also referred to as a **multiplex identifier** or "MID ...
Cite

System and method for detection of HIV integrase variants
BB Seaton, EPE Sullivan - US Patent App. 12/..., 2009 - Google Patents
... exist on either strand and include a single base position or a **plurality** of base ... selec- tion methods known in the art to selectively isolate nucleic acid **fragments** of the ... sequencing methods, quality control elements, unique identifiers (also referred to as a **multiplex identifier** or "MID ...
All 2 versions Cite

Semantic processor storage server architecture
C Webb, P Bose, K Nellis, PJ Howard, P Sladen... - WO Patent App. PCT/..., 2005 - google.com
... A MID (**Multiplex Identifier**) allows a client to use the same PID for multiple outstanding transactions, by using a different MID for each transaction. ... PR code memory 2220 contains a **plurality** of PR codes that are used to access a corresponding production rule stored in the ...
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EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L3	28	(brenner.in. or mikawa.in. or osborne.in. or slater.in. or population.as.) and (intramolecular or tagging) near5 (nucleic or dna or polynucleotide)	USPAT; UPAD	OR	ON	2013/08/12 10:13
L4	27	l3 and ("multiplex identifier" or multiplexidentifier or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or tag$3) near5 (nucleic or dna)	USPAT; UPAD	OR	ON	2013/08/12 10:13
L5	4	l4 and (nucleic or dna) near5 molecule same (multiple or plurality) near5 (segment or fragment or section or region)	USPAT; UPAD	OR	ON	2013/08/12 10:20

8/ 12/ 2013 10:32:02 AM
C:\ Users\ nbhat1\ Documents\ EAST\ Workspaces\ 13859450-8-6-13.wsp

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	66	(brenner.in. or mikawa.in. or osborne.in. or slater.in. or population.as.) and (intramolecular or tagging) near5 (nucleic or dna or polynucleotide)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/12 10:11
L2	57	l1 and ("multiplex identifier" or multiplexidentifier or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or tag$3) near5 (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/12 10:12

8/12/2013 10:32:37 AM
C:\Users\nbhat1\Documents\EAST\Workspaces\13859450-8-6-13.wsp

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	13859450
Filing Date	April 9, 2013
First Named Inventor	Sydney Brenner
Art Unit	1634
Examiner Name	Bhat N.
Attorney Docket Number	CGLC-020CON2

13859450 - GAU: 1634

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	1	20070238113	A1	2007-10-11	KANDA, e al.	
	2	20070259357	A1	2007-11-08	BRENNER	

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	1	2004/061083	WO	A2	2004-07-22	AMGEN INC		☐
	2	2007/018601	WO	A1	2007-02-15	RUBICON GENOMICS INC		☐

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /N.B./

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Attorney Docket Number	CGLC-020CON2

13859450 - GAU: 1634

	3	1841879	EP	A2	2007-10-10	POPULATION GENETICS TECHNOLOGI		☐
	4	1672064	EP	A1	2006-06-21	RIKEN		☐

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Filing Date	2013-04-09
First Named Inventor	Brenner, Sydney
Art Unit	1634
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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 December 2008 (11.12.2008)

PCT

(10) International Publication Number
WO 2008/150432 A1

(51) International Patent Classification:
C12Q 1/68 (2006.01)

(21) International Application Number:
PCT/US2008/006822

(22) International Filing Date: 29 May 2008 (29.05.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/941,381 1 June 2007 (01.06.2007) US

(63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/941,381 (CIP)
Filed on 1 June 2007 (01.06.2007)

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US (patent), UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with sequence listing part of description published separately in electronic form and available upon request from the International Bureau*

(54) Title: SYSTEM AND METHOD FOR IDENTIFICATION OF INDIVIDUAL SAMPLES FROM A MULTIPLEX MIXTURE

(57) Abstract: An embodiment of an identifier element for identifying an origin of a template nucleic acid molecule is described that comprises a nucleic acid element comprising a sequence composition that enables detection of an introduced error in sequence data generated from the nucleic acid element and correction of the introduced error, where the nucleic acid element is constructed to couple with the end of a template nucleic acid molecule and identifies an origin of the template nucleic acid molecule.

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SYSTEM AND METHOD FOR IDENTIFICATION OF INDIVIDUAL SAMPLES FROM A MULTIPLEX MIXTURE

FIELD OF THE INVENTION

The present invention relates to the fields of molecular biology and bioinformatics. More specifically, the invention relates to associating a unique identifier (UID) element, which is sometimes also referred to as a multiplex identifier (MID), with one or more nucleic acid elements derived from a specific sample, combining the associated elements from the sample with associated elements from one or more other samples into a multiplex mixture of said samples, and identifying each identifier and its associated sample from data generated by what are generally referred to as "Sequencing" techniques.

BACKGROUND OF THE INVENTION

There are a number of "sequencing" techniques known in the art amenable for use with the presently described invention such as, for instance, techniques based upon what are referred to as Sanger sequencing methods commonly known to those of ordinary skill in the art that employ termination and size separation techniques. Other classes of powerful high throughput sequencing techniques for determining the identity or sequence composition of one or more nucleotides in a nucleic acid sample include what are referred to as "Sequencing-by-synthesis" techniques (SBS), "Sequencing-by-Hybridization" (SBH), or "Sequencing-by-Ligation" (SBL) techniques. Of these, SBS methods provide many desirable advantages over previously employed sequencing methods that include, but are not limited to the massively parallel generation of a large volume of high quality sequence information at a low cost relative to previous techniques. The term "massively parallel" as used herein generally refers to the simultaneous generation of sequence information from many different template molecules in parallel where the individual template molecule or population of substantially identical template molecules are separated or compartmentalized and simultaneously exposed to sequencing processes which may include a iterative series of reactions thereby producing an independent sequence read representing the nucleic acid composition of each template molecule. In other words, the advantage includes the ability to simultaneously sequence multiple nucleic acid elements associated with many different samples or different nucleic acid elements existing within a sample.

Typical embodiments of SBS methods comprise the stepwise synthesis of a single strand of polynucleotide molecule complementary to a template nucleic acid molecule whose

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nucleotide sequence composition is to be determined. For example, SBS techniques typically operate by adding a single nucleic acid (also referred to as a nucleotide) species to a nascent polynucleotide molecule complementary to a nucleic acid species of a template molecule at a corresponding sequence position. The addition of the nucleic acid species to the nascent molecule is generally detected using a variety of methods known in the art that include, but are not limited to what are referred to as pyrosequencing or fluorescent detection methods such as those that employ reversible terminators or energy transfer labels including fluorescent resonant energy transfer dyes (FRET). Typically, the process is iterative until a complete (i.e. all sequence positions are represented) or desired sequence length complementary to the template is synthesized.

Further, as described above many embodiments of SBS are enabled to perform sequencing operations in a massively parallel manner. For example, some embodiments of SBS methods are performed using instrumentation that automates one or more steps or operation associated with the preparation and/or sequencing methods. Some instruments employ elements such as plates with wells or other type of microreactor configuration that provide the ability to perform reactions in each of the wells or microreactors simultaneously. Additional examples of SBS techniques as well as systems and methods for massively parallel sequencing are described in US Patent Nos. 6,274,320; 6,258,568; 6,210,891, 7,211,390; 7,244,559; 7,264,929; 7,335,762; and 7,323,305 each of which is hereby incorporated by reference herein in its entirety for all purposes; and US Patent Application Serial No. 11/195,254, which is hereby incorporated by reference herein in its entirety for all purposes.

It may also be desirable in some embodiments of SBS, to generate many substantially identical copies of each template nucleic acid element that for instance, provides a stronger signal when one or more nucleotide species is incorporated in each nascent molecule in a population comprising the copies of a template nucleic acid molecule. There are many techniques known in the art for generating copies of nucleic acid molecules such as, for instance, amplification using what are referred to as bacterial vectors, "Rolling Circle" amplification (described in US Patent Nos. 6,274,320 and 7,211,390, incorporated by reference above), isothermal amplification techniques, and Polymerase Chain Reaction (PCR) methods, each of the techniques are applicable for use with the presently described invention. One PCR technique that is particularly amenable to high throughput applications include what are referred to as emulsion PCR methods.

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Typical embodiments of emulsion PCR methods include creating stable emulsion of two immiscible substances and are resistant to blending together where one substance is dispersed within a second substance. The emulsions may include droplets suspended within another fluid and are sometimes also referred to as compartments, microcapsules, microreactors, microenvironments, or other name commonly used in the related art. The droplets may range in size depending on the composition of the emulsion components and formation technique employed. The described emulsions create the microenvironments within which chemical reactions, such as PCR, may be performed. For example, template nucleic acids and all reagents necessary to perform a desired PCR reaction may be encapsulated and chemically isolated in the droplets of an emulsion. Thermo cycling operations typical of PCR methods may be executed using the droplets to amplify an encapsulated nucleic acid template resulting in the generation of a population comprising many substantially identical copies of the template nucleic acid. Also in the present example, some or all of the described droplets may further encapsulate a solid substrate such as a bead for attachment of nucleic acids, reagents, labels, or other molecules of interest.

Embodiments of an emulsion useful with the presently described invention may include a very high density of droplets or microcapsules enabling the described chemical reactions to be performed in a massively parallel way. Additional examples of emulsions and their uses for sequencing applications are described in US Patent Application Serial Nos. 10/861,930; 10/866,392; 10/767,899; 11/045,678 each of which are hereby incorporated by reference herein in its entirety for all purposes.

Those of ordinary skill in the related art will appreciate that advantages provided by the massively parallel nature of the amplification and sequencing methods described herein may be particularly to amenable for processing what may be referred to as a "Multiplex" sample. For example, a multiplex composition may include representatives from multiple samples such as samples from multiple individuals. It may be desirable in many applications to combine multiple samples into a single multiplexed sample that may be processed in one operation as opposed to processing each sample separately. Thus the result may typically include a substantial savings in reagent, labor, and instrument usage and cost as well as a significant savings in processing time invested. The described advantages of multiplex processing become more pronounced as the numbers of individual samples increase. Further, multiplex processing has application in research as well as diagnostic contexts. For example, it may be desirable in many applications to employ a single multiplexed sample in an

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amplification reaction and subsequently processing the amplified multiplex composition in a single sequencing run.

One problem associated with processing a multiplex composition then becomes identifying the association between each sample of origin and the sequence data generated from a template molecule derived from said sample. A solution to this problem includes associating an identifier such as a nucleic acid sequence that specifically identifies the association of each template molecule with its sample of origin. An advantage of this solution is that the sequence information of the associated nucleic acid sequence is embedded in the sequence data generated from the template molecule and may be bioinformatically analyzed to associate the sequence data with its sample of origin.

Previous studies have described associating nucleic acid sequence identifiers with 5' primers coupled with target sequences for multiplex processing. One such study is that of Binladen et al. (Binladen J, Gilbert MTP, Bollback JP, Panitz F, Bendixen C (2007) The use of coded PCR Primers Enables High-Throughput Sequencing of Multiple Homolog Amplification Products by Parallel 454 Sequencing. PLoS ONE 2(2): e197.doi:10.1371/journal.pone.0000197 (published online February 14, 2007, which is hereby incorporated by reference herein in its entirety for all purposes). As mentioned above, Binladen et al. describe associating short sequence identifiers with target sequences to be processed in a multiplex sample producing sequence data that is subsequently bioinformatically analyzed to associate the short identifiers with their sample of origin. However, there are limitations to simply attaching a nucleic acid identifier of generic sequence composition to a template molecule and identifying the sequence of said identifier in the generated sequence data. Of primary concern is the introduction of error into the sequence data from various mechanisms. Such mechanisms typically work in combination with each other and are generally not individually identifiable from the sequence data. Thus because of introduced error, an end user may not be able to identify the association between the sequence data with its sample of origin, or possibly worse fail to identify that an error has occurred and mis-assign sequence data to a sample of origin that is incorrect.

There are two important sources of error introduction to consider, although other sources may also exist. First is error introduced by the sequencing operation that may in some cases be referred to a "flow error". For example, flow error may include polymerase errors that include incorporation of an incorrect nucleotide species by a polymerase enzyme. A sequencing operation may also introduce what may be referred to as phasic synchrony error that include what are referred to as "carry forward" and "incomplete extension" (the

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combination of phasic synchrony error is sometimes referred to as CAFIE error). Phasic synchrony error and methods of correction are further described in PCT Application Serial No. US2007/004187, titled "System and Method for Correcting Primer Extension Errors in Nucleic Acid Sequence Data", filed February 15, 2007 which is hereby incorporated by reference herein in its entirety for all purposes.

Second is error introduced from processes that are independent of the sequencing operations such as primer synthesis or amplification error. For example, oligonucleotide primers synthesized for PCR may include one or more UID elements of the presently described invention, where error may be introduced in the synthesis of the primer/UID element that is then employed as a sequencing template. High fidelity sequencing of the UID element faithfully reproduces the synthesized error in sequence data. Also in the present example, polymerase enzymes commonly employed in PCR methods are known for having a measure of replication error, where for instance an error in replication may be introduced by the polymerase in 1 of every 10,000; 100,000; or 1,000,000 bases amplified.

Therefore, it is significantly advantageous to employ unique identifiers that are 1) resistant to error introduction; 2) enable detection of introduced error; and 3) enable correction of introduced error. The presently described invention addresses these problems and provides systems and methods for associating unique identifiers that provide better recognition and identification characteristics resulting in improved data quality and experimental efficiency.

SUMMARY OF THE INVENTION

Embodiments of the invention relate to the determination of the sequence of nucleic acids. More particularly, embodiments of the invention relate to methods and systems for correcting errors in data obtained during the sequencing of nucleic acids and associating the nucleic acids with their origin.

An embodiment of an identifier element for identifying an origin of a template nucleic acid molecule is described that comprises a nucleic acid element comprising a sequence composition that enables detection of an introduced error in sequence data generated from the nucleic acid element and correction of the introduced error, where the nucleic acid element is constructed to couple with the end of a template nucleic acid molecule and identifies an origin of the template nucleic acid molecule.

Also, an embodiment of a method for identifying an origin of a template nucleic acid molecule is described that comprises the steps of identifying a first identifier sequence from

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sequence data generated from a template nucleic acid molecule; detecting an introduced error in the first identifier sequence; correcting the introduced error in the first identifier sequence; associating the corrected first identifier sequence with a first identifier element coupled to the template molecule; and identifying an origin of the template molecule using the association of the corrected first identifier sequence with the first identifier element.

In some implementations, the method further comprises the steps of identifying a second identifier sequence from the sequence data generated from the template nucleic acid molecule; detecting an introduced error in the second identifier sequence; correcting the introduced error in the second identifier sequence; associating the corrected second identifier sequence with a second identifier element coupled with the template nucleic acid molecule; and identifying an origin of the template nucleic acid molecule using the association of the corrected second identifier sequence with the second identifier element combinatorially with the association of the corrected first identifier sequence with the first identifier element.

Further, an embodiment of a kit for identifying an origin of a template nucleic acid molecule is described that comprises a set of nucleic acid elements each comprising a distinctive sequence composition that enables detection of an introduced error in sequence data generated from each nucleic acid element and correction of the introduced error, wherein each of the nucleic acid elements is constructed to couple with the end of a template nucleic acid molecule and identifies the origin of the template nucleic acid molecule.

In addition, an embodiment of a computer comprising executable code stored in system memory is described where the executable code performs a method for identifying an origin of a template nucleic acid molecule comprising the steps of identifying an identifier sequence from sequence data generated from a template nucleic acid molecule; detecting an introduced error in the identifier sequence; correcting the introduced error in the identifier sequence; associating the corrected identifier sequence with an identifier element coupled with the template molecule; and identifying an origin of the template molecule using the association of the corrected identifier sequence with the identifier element.

The above embodiments and implementations are not necessarily inclusive or exclusive of each other and may be combined in any manner that is non-conflicting and otherwise possible, whether they be presented in association with a same, or a different, embodiment or implementation. The description of one embodiment or implementation is not intended to be limiting with respect to other embodiments and/or implementations. Also, any one or more function, step, operation, or technique described elsewhere in this specification may, in alternative implementations, be combined with any one or more

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function, step, operation, or technique described in the summary. Thus, the above embodiment and implementations are illustrative rather than limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and further features will be more clearly appreciated from the following detailed description when taken in conjunction with the accompanying drawings. In the drawings, like reference numerals indicate like structures, elements, or method steps and the leftmost digit of a reference numeral indicates the number of the figure in which the references element first appears (for example, element 160 appears first in Figure 1). All of these conventions, however, are intended to be typical or illustrative, rather than limiting.

Figure 1 is a functional block diagram of one embodiment of a sequencing instrument and computer system amenable for use with the presently described invention;

Figure 2A is a simplified graphical representation of one embodiment of an adaptor element amenable for use with genomic libraries comprising a UID component;

Figure 2B is a simplified graphical representation of one embodiment of an adaptor element amenable for use with amplicons comprising a UID component; and

Figure 3 is a simplified graphical representation of one embodiment of computed error balls representing compatibility of UID elements of different sequence composition.

DETAILED DESCRIPTION OF THE INVENTION

As will be described in greater detail below, embodiments of the presently described invention include systems and methods for associating a unique identifier hereafter referred to as a UID element with one or more nucleic acid molecules from a sample. The UID elements are resistant to introduced error in sequence data, and enable detection and correction of error. Further, the invention includes combining or pooling those UID associated nucleic acid molecules with similarly UID associated (sometimes also referred to as "labeled") nucleic acid molecules from one or more other samples, and sequencing each nucleic acid molecule in the pooled sample to generate sequence data for each nucleic acid. The presently described invention further includes systems and methods for designing the sequence composition for each UID element and analyzing the sequence data of each nucleic acid to identify an embedded UID sequence code and associating said code with the sample identity.

a. General

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The terms "flowgram" and "pyrogram" may be used interchangeably herein and generally refer to a graphical representation of sequence data generated by SBS methods.

Further, the term "read" or "sequence read" as used herein generally refers to the entire sequence data obtained from a single nucleic acid template molecule or a population of a plurality of substantially identical copies of the template nucleic acid molecule.

The terms "run" or "sequencing run" as used herein generally refer to a series of sequencing reactions performed in a sequencing operation of one or more template nucleic acid molecule.

The term "flow" as used herein generally refers to a serial or iterative cycle of addition of solution to an environment comprising a template nucleic acid molecule, where the solution may include a nucleotide species for addition to a nascent molecule or other reagent such as buffers or enzymes that may be employed to reduce carryover or noise effects from previous flow cycles of nucleotide species.

The term "flow cycle" as used herein generally refers to a sequential series of flows where a nucleotide species is flowed once during the cycle (i.e. a flow cycle may include a sequential addition in the order of T, A, C, G nucleotide species, although other sequence combinations are also considered part of the definition). Typically the flow cycle is a repeating cycle having the same sequence of flows from cycle to cycle.

The term "read length" as used herein generally refers to an upper limit of the length of a template molecule that may be reliably sequenced. There are numerous factors that contribute to the read length of a system and/or process including, but not limited to the degree of GC content in a template nucleic acid molecule.

A "nascent molecule" generally refers to a DNA strand which is being extended by the template-dependent DNA polymerase by incorporation of nucleotide species which are complementary to the corresponding nucleotide species in the template molecule.

The terms "template nucleic acid", "template molecule", "target nucleic acid", or "target molecule" generally refer to a nucleic acid molecule that is the subject of a sequencing reaction from which sequence data or information is generated.

The term "nucleotide species" as used herein generally refers to the identity of a nucleic acid monomer including purines (Adenine, Guanine) and pyrimidines (Cytosine, Uracil, Thymine) typically incorporated into a nascent nucleic acid molecule.

The term "monomer repeat" or "homopolymers" as used herein generally refers to two or more sequence positions comprising the same nucleotide species (i.e. a repeated nucleotide species).

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The term "homogeneous extension", as used herein, generally refers to the relationship or phase of an extension reaction where each member of a population of substantially identical template molecules is homogenously performing the same extension step in the reaction.

The term "completion efficiency" as used herein generally refers to the percentage of nascent molecules that are properly extended during a given flow.

The term "incomplete extension rate" as used herein generally refers to the ratio of the number of nascent molecules that fail to be properly extended over the number of all nascent molecules.

The term "genomic library" or "shotgun library" as used herein generally refers to a collection of molecules derived from and/or representing an entire genome (i.e. all regions of a genome) of an organism or individual.

The term "amplicon" as used herein generally refers to selected amplification products such as those produced from Polymerase Chain Reaction or Ligase Chain Reaction techniques.

The term "keypass" or "keypass mapping" as used herein generally refers to a nucleic acid "key element" associated with a template nucleic acid molecule in a known location (i.e. typically included in a ligated adaptor element) comprising known sequence composition that is employed as a quality control reference for sequence data generated from template molecules. The sequence data passes the quality control if it includes the known sequence composition associated with a Key element in the correct location.

The term "blunt end" or "blunt ended" as used herein generally refers to a linear double stranded nucleic acid molecule having an end that terminates with a pair of complementary nucleotide base species, where a pair of blunt ends are always compatible for ligation to each other.

Some exemplary embodiments of systems and methods associated with sample preparation and processing, generation of sequence data, and analysis of sequence data are generally described below, some or all of which are amenable for use with embodiments of the presently described invention. In particular the exemplary embodiments of systems and methods for preparation of template nucleic acid molecules, amplification of template molecules, generating target specific amplicons and/or genomic libraries, sequencing methods and instrumentation, and computer systems are described.

In typical embodiments, the nucleic acid molecules derived from an experimental or diagnostic sample must be prepared and processed from its raw form into template molecules

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amenable for high throughput sequencing. The processing methods may vary from application to application resulting in template molecules comprising various characteristics. For example, in some embodiments of high throughput sequencing it is preferable to generate template molecules with a sequence or read length that is at least the length a particular sequencing method can accurately produce sequence data for. In the present example, the length may include a range of about 25-30 base pairs, about 30-50 base pairs, about 50-100 base pairs, about 100-200 base pairs, about 200-300 base pairs, or about 350-500 base pairs, or other length amenable for a particular sequencing application. In some embodiments, nucleic acids from a sample, such as a genomic sample, are fragmented using a number of methods known to those of ordinary skill in the art. In preferred embodiments, methods that randomly fragment (i.e. do not select for specific sequences or regions) nucleic acids are employed that include what is referred to as nebulization or sonication. It will however, be appreciated that other methods of fragmentation such as digestion using restriction endonucleases may be employed for fragmentation purposes. Also in the present example, some processing methods may employ size selection methods known in the art to selectively isolate nucleic acid fragments of the desired length.

Also, it is preferable in some embodiments to associate additional functional elements with each template nucleic acid molecule. The elements may be employed for a variety of functions including, but not limited to, primer sequences for amplification and/or sequencing methods, quality control elements, unique identifiers that encode various associations such as with a sample of origin or patient, or other functional element. For example, some embodiments may associate priming sequence elements or regions comprising complementary sequence composition to primer sequences employed for amplification and/or sequencing. Further, the same elements may be employed for what may be referred to as "strand selection" and immobilization of nucleic acid molecules to a solid phase substrate. In the present example, two sets of priming sequence regions (hereafter referred to as priming sequence A, and priming sequence B) may be employed for strand selection where only single strands having one copy of priming sequence A and one copy of priming sequence B is selected and included as the prepared sample. The same priming sequence regions may be employed in methods for amplification and immobilization where, for instance priming sequence B may be immobilized upon a solid substrate and amplified products are extended therefrom.

Additional examples of sample processing for fragmentation, strand selection, and addition of functional elements and adaptors are described in U.S. Patent Application Serial

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No. 10/767,894, titled "Method for preparing single-stranded DNA libraries", filed January 28, 2004; and U.S. Provisional Application Serial No. 60/941,381, titled "System and Method for Identification of Individual Samples from a Multiplex Mixture", filed June 1, 2007, each of which is hereby incorporated by reference herein in its entirety for all purposes.

Various examples of systems and methods for performing amplification of template nucleic acid molecules to generate populations of substantially identical copies are described. It will be apparent to those of ordinary skill that it is desirable in some embodiments of SBS to generate many copies of each nucleic acid element to generate a stronger signal when one or more nucleotide species is incorporated into each nascent molecule associated with a copy of the template molecule. There are many techniques known in the art for generating copies of nucleic acid molecules such as, for instance, amplification using what are referred to as bacterial vectors, "Rolling Circle" amplification (described in US Patent Nos. 6,274,320 and 7,211,390, incorporated by reference above) and Polymerase Chain Reaction (PCR) methods, each of the techniques are applicable for use with the presently described invention. One PCR technique that is particularly amenable to high throughput applications include what are referred to as emulsion PCR methods (also referred to as emPCR™ methods).

Typical embodiments of emulsion PCR methods include creating a stable emulsion of two immiscible substances creating aqueous droplets within which reactions may occur. In particular, the aqueous droplets of an emulsion amenable for use in PCR methods may include a first fluid such as a water based fluid suspended or dispersed in what may be referred to as a discontinuous phase within another fluid such as an oil based fluid. Further, some emulsion embodiments may employ surfactants that act to stabilize the emulsion that may be particularly useful for specific processing methods such as PCR. Some embodiments of surfactant may include non-ionic surfactants such as sorbitan monooleate (also referred to as Span™ 80), polyoxyethylenesorbitsan monooleate (also referred to as Tween™ 80), or in some preferred embodiments dimethicone copolyol (also referred to as Abil® EM90), polysiloxane, polyalkyl polyether copolymer, polyglycerol esters, poloxamers, and PVP/hexadecane copolymers (also referred to as Unimer U-151), or in more preferred embodiments a high molecular weight silicone polyether in cyclopentasiloxane (also referred to as DC 5225C available from Dow Corning).

The droplets of an emulsion may also be referred to as compartments, microcapsules, microreactors, microenvironments, or other name commonly used in the related art. The aqueous droplets may range in size depending on the composition of the emulsion components or composition, contents contained therein, and formation technique employed.

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The described emulsions create the microenvironments within which chemical reactions, such as PCR, may be performed. For example, template nucleic acids and all reagents necessary to perform a desired PCR reaction may be encapsulated and chemically isolated in the droplets of an emulsion. Additional surfactants or other stabilizing agent may be employed in some embodiments to promote additional stability of the droplets as described above. Thermocycling operations typical of PCR methods may be executed using the droplets to amplify an encapsulated nucleic acid template resulting in the generation of a population comprising many substantially identical copies of the template nucleic acid. In some embodiments, the population within the droplet may be referred to as a "clonally isolated", "compartmentalized", "sequestered", "encapsulated", or "localized" population. Also in the present example, some or all of the described droplets may further encapsulate a solid substrate such as a bead for attachment of template or other type of nucleic acids, reagents, labels, or other molecules of interest.

Embodiments of an emulsion useful with the presently described invention may include a very high density of droplets or microcapsules enabling the described chemical reactions to be performed in a massively parallel way. Additional examples of emulsions employed for amplification and their uses for sequencing applications are described in US Patent Application Serial Nos. 10/861,930; 10/866,392; 10/767,899; 11/045,678 each of which are hereby incorporated by reference herein in its entirety for all purposes.

Also, an exemplary embodiment for generating target specific amplicons for sequencing is described that includes using sets of nucleic acid primers to amplify a selected target region or regions from a sample comprising the target nucleic acid. Further, the sample may include a population of nucleic acid molecules that are known or suspected to contain sequence variants and the primers may be employed to amplify and provide insight into the distribution of sequence variants in the sample.

For example a method for identifying a sequence variant by specific amplification and sequencing of multiple alleles in a nucleic acid sample may be performed. The nucleic acid is first subjected to amplification by a pair of PCR primers designed to amplify a region surrounding the region of interest or segment common to the nucleic acid population. Each of the products of the PCR reaction (amplicons) is subsequently further amplified individually in separate reaction vessels such as an emulsion based vessel described above. The resulting amplicons (referred to herein as second amplicons), each derived from one member of the first population of amplicons, are sequenced and the collection of sequences, from different emulsion PCR amplicons, are used to determine an allelic frequency.

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Some advantages of the described target specific amplification and sequencing methods include a higher level of sensitivity than previously achieved. Further, embodiments that employ high throughput sequencing instrumentation such as for instance embodiments that employ what is referred to as a PicoTiterPlate® array of wells provided by 454 Life Sciences Corporation, the described methods can be employed to sequence over 100,000 or over 300,000 different copies of an allele per run or experiment. Also, the described methods provide a sensitivity of detection of low abundance alleles which may represent 1% or less of the allelic variants. Another advantage of the methods includes generating data comprising the sequence of the analyzed region. Importantly, it is not necessary to have prior knowledge of the sequence of the locus being analyzed.

Additional examples of target specific amplicons for sequencing are described in U.S. Patent Application Serial No. 11/104,781, titled "Methods for determining sequence variants using ultra-deep sequencing", filed April 12, 2005, which is hereby incorporated by reference herein in its entirety for all purposes.

Further, embodiments of sequencing may include Sanger type techniques, what is referred to as polony sequencing techniques, nanopore and other single molecule detection techniques, or reversible terminator techniques. As described above a preferred technique may include Sequencing by Synthesis methods. For example, some SBS embodiments sequence populations of substantially identical copies of a nucleic acid template and typically employ one or more oligonucleotide primers designed to anneal to a predetermined, complementary position of the sample template molecule or one or more adaptors attached to the template molecule. The primer/template complex is presented with a nucleotide species in the presence of a nucleic acid polymerase enzyme. If the nucleotide species is complementary to the nucleic acid species corresponding to a sequence position on the sample template molecule that is directly adjacent to the 3' end of the oligonucleotide primer, then the polymerase will extend the primer with the nucleotide species. Alternatively, in some embodiments the primer/template complex is presented with a plurality of nucleotide species of interest (typically A, G, C, and T) at once, and the nucleotide species that is complementary at the corresponding sequence position on the sample template molecule directly adjacent to the 3' end of the oligonucleotide primer is incorporated. In either of the described embodiments, the nucleotide species may be chemically blocked (such as at the 3'-O position) to prevent further extension, and need to be deblocked prior to the next round of synthesis. It will also be appreciated that the process of adding a nucleotide species to the

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end of a nascent molecule is substantially the same as that described above for addition to the end of a primer.

As described above, incorporation of the nucleotide species can be detected by a variety of methods known in the art, e.g. by detecting the release of pyrophosphate (PPi) (examples described in US Patent Nos. 6,210,891; 6,258,568; and 6,828,100, each of which is hereby incorporated by reference herein in its entirety for all purposes), or via detectable labels bound to the nucleotides. Some examples of detectable labels include but are not limited to mass tags and fluorescent or chemiluminescent labels. In typical embodiments, unincorporated nucleotides are removed, for example by washing. Further, in some embodiments the unincorporated nucleotides may be subjected to enzymatic degradation such as, for instance, degradation using the apyrase enzyme as described in U.S. Provisional Patent Application Serial No. 60/946,743, titled System and Method For Adaptive Reagent Control in Nucleic Acid Sequencing, filed June 28, 2007, which is hereby incorporated by reference herein in its entirety for all purposes. In the embodiments where detectable labels are used, they will typically have to be inactivated (e.g. by chemical cleavage or photobleaching) prior to the following cycle of synthesis. The next sequence position in the template/polymerase complex can then be queried with another nucleotide species, or a plurality of nucleotide species of interest, as described above. Repeated cycles of nucleotide addition, extension, signal acquisition, and washing result in a determination of the nucleotide sequence of the template strand. Continuing with the present example, a large number or population of substantially identical template molecules (e.g. 10^3, 10^4, 10^5, 10^6 or 10^7 molecules) are typically analyzed simultaneously in any one sequencing reaction, in order to achieve a signal which is strong enough for reliable detection.

In addition, it may be advantageous in some embodiments to improve the read length capabilities and qualities of a sequencing process by employing what may be referred to as a "paired-end" sequencing strategy. For example, some embodiments of sequencing method have limitations on the total length of molecule from which a high quality and reliable read may be generated. In other words, the total number of sequence positions for a reliable read length may not exceed 25, 50, 100, or 150 bases depending on the sequencing embodiment employed. A paired-end sequencing strategy extends reliable read length by separately sequencing each end of a molecule (sometimes referred to as a "tag" end) that comprise a fragment of an original template nucleic acid molecule at each end joined in the center by a linker sequence. The original positional relationship of the template fragments is known and thus the data from the sequence reads may be re-combined into a single read having a longer

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high quality read length. Further examples of paired-end sequencing embodiments are described in US Patent Application Serial No. 11/448,462, titled "Paired end sequencing", filed June 6, 2006, and in US Provisional Patent Application Serial No. 60/026,319, titled "Paired end sequencing", filed February 5, 2008, each of which is hereby incorporated by reference herein in its entirety for all purposes.

Some examples of SBS apparatus may implement some or all of the methods described above may include one or more of a detection device such as a charge coupled device (i.e. CCD camera), a microfluidics chamber or flow cell, a reaction substrate, and/or a pump and flow valves. Taking the example of pyrophosphate based sequencing, embodiments of an apparatus may employ a chemiluminescent detection strategy that produces an inherently low level of background noise.

In some embodiments, the reaction substrate for sequencing may include what is referred to as a PicoTiterPlate® array (also referred to as a PTP® plate) formed from a fiber optics faceplate that is acid-etched to yield hundreds of thousands of very small wells each enabled to hold a population of substantially identical template molecules. In some embodiments, each population of substantially identical template molecule may be disposed upon a solid substrate such as a bead, each of which may be disposed in one of said wells. For example, an apparatus may include a reagent delivery element for providing fluid reagents to the PTP plate holders, as well as a CCD type detection device enabled to collect photons of light emitted from each well on the PTP plate. Further examples of apparatus and methods for performing SBS type sequencing and pyrophosphate sequencing are described in US Patent No 7,323,305 and US Patent Application Serial No. 11/195,254 both of which are incorporated by reference above.

In addition, systems and methods may be employed that automate one or more sample preparation processes, such as the emPCR™ process described above. For example, microfluidic technologies may be employed to provide a low cost, disposable solution for generating an emulsion for emPCR processing, performing PCR Thermocycling operations, and enriching for successfully prepared populations of nucleic acid molecules for sequencing. Examples of microfluidic systems for sample preparation are described in U.S. Provisional Patent Application Serial No. 60/915,968, titled "System and Method for Microfluidic Control of Nucleic Acid amplification and Segregation", filed May 4, 2007, which is hereby incorporated by reference herein in its entirety for all purposes.

Also, the systems and methods of the presently described embodiments of the invention may include implementation of some design, analysis, or other operation using a

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computer readable medium stored for execution on a computer system. For example, several embodiments are described in detail below to process detected signals and/or analyze data generated using SBS systems and methods where the processing and analysis embodiments are implementable on computer systems.

An exemplary embodiment of a computer system for use with the presently described invention may include any type of computer platform such as a workstation, a personal computer, a server, or any other present or future computer. Computers typically include known components such as a processor, an operating system, system memory, memory storage devices, input-output controllers, input-output devices, and display devices. It will be understood by those of ordinary skill in the relevant art that there are many possible configurations and components of a computer and may also include cache memory, a data backup unit, and many other devices.

Display devices may include display devices that provide visual information, this information typically may be logically and/or physically organized as an array of pixels. An interface controller may also be included that may comprise any of a variety of known or future software programs for providing input and output interfaces. For example, interfaces may include what are generally referred to as "Graphical User Interfaces" (often referred to as GUI's) that provide one or more graphical representations to a user. Interfaces are typically enabled to accept user inputs using means of selection or input known to those of ordinary skill in the related art.

In the same or alternative embodiments, applications on a computer may employ an interface that includes what are referred to as "command line interfaces" (often referred to as CLI's). CLI's typically provide a text based interaction between an application and a user. Typically, command line interfaces present output and receive input as lines of text through display devices. For example, some implementations may include what are referred to as a "shell" such as Unix Shells known to those of ordinary skill in the related art, or Microsoft Windows Powershell that employs object-oriented type programming architectures such as the Microsoft .NET framework.

Those of ordinary skill in the related art will appreciate that interfaces may include one or more GUI's, CLI's or a combination thereof.

A processor may include a commercially available processor such as a Centrino®, Core™ 2, Itanium® or Pentium® processor made by Intel Corporation, a SPARC® processor made by Sun Microsystems, an Athalon™ or Opteron™ processor made by AMD corporation, or it may be one of other processors that are or will become available. Some

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embodiments of a processor may include what is referred to as Multi-core processor and/or be enabled to employ parallel processing technology in a single or multi-core configuration. For example, a multi-core architecture typically comprises two or more processor "execution cores". In the present example each execution core may perform as an independent processor that enables parallel execution of multiple threads. In addition, those of ordinary skill in the related will appreciate that a processor may be configured in what is generally referred to as 32 or 64 bit architectures, or other architectural configurations now known or that may be developed in the future.

A processor typically executes an operating system, which may be, for example, a Windows®-type operating system (such as Windows® XP or Windows Vista®) from the Microsoft Corporation; the Mac OS X operating system from Apple Computer Corp. (such as 7.5 Mac OS X v10.4 "Tiger" or 7.6 Mac OS X v10.5 "Leopard" operating systems); a Unix® or Linux-type operating system available from many vendors or what is referred to as an open source; another or a future operating system; or some combination thereof. An operating system interfaces with firmware and hardware in a well-known manner, and facilitates the processor in coordinating and executing the functions of various computer programs that may be written in a variety of programming languages. An operating system, typically in cooperation with a processor, coordinates and executes functions of the other components of a computer. An operating system also provides scheduling, input-output control, file and data management, memory management, and communication control and related services, all in accordance with known techniques.

System memory may include any of a variety of known or future memory storage devices. Examples include any commonly available random access memory (RAM), magnetic medium such as a resident hard disk or tape, an optical medium such as a read and write compact disc, or other memory storage device. Memory storage devices may include any of a variety of known or future devices, including a compact disk drive, a tape drive, a removable hard disk drive, USB or flash drive, or a diskette drive. Such types of memory storage devices typically read from, and/or write to, a program storage medium (not shown) such as, respectively, a compact disk, magnetic tape, removable hard disk, USB or flash drive, or floppy diskette. Any of these program storage media, or others now in use or that may later be developed, may be considered a computer program product. As will be appreciated, these program storage media typically store a computer software program and/or data. Computer software programs, also called computer control logic, typically are stored in

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system memory and/or the program storage device used in conjunction with memory storage device.

In some embodiments, a computer program product is described comprising a computer usable medium having control logic (computer software program, including program code) stored therein. The control logic, when executed by a processor, causes the processor to perform functions described herein. In other embodiments, some functions are implemented primarily in hardware using, for example, a hardware state machine. Implementation of the hardware state machine so as to perform the functions described herein will be apparent to those skilled in the relevant arts.

Input-output controllers could include any of a variety of known devices for accepting and processing information from a user, whether a human or a machine, whether local or remote. Such devices include, for example, modem cards, wireless cards, network interface cards, sound cards, or other types of controllers for any of a variety of known input devices. Output controllers could include controllers for any of a variety of known display devices for presenting information to a user, whether a human or a machine, whether local or remote. In the presently described embodiment, the functional elements of a computer communicate with each other via a system bus. Some embodiments of a computer may communicate with some functional elements using network or other types of remote communications.

As will be evident to those skilled in the relevant art, an instrument control and/or a data processing application, if implemented in software, may be loaded into and executed from system memory and/or a memory storage device. All or portions of the instrument control and/or data processing applications may also reside in a read-only memory or similar device of the memory storage device, such devices not requiring that the instrument control and/or data processing applications first be loaded through input-output controllers. It will be understood by those skilled in the relevant art that the instrument control and/or data processing applications, or portions of it, may be loaded by a processor in a known manner into system memory, or cache memory, or both, as advantageous for execution.

Also a computer may include one or more library files, experiment data files, and an internet client stored in system memory. For example, experiment data could include data related to one or more experiments or assays such as detected signal values, or other values associated with one or more SBS experiments or processes. Additionally, an internet client may include an application enabled to accesses a remote service on another computer using a network and may for instance comprise what are generally referred to as "Web Browsers". In the present example some commonly employed web browsers include Microsoft® Internet

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Explorer 7 available from Microsoft Corporation, Mozilla Firefox® 2 from the Mozilla Corporation, Safari 1.2 from Apple Computer Corp., or other type of web browser currently known in the art or to be developed in the future. Also, in the same or other embodiments an internet client may include, or could be an element of, specialized software applications enabled to access remote information via a network such as a data processing application for SBS applications.

A network may include one or more of the many various types of networks well known to those of ordinary skill in the art. For example, a network may include a local or wide area network that employs what is commonly referred to as a TCP/IP protocol suite to communicate. A network may include a network comprising a worldwide system of interconnected computer networks that is commonly referred to as the internet, or could also include various intranet architectures. Those of ordinary skill in the related arts will also appreciate that some users in networked environments may prefer to employ what are generally referred to as "firewalls" (also sometimes referred to as Packet Filters, or Border Protection Devices) to control information traffic to and from hardware and/or software systems. For example, firewalls may comprise hardware or software elements or some combination thereof and are typically designed to enforce security policies put in place by users, such as for instance network administrators, etc.

b. Embodiments of the presently described invention

As described above, the presently described invention comprises associating one or more embodiments of a UID element having a known and identifiable sequence composition with a sample, and coupling the embodiments of UID element with template nucleic acid molecules from the associated samples. The UID coupled template nucleic acid molecules from a number of different samples are pooled into a single "Multiplexed" sample or composition that can then be efficiently processed to produce sequence data for each UID coupled template nucleic acid molecule. The sequence data for each template nucleic acid is de-convoluted to identify the sequence composition of coupled UID elements and association with sample of origin identified. For example, a multiplexed composition may include representatives from about 384 samples, about 96 samples, about 50 samples, about 20 samples, about 16 samples, about 10 samples, or other number of samples. Each sample may be associated with a different experimental condition, treatment, species, or individual in a research context. Similarly, each sample may be associated with a different tissue, cell, individual, condition, or treatment in a diagnostic context. Those of ordinary skill in the

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related art will appreciate that the numbers of samples listed above are for the purposes of example and thus should not be considered limiting.

Typically, systems and methods are employed for processing samples to generate sequence data as well as for interpretation of the sequence data. Figure 1 provides an illustrative example of sequencing instrument 100 employed to execute sequencing processes using reaction substrate 105 that for instance may include the PTP® plate substrate described above. Also illustrated in Figure 1 is computer 130 that may for instance execute system software or firmware for processing as well as perform analysis functions. In the example of Figure 1, computer 130 may also store application 135 in system memory for execution, where application 135 may perform some or all of the data processing functions described herein. It will also be understood that application 135 may be stored on other computer or server type structures for execution and perform some or all of its functions remotely communicating over networks or transferring information via standard media. For instance, processed target molecules in a multiplex sample may be loaded onto reaction substrate 105 by user 101 or some automated embodiment then sequenced in a massively parallel manner using sequencing instrument 100 to produce sequence data representing the sequence composition of each target molecule. Importantly, user 101 may include any user such as independent researcher, university, or corporate entity. In the present example, sequencing instrument 100, reaction substrate 105, and/or computer 130 may include some or all of the components and characteristics of the embodiments generally described above.

In preferred embodiments, the sequence composition of each UID element is easily identifiable and resistant to introduced error from sequencing processes. Some embodiments of UID element comprise a unique sequence composition of nucleic acid species that has minimal sequence similarity to a naturally occurring sequence. Alternatively, embodiments of a UID element may include some degree of sequence similarity to naturally occurring sequence.

Also, in preferred embodiments the position of each UID element is known relative to some feature of the template nucleic acid molecule and/or adaptor elements coupled to the template molecule. Having a known position of each UID is useful for finding the UID element in sequence data and interpretation of the UID sequence composition for possible errors and subsequent association with the sample of origin.

For example, some features useful as anchors for positional relationship to UID elements may include, but are not limited to the length of the template molecule (i.e. the UID element is known to be so many sequence positions from the 5' or 3' end), recognizable sequence

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markers such as a Key element (described in greater detail below) and/or one or more primer elements positioned adjacent to a UID element. In the present example, The Key and primer elements generally comprise a known sequence composition that typically does not vary from sample to sample in the multiplex composition and may be employed as positional references for searching for the UID element. An analysis algorithm implemented by application 135 may be executed on computer 130 to analyze generated sequence data for each UID coupled template to identify the more easily recognizable Key and/or primer elements, and extrapolate from those positions to identify a sequence region presumed to include the sequence of the UID element. Application 135 may then process the sequence composition of the presumed region and possibly some distance away in the flanking regions to positively identify the UID element and its sequence composition.

Also, as will be described in greater detail below in some embodiments the sequence data generated from each Key and/or one or more primer elements may be analyzed to determine a measure of the relative error rate for the sequencing run. The measure of error rate may then be employed in the analysis of the sequence data generated for the UID element. For example, if the error rate is excessive and is above a predetermined threshold it may also be assumed that a similar rate of error exists in the sequence data generated for the UID element, and thus the sequence data for the entire template may be filtered out as suspect. Further, in embodiments where a UID element is coupled to each end of a linear template molecule an error rate may be established for each end and asymmetrically analyzed. Importantly, it will be appreciated that in some embodiments, particularly sequencing technology capable of producing "long" read lengths (i.e. of about 100 base pairs or greater) the error rate in the sequence data may differ between the 5' end and the 3' end.

In preferred embodiments, a UID element is associated with an adaptor enabled to operatively couple with the end of a template nucleic acid molecule. In typical high throughput sequencing applications it is desirable that the template nucleic acid molecules are linear where an adaptor may be coupled to each end. Figures 2A and 2B provide illustrative examples of embodiments of adaptor composition for various applications comprising one or more UID elements. It will, however, be appreciated that various adaptor configurations may be employed for different amplification and sequencing strategies. Figure 2A provides an illustrative example of adaptor element 200 that comprises an embodiment of an adaptor amenable for use with amplification and sequencing of Genomic Libraries. It will also be appreciated that adaptor element 200 may also be amenable for libraries of template molecules independently amplified with target specific sequences independently of the

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adaptor element described herein. Adaptor element 200 comprises several components that include primer 205, key 207, and UID 210. Also, Figure 2B provides an illustrative example of one embodiment of adaptor 220 amenable for use with amplification and sequencing of Amplicons. Adaptor element 220 comprises several similar components to adaptor 200 that include primer 205, key 207, UID 210, with the addition of target specific element 225. It will be appreciated that the relative arrangement of components provided in Figures 2A and 2B are for illustrative purposes and should not be considered limiting.

In some alternative embodiments, the UID 210 elements are not associated with adaptor elements as described above. Rather, the UID 210 elements may be considered separate elements that may be independently coupled to an already adapted template molecule, or non-adapted template molecule. This strategy may be useful in some circumstances to avoid negative effects associated with a particular step or assay. For example, it may be advantageous in some embodiments to ligate the UID 210 elements to each population of substantially identical template molecules after copies have been produced from an amplification step. By coupling the UID elements to the adapted template molecules post-amplification, errors introduced by the amplification method are avoided. In the present example, PCR amplification methods that employ polymerases are known to have a certain rates of introduced error based, at least in part, upon the type of polymerase or polymerase blends (i.e. a blend may include a mixture of what may be referred to as a "high fidelity" polymerase and a polymerase with "proof reading" capability) employed and the number of cycles of amplification.

It will also be appreciated that multiple embodiments of adaptor 200 or 220 may be employed with each template molecule, such as one embodiment of adaptor 200 or 220 at each end of a linear template molecule prepared for sequencing. However, in some embodiments the positional arrangement of elements within adaptor 200 or 220 may be reversed (i.e. the elements of adaptor 200 or 220 are in a palindromic arrangement from the example illustrated in Figure 2A or 2B) at the 3' end relative the arrangement of elements in adaptor 200 or 220 at the 5' end. For example, an embodiment of element 220 may be positioned on each end of substantially every template molecule from a library of amplicons in a multiplex composition, thus 2 embodiments of UID 210 may be employed in a combinatorial manner for identification which will be discussed in greater detail below.

Primer 205 may include a primer species (or a primer of a primer pair) such as is described above with respect to emulsion PCR embodiments (i.e. Primer A and Primer B). Also, primer 205 may include a primer species employed for an SBS sequencing reaction

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also as described above. Further, primer 205 may include what is referred to as a bipartite PCR/sequencing primer useable for both the emulsion PCR and SBS sequencing processes. Key 207 may include what may be referred to as a "discriminating key sequence" that refers to a short sequence of nucleotide species such as a combination of the four nucleotide species (i.e., A, C, G, T). Typically, key 207 may employed for quality control of sequence data, where for example key 207 may be located immediately adjacent primer 205 or within close proximity and include one of each of the four nucleotide species in a known sequence arrangement (i.e. TCAG). Therefore, the fidelity of the sequencing method should be represented in the sequence data for each of the 4 nucleotide species in key 207 and may pass quality control metrics if each of the 4 nucleotide species is faithfully represented. For example, an error for one of the nucleotide species represented in the sequence data generated from key 207 could indicate a problem in the sequencing process associated with that nucleotide species. Such error may be from mechanical failure of one or more components of sequencing instrument 100, low quality or supply of reagent, operating script error, or other source of systematic type error that may occur. Thus, if such systematic type error is detected in key 207 that sequence data generated for the run of that template molecule may not pass quality metrics and will typically be rejected.

The same discriminating sequence for key 207 can be used for an entire library of DNA fragments, or alternatively different sequence compositions may be associated with portions of the library for different purposes. Further examples of primer and key elements associated with primer 205 and key 207 are described in U.S. Patent Application Serial No. 10/767,894, incorporated by reference above.

Target specific element 225 includes a sequence composition that specifically recognizes a region of a genome. For example, Target specific element 225 may be employed as a primer sequence to amplify and produce amplicon libraries of specific targeted regions for sequencing such as those found within genomes, tissue samples, heterogeneous cell populations or environmental samples. These can include, for example, PCR products, candidate genes, mutational hot spots, evolutionary or medically important variable regions. It could also be used for applications such as whole genome amplification with subsequent whole genome sequencing by using variable or degenerate amplification primers. Further examples describing the use of target specific sequences with bipartite primers are described in U.S. Patent Application Serial No. 11/104,781, titled "Methods for determining sequence variants using ultra-deep sequencing", filed April 12, 2005, which is hereby incorporated by reference herein in its entirety for all purposes.

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Some embodiments of UID 210 may be particularly amenable for use with relatively small numbers of sample associations in a multiplex sample. In particular, when there are only a small number of associations to identify in a multiplex sample, each sample is associated with a distinct implementation of UID 210 comprising a sequence composition that is sufficiently unique from each other as to enable easy detection and correction of introduced error. In some embodiments, groups of compatible UID 210 sequence elements are clustered into "sets" as will be described in greater detail below. For example, a set of UID 210 elements may include 14 members that may be employed to uniquely identify up to 14 associations with samples, where each member is associated with a single sample.

It will be appreciated that as the number of associations to identify grows, it becomes increasingly difficult to design distinct embodiments of UID 210 for each association that meet the design criteria and desired characteristics. In such cases, it may be advantageous to employ multiple UID 210 elements combinatorially to uniquely associate the template molecules with their sample of origin, where one embodiment of UID 210 may be positioned at each end of a linear template molecule. For example, the number of associations to identify between the sequence data generated from template molecules and the sample of origin may become too large to accommodate given the necessary design parameters and characteristics of UID 210. In particular, it is undesirable in many embodiments to employ a distinct UID element for each association when the number a samples would require a sequence length for UID 210 that is undesirably long for the design criteria that includes a specific number of flow cycle iterations and number of sequence positions taken up by the UID element. In the present example, in embodiments of sequencing technology that generate "long" read lengths UID 210 may comprise up to 10 sequence positions. Alternatively, other embodiments of sequencing technology may generate relatively short read lengths of about 25-50 sequence positions, and thus it is desirable that UID 210 is short in order to optimize the read length for the template molecule. In the present example, UID 210 may be designed for short read lengths comprising up to 4 sequence positions, up to 6 sequence positions, or up to 8 sequence positions, depending, at least in part, upon the application.

As described above, embodiments for design and implementation of UID 210 amenable for both small and large numbers of associations is to employ a "set" of UID 210 elements each meeting the preferred design criteria and characteristics. In some applications, such as the design of UID 210 elements with sequence composition that enable accurate error detection and correction features it is desirable to use the "set" strategy presently described.

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For example, as will be described in greater detail below the sequence composition for the UID elements in a set must be sufficiently distinct from each other in order to enable error detection and correction thereby limiting the compatible members available for a particular set. However, UID 210 members from multiple sets may be combinatorially employed with a template molecule where the members of each set are located at different relative positions and are thus easily interpretable.

In order to overcome the problems of a large number of associations to identify described above, two or more members from a set of UID 210 elements may be employed in a combinatorial manner. For example, a set of UID 210 elements may include 10, 12, 14, or other number of members comprising a 10-mer sequence length. In some embodiments, two UID 210 elements may be associated with each template molecule and used combinatorially to identify up to 144 different associations (i.e. 12 UID members for use with element 1 multiplied by 12 UID members for use with element 2 results in 144 possible combinations of UID elements 1 and 2 that may be employed to uniquely identify an association).

Those of ordinary skill in the related art will appreciate that alternative embodiments may be employed where each UID 210 element associated with a template molecule may include a subset of the total number of UID members from the set (i.e. use a portion of the members of the set). In other words, of the 12 members of a complete set, only 8 may be employed at one element position. There are a number of reasons why it may be desirable to use a subset of UID members that includes having a need for a smaller number of associations to identify (i.e. smaller number of combinations), physical or practical experimental conditions such as equipment or software limitations, or preferred combinations of UID members of a set in element positions. For instance, a first element may employ all 12 UID members from a set and a second element may employ a subset of 8 UID members from the same or different set yielding 96 possible combinations.

UID 210 elements used in combinatorial strategies may be configured in a variety of positional arrangements relative to the position of the template molecule. For example, a strategy that utilizes 2 UID 210 elements combinatorially to identify the association of each template molecule with its sample of origin may include a UID element positioned at each end of a linear template molecule (i.e. one UID 210 element at the 5' end and another at the 3' end). In the present example, each UID 210 element may be associated with an adaptor element, such as adaptor 200 or 220, employed in a target specific amplicon or genomic library sequencing strategy as discussed above. Thus, the sequence data associated with a template molecule would include the sequence composition of a UID element at each end of

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the amplicon. The combination of the UID elements may then be used to associate the sequence data with the sample of origin of the template molecule.

In some alternative embodiments, a UID 210 element may be incorporated in an adaptor element at each end of a linear template molecule as described above. However, the read length of the template molecule may be greater than the ability of the sequencing technology to handle. In such a case, the template molecule may be sequenced from each end independently (i.e. a separate sequencing run for each end), where the UID 210 element associated with the end may be employed as a single UID 210 identifier.

In addition it may be desirable in some embodiments to assign more that one UID 210 element per sample, or more than one combinations of UID 210 elements. Such a strategy may provide redundancy to protect against possible unintended biases introduced by various source, which could include the UID 210 element itself. For example, a sample with a population of template molecules may be sub-divided in sub-samples each using a distinctive UID 210 element for the association. In such a case, the redundancy of the different UID 210 elements for the same population of template molecules from a sample provides for greater confidence that the correct associations will be identified or if the error is too great to make a correct identification of the association with confidence.

As generally described above, embodiments of the presently described invention include one or more UID 210 elements operatively coupled to each template molecule for the purpose of identifying the association between the template molecule and the sequence data generated therefrom with a sample of origin. One or more embodiments of a UID element may be operatively coupled to one or more components of an adaptor and a template molecule using a variety of methods known in the art that include but are not limited to ligation techniques. Methods for ligating nucleic acid molecules to one another are generally known in the art and include employing a ligase enzyme for what is referred to as sticky end or blunt end ligation. Further examples of coupling adaptor elements to template molecules using ligation as described in U.S. Patent Application Serial No. 10/767,894, titled "Method for preparing single-stranded DNA libraries", filed January 28, 2004; and U.S. Provisional Patent Application Serial No. 60/031,779, titled "System and Method for Improved Processing of Nucleic Acids for Production of Sequencable Libraries" filed February 27, 2008, each of which is hereby incorporated by reference herein in its entirety for all purposes). For example, a large template nucleic acid or whole genomic DNA sample may be fragmented by mechanical (i.e. nebulization, sonication) or enzymatic means (i.e. DNase I), the resulting ends of each fragment may be polished for compatibility with adaptor

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elements (i.e. polishing using what is referred to as an exonuclease, such as BAL32 nuclease or Mung Bean nuclease), and each fragment may be ligated to one or more adaptor elements (i.e. using T4 DNA ligase). In the present example, each adaptor element is directionally ligated to the fragment such as for instance by selective binding between the 3' end of the adaptor and the 5' end of the fragment.

In some embodiments, UID 210 elements may be provided to user 101 in the form of a kit, where the kit could include adaptors comprising incorporated UID 210 elements as illustrated in Figures 2A and 2B. Or, the kit could include UID 210 as independent elements that enable user 101 to incorporate as they desire.

As described above, embodiments of UID 210 should comprise a number of preferred characteristics or design criteria that include but are not limited to a) each UID element comprises a minimal sequence length requiring a minimal number of synthesis or flow cycles, b) each UID element comprises sequence distinctiveness, c) each UID element comprises resistance to introduced error, and d) each UID element does not interfere with amplification methods (such as PCR, or cloning into vectors).

Also, some embodiments of UID element design may also consider physical characteristics or design criteria of nucleic acids that include some or all of i) UID sequence composition selected to resist formation of what are referred to as "hairpins" (also referred to as a "hairpin loop" or "stem loop") and "primer dimers"; ii) UID elements comprise preferred melting temperature (i.e. 40°C) and/or Gibbs free energy (i.e. ΔG cutoff of -1.5) characteristics. Aspects of some of the desirable characteristics and their impact on UID design are described in greater detail below.

One important characteristic of a UID element is that it should include a minimal number of bases or sequence positions required to satisfy the needs of other characteristic requirements. For example, each UID element should comprise the minimum sequence length required to uniquely identify a desired number of associations between the template molecule/sequence data and their samples of origin. A desired number of associations may include identification of template molecules/sequence data associated with at least 12 different samples, at least 96 different samples, at least 384 different samples, or a greater number of samples that may be contemplated in the future. In other words the sequence length of the UID should be no longer than necessary in order to conserve the number of positions (i.e. what may be referred to as "sequence real estate") of the read length for the template molecule. Further, the minimum sequence length should consume or require a minimum number of flow cycles of the set of nucleotide species to generate the sequence

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data for each UID element. Minimizing the number of nucleotide species flow cycles required to generate sequence data for the UID elements provides advantages in reagent cost, instrument usage (i.e. processing time), data quality, and read length. For instance, each additional flow cycle increases the probability of introducing CAFIE error, and reagent usage. In the present example, it is preferable that each 10-mer UID element require only 5 nucleotide species flow cycles to generate sequence data for each UID element.

Another important characteristic includes sequence distinctiveness of each UID element. The term "sequence distinctiveness" as used herein generally refers to a distinguishable difference between a plurality of UID sequences such that each sequence is easily recognizable from every other UID sequence that is the subject of comparison. In particular each UID element needs to comprise a measure of sequence distinctiveness that enables easy detection of introduced error and correction of some or all of the error. Further, it is generally preferable that each UID element be free of repetitive sequence composition and should not include a sequence composition recognized by restriction enzymes. In other words it is undesirable for UID elements to include consecutive monomers having the same composition of nucleotide species. For example, preferred embodiments of the sequence distinctiveness of each UID element enable detection of up to 3 sequence positions with introduced errors and correction of up to 2 sequence positions with introduced errors in a 10-mer element (i.e. 10 total sequence positions). Those of ordinary skill will appreciate that the introduced error may include what are referred to as "insertions", "deletions", "substitutions", or some combination thereof (i.e. a combination of an insertion and deletion at the same sequence position will appear to be a substitution and would be counted as a single error event). Also, the level of error detection and correction may depend, at least in part, upon the sequence length of the UID element. Further, introduced errors outside (i.e. upstream or downstream) of UID 210 may have effects on the interpretation of sequence composition for UID 210. This will be discussed further below in the context of decoding or analysis of sequence data for UID identification.

A further characteristic that is also desirable comprises resistance to introduced error. For example, monomer repeats in nucleic acid sequence such as that of the template molecule or other sequence elements may cause errors in a sequence read. The error may include an over or under representation or call of the number of repeated monomers. It is therefore desirable that the UID elements do not begin or end with the same nucleotide species as the adjacent monomer of a neighboring sequence element (i.e. creating monomer repeats between sequence elements or components). In the present example, a neighboring sequence

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element, such as key 207 illustrated in Figures 2A and 2B, may end with a "G" nucleotide species. Therefore, a UID element such as UID 210, should not begin with the same "G" nucleotide species to avoid the increased possibility introduced error from the repeated "G" species.

Another source of error that is particularly relevant in SBS contexts, include what are referred to as "carry forward" or "incomplete extension" effects (sometimes referred to as CAFIE effects). For example, a small fraction of template nucleic acid molecules in each amplified population of a nucleic acid molecule from a sample (i.e. a population of substantially identical copies amplified from a nucleic acid molecule template) loses or falls out of phasic synchronism with the rest of the template nucleic acid molecules in the population (that is, the reactions associated with the fraction of template molecules either get ahead of, or fall behind, the other template molecules in the sequencing reaction run on the population) . Additional description of CAFIE mechanisms and methods of correcting CAFIE error are further described in PCT Application Serial No US2007/004187, titled "System and Method For Correcting Primer Extension Errors in Nucleic Acid Sequence Data", filed February 15, 2007, which is hereby incorporated by reference herein in its entirety for all purposes.

Also, it will be appreciated that some types of error may occur at higher frequency than other types and/or have greater consequences than other types of error. For example, deletion error may have more significant impact than substitution error. It is therefore advantageous to design each UID element so that it is weighted more heavily to deal with the more frequent or more deleterious types of error.

As stated previously, it is not typically desirable to randomly or non-selectively design the sequence composition of UID elements. An illustrative example of two improperly designed UID elements and the potential for problems with error detection/correction using such UID elements is presented in Table 1.

Table 1:

UID Element 1	Generated UID Sequence	UID Element 2
ACTGA (SEQ ID NO: 1)	AGTGA (SEQ ID NO: 2)	AGCGA (SEQ ID NO: 3)

In the example of table 1, it is apparent that the UID sequence represented as generated UID sequence contains an error (i.e. the presence of at least one error is detected) if either UID element 1 or 2 is the original sequence element. However, it is not clear from the

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sequence composition of the Generated UID sequence whether UID element 1 or UID element 2 was the actual UID element because a single error in either could result in the generated sequence. In other words, it is possible that one error was introduced in UID element 1 transforming the "C" nucleotide species at the second position to a "G" species. It is also possible that one error was introduced in UID element 2 transforming the "C" nucleotide species at the third position to a "T" species. Given the sequence information, the error is detected but it is not possible to infer which UID element was the original element and thus cannot be corrected. Therefore, the association of the generated UID sequence with either UID element 1 or 2 cannot be positively made, and thus the sample of origin for the template molecule coupled to one of the UID elements cannot be identified and the generated sequence information may need to be thrown out. In other words, the design of UID elements 1 and 2 are not sufficiently distinct from each other to recover from the described type of introduced error.

The potential result of poor UID design is further exemplified in Table 2.

Table 2:

UID Element 1	UID Element 2
CTACC (SEQ ID NO: 4)	CTGCC (SEQ ID NO: 5)

The example of Table 2 provides an even clearer picture of the potential consequences where a substitution event in UID element 1 of an A nucleotide species at the third position to a G nucleotide species, which is one of the most common types of error introduced by PCR processes, results in an exact match with the sequence composition of UID 210 element. Thus the poor UID 210 design results in an undetectable error that would likely result in the mis-assignment of the sequence data to a sample of origin.

Various methods may be employed to design UID elements comprising sequence composition that meets the necessary design criteria. Also, application 135 illustrated in Figure 1 may be employed for designing UID 210 using some or all of the methods described herein. For example, "Brute Force" methods may be employed that compute every possible sequence composition for a given length and the possible conflicts with other sequence composition given a set of parameters associated with the design criteria. In the present example, the sequence composition of 10 mer UID elements may be computed for detection of up to 3 sequence positions with introduced errors and correction of up to 2 sequence positions with introduced errors.

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Design of a preferred sequence composition for members of a set of UID 210 elements meeting the most stringent design criteria given the characteristics described above presents a computational challenge. Mathematical methods known to those of skill in the art may be applied to compute the possible sequence composition for members of a set given the design constraints. For example, mathematical transformations of all possible combinations of sequence composition may be computed given the design constraints to generate what may be referred to as "Error Balls" or "Error Clouds" to determine the potential compatibility of each UID element with the other members in a set. Compatibility of sequence composition for potential UID elements may be visually illustrated as non-overlapping error balls. For example, Figure 3 provides an illustrative representation of what may be referred to as "space potential" for computed error balls for UID 310, UID 320, UID 330, UID 340, and UID 350 comprising some or all of the design criteria described above such as number of flow cycles, and sequence length requirements. As illustrated in Figure 3 the error balls for UID 310, UID 320, and UID 330 do not overlap and thus represent sequence composition of compatible UID 210 elements. Further, UID 340 overlaps with UID 320 and UID 350 representing a sequence composition for a UID element that is not compatible. However UID 340 does not overlap with UID 310 and UID 330 and thus represents compatible sequence composition for each non-overlapping UID element.

Alternatively, a more computationally efficient approach may be employed that uses what is referred to in the art as "Dynamic Programming" techniques. The term "Dynamic Programming" as used herein generally refers to methods for solving problems that comprise overlapping sub-problems and optimal structure. Dynamic programming techniques are typically substantially more computationally efficient than methods with no *a priori* knowledge.

Some embodiments of dynamic programming technique include computing what may be referred to as the "minimum edit distance" for strings of characters such as strings of nucleic acid species. In other words, each UID member element in a set may be considered a string of characters representing the nucleic acid species composition. The term "minimum edit distance" as used herein generally refers to the minimum number of point mutations required to change a first string into a second string. Further, the term "point mutation" as used herein generally refers to and includes a change of character composition at a location in a string referred to as a substitution of a character for another in a string; an insertion of a character into a string; or a deletion of a character from a string. For example, the minimum edit distance may be computed for each potential member of a set of UID 210 elements

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against all other members of the set. Subsequently the minimum edit distances may be compared and members of the set of UID 210 elements selected based, at least in part, upon each member of the set having a sufficiently high minimum edit distance from all other members to meet the specified criteria. Systems and methods for computing minimum edit distance are well known to those of ordinary skill in the related art and may be implemented in a number of ways.

Another important aspect of the presently described invention is directed to the analysis of sequence data to "decode" or identify the UID 210 sequence elements within the data. In some embodiments an algorithm may be implemented in computer code as application 135 that processes the sequence data from each run and identify UID 210 as well as perform any error detection or corrections functions. It is important to recognize that methods of error detection and correction in strings of information have been employed in the computer arts particularly in the area of electronically stored and transmitted data. For example, the problem of "inversion" of bits of data from one form into another occurs when data is transmitted over networks or stored in electronic media. The inversion of bits presents a problem with respect to the integrity of stored or transmitted data and is analogous to the presently described substitution type of error. Methods of detection and correction of inversion error is described in J. F. Wakerly, "Detection of unidirectional multiple errors using low cost arithmetic codes," IEEE Trans. Comput., vol. C-24, pp. 210-212, Feb. 1975.; and J. F. Wakerly, Error Detecting Codes, Self-Checking Circuits and Applications. Amsterdam, The Netherlands: North-Holland, 1978, both of which are hereby incorporated by reference herein in their entireties for all purposes.

However, the methods of detecting and correcting inversion error described above are not applicable to the problem of error detection and correction in sequence data and more specifically errors in UID elements. Importantly, the problem in sequence data is substantially more complex because it deals with the problems of substitutions and deletions as well as substitutions that create phasing problems and complicate the interpretation of information at each sequence position.

As described above, UID 210 may be located at a known position relative to other easily identifiable elements such as primer 205, key 207, the 5' or 3' end of the sequence, etc. However, just as introduced error within UID 210 has deleterious effects, error outside of the region of the UID 210 element may also affect the efficiency of identifying each UID 210 element. Further, some types of error outside of the region defined by UID 210 may contribute to and count as errors within UID 210 sequence. For example, insertion events

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may occur and be represented in the sequence data preceding (i.e. upstream of) UID 210 element that may be difficult to interpret. In the present example, an insertion event could include the insertion of one or more G nucleotide species bases at the end of key 207 comprising a TCAG sequence composition as may occur when a nucleotide species at a sequence position is "overcalled". However, an application that interprets the data will not know that it is an insertion event and cannot rule out the possibility of a substitution event that provided a G nucleotide in place of a different nucleotide species at the first sequence position of UID 210. In other words, the error outside of UID 210 will force the algorithm to decide if the error is an insertion that shifts where it should look for the first sequence position of UID 210 or whether it is a substitution event.

Continuing the example from above, an algorithm or user may look for the UID 210 element immediately adjacent to another known element such as key 207 as illustrated in Figures 2A and 2B, but the insertion of one base between key 207 and UID 210 may typically be assigned as belonging to UID 210 (counts as a first insertion error). Additionally, the algorithm or user expects UID 210 to be a certain length (i.e. 10 sequence positions) and thus truncates the last sequence position of the actual UID element because of the first insertion (counts as a second deletion error). Thus, it is clear that errors outside of the UID region can have substantial effect on finding and interpreting the sequence composition of UID 210.

In some embodiments, errors outside of the region defined by UID 210 may be particularly troublesome at the 3' end of a nascent molecule. For example, some embodiments of SBS sequence from 5' to 3' ends (i.e. adding nucleotide species to 3' end of nascent molecule) where cumulative errors (such as CAFIE type error described above) and the rate of introduced error may be increasingly higher as the sequence run gets longer at the 3' end. Thus, it may be more practical and effective to use certain assumptions rather than stringent criteria to identify UID 210. Also as described above, assumptions used for the 5' may be different than assumptions employed for the 3' end and may be referred to as "Asymmetric". For example, it may be assumed that there will never be more than 3 sequence position errors present at the 5' end which would be consistent with empirical evidence. However, in the present example at the 3' end it may be assumed that there will never be more than 4 sequence position errors due to the increased possibility of error at the 3' end. Because of the asymmetric difference in detectable error at each end, it may also be inferred that the amount of that error that is correctable may also be different. In the present example, the correctable error at the 5' end may be 2 sequence positions as described above, however the correctable error at the 3' end may only be 1 sequence position. Also, further

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assumptions may be employed at the 3' end that may not be employed for the 5' end. Such an assumption could include the existence of one or more "no called" positions in close proximity to UID 210.

In the present example, an embodiment of adaptor element 200 or 220 is present at the 3' end of a template nucleic acid in a palindromic arrangement to that illustrated in Figure 2A or 2B (as described above). It will be appreciated however, that the present example refers to a difference in the arrangement of elements and that the elements associated with each adaptor do not need to have the same composition (i.e. the 3' end may include the sequence composition of a first UID element and the 5' end may include a UID elements with different sequence composition). It will further be appreciated that some embodiments will not necessarily include the same composition of elements in each adaptor (i.e. an adaptor at the 5' end may include a UID 210 element and the adaptor on the 3' may not, or vice versa). Also, there may be inherent internal controls of the sequence quality of primer element 205 with respect to resistance to introduced error. For instance, error introduced into the sequence composition of primer 205 would negatively affect its hybridization qualities to its respective target and thus not be amplified in a PCR process and therefore not represented in populations of template molecule for sequencing. This inherent quality control of primer 205 is useful for finding UID 210, because the sequence composition of primer 205 is known and can be assumed to be substantially free of error with the exception of some sequencing related error. Also as described above, key element 207 is employed for quality control purposes and it also useful as a positional reference in the same context. Thus, in the present example primer 205 and/or key 207 may serve as easily identifiable anchor points of reference for identifying UID 210 using the known positional relationships between elements. For instance, a user or algorithm, such as an algorithm implemented by application 135, may look for UID 210 located immediately adjacent to key 207, or some known distance away, based, at least in part, upon the assumptions.

Furthermore, once a user or algorithm has identified the sequence composition of a putative UID 210 element, the step of error identification and correction occurs. Embodiments of the presently described invention compare the sequence composition of the putative UID 210 element against the sequence compositions of the UID 210 members in the set. A perfect match is associated with its sample of origin. If no perfect match is found, then the closest UID 210 elements having a sequence composition to the putative sequence are analyzed to determine possible insertion, deletion, or substitution errors that could have occurred. For example, the closest UID 210 element to the putative UID 210 element is

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identified or the putative UID 210 element is deemed to have too many errors. In the present example, the minimum edit distance may be computed between sequence composition of the putative UID 210 element against the sequence composition of all members of the UID 210 set or select members. The minimum edit distance may be computed using the parameters of detecting up to 3 sequence position errors with the possibility of correcting up to 2 sequence position errors. In the present example, the UID 210 member with the closest or shortest minimum edit distance to the putative UID 210 element given the parameter constraints (i.e. detection/correction) may be assigned as the sequence composition of the putative UID 210 element. Also, if the minimum edit distance calculation determines that 3 sequence position errors have occurred then, the putative UID 210 element may be assigned as unusable and not associated with a sample of origin.

Those of ordinary skill in the art will appreciate that when the UID 210 elements are employed in a combinatorial manner, each UID 210 element is typically independently analyzed. Then the combination of identified UID 210 elements may be compared against the known combinations assigned to samples of origin to identify the association of the sequence data and its specific sample of origin.

In preferred embodiments, a UID 210 finding algorithm is implemented using application 135 stored for execution on computer 130 as described above. Further, the same or other application may perform the step of associating the identified UID 210 from sequence data with the sample of origin and providing the results to a user via an interface and/or storing the results in electronic media for subsequent analysis or use.

Example 1- Design of UID elements considering a limited number of design constraints

The design of sequence composition for potential UID elements were computed considering detection, correction, and hairpin design constraints.

First a sequence length of 10 base pairs for each UID element were computed yielding 1,048,576 possible elements.

Next, of those possible elements UID elements were selected that have no monomer repeats, require only 5 flow cycles (20 flows) or less, do not begin with the "G" nucleotide species were computed yielding 34,001 possible elements.

A further step of filtering to exclude hairpins at a temperature of 40°C with a ΔG=-1.5 yielded 26,278 possible elements.

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Finally, 5,000 of those possible elements were selected randomly to search for compatible sets or clusters that could correct 2 sequence position errors and detect 3 sequence position errors, yielding:

32,999 sets of 12 members

3,625 sets of 13 members

24 sets of 14 members

Example 2- Exemplary computer code for creating UID sequence elements

UIDCreate.java class file that runs a search using 1 of 3 techniques, comprising (1) based on error clouds, (2) based on edit distance, and (3) based on edit distance, with an additional efficiency strategy of using a "safety map" to precompute the edit distance which gives the software the ability to effectively look ahead in the search in advance of trying candidate selections.

```
package com.fourfivefour.amplicons;


import java.util.ArrayList;
import java.util.Arrays;
import java.util.Comparator;
import java.util.HashMap;
import java.util.HashSet;
import java.util.Iterator;
import java.util.List;
import java.util.Map;
import java.util.Set;

public class UIDCreate {
        static int maxReportSize = 0;

        public enum SearchType { ErrorCloud, EditDistance, SafetyMapEditDistance; }

        /**
         * Driver to search for a compatible set of UID sequences of a given set size
         * using one of three different search methods.
         *
         * @param candidateSequences  A set of sequences from which to select.
         * @param setSize             The desired number of sequences in the
         *                                                      solution.
         * @param errsToCorrect               The number of errors that must be able to be
         *                    corrected to obtain the original sequence.
         * @param errsToDetect        The number of errors that must be able to be
         *                    detected, but not necessarily corrected.
         * @param searchType                  The search strategy to use.
         * @return                                    A set of sequences of the requested set
size
```


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```
         *                    that is a subset of the candidate sequences
         *                    and which can be distinguished according to
         *                    the error correction criteria.
         */
        public static Set<Sequence> searchCompatibleSet(Set<Sequence>
candidateSequences,
                        int setSize, int errsToCorrect, int errsToDetect, SearchType
searchType) {

                if (errsToCorrect > errsToDetect) {
                        throw new RuntimeException("The numbers of errors to correct
("+errsToCorrect+
                                                        ") must be <= the
number to detect ("+errsToDetect+")");
                }

                List<Sequence> candidates = new
ArrayList<Sequence>(candidateSequences);

                switch (searchType) {
                        case ErrorCloud:
                                return searchCompatibleSetUsingErrorClouds(candidates,
                                        setSize, errsToCorrect, errsToDetect, new
HashMap<Sequence,List<Set<Sequence>>>());
                        case EditDistance:
                                return searchCompatibleSetUsingEditDistance(candidates,
                                        setSize, errsToCorrect, errsToDetect, new
HashSet<Sequence>()
                                        );
                        case SafetyMapEditDistance:
                                return
searchCompatibleSetUsingSafetyMap(candidateSequences,

                 setSize, errsToCorrect, errsToDetect);
                        default:
                                return null;
                }
        }


        /**
         * Return a string representing the current search state.
         *
         * The resulting string encodes the current subset of sequences currently
         * under consideration, independent of the order in which they are
         * being considered.  By keeping track of this string one may ensure
         * that equivalent regions of the search space that just happen to
         * encounter sequences in a different order are not redundantly searched
         *
         * @param currentState  A set of sequences defining the current
```


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```
         *                search state.
         * @return          A string that is unique for a set of sequences
         *                and independent of their order.
         */
        public static String searchStateString (Set<Sequence> currentState) {
                Sequence [] currentStateArray = currentState.toArray(new Sequence[0]);
                Arrays.sort(currentStateArray);
                StringBuffer sb = new StringBuffer();
                for (Sequence state : currentStateArray) {
                        sb.append(state.getSequence());
                        sb.append(';');
                }
                return sb.toString();
        }


        /**
         * From the set of candidates, select a set of compatible sequences that
         * can correct and detect the desired number of errors.
         *
         * This strategy uses a pre-calculated edit distance between pairs of
         * sequences to know, in advance, which sequences are compatible with
         * each other.  This pair-wise information forms a "safety map" of
         * compatible pairs that allow more efficient forward-looking knowledge
         * of what sequences will still be compatible after other sequences
         * are added to the solution set.
         *
         * @param candidateSequences Sequence set from which to select.
         * @param setSize          The desired set size to generate.
         * @param errsToCorrect    The numbers of errors that must be able
         *                       to be corrected.
         * @param errsToDetect     The number of errors that must merely be
         *                       detected.
         *
         * @return A set of sequences that meet the desired criteria.
         */
        public static Set<Sequence> searchCompatibleSetUsingSafetyMap (
                        Set<Sequence> candidateSequences,
                        int setSize, int errsToCorrect, int errsToDetect)
        {
                Map<Sequence,Set<Sequence>> safetyMap = new
HashMap<Sequence,Set<Sequence>>();

                /* Safety map is computed on a subset of the candidates in
                 * case there are too many candidates.
                 */
                final int maxSubsetSize = 3000;

                Sequence[] fullSequenceList = candidateSequences.toArray(new
Sequence[0]);
```


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```
        final int numSequencesToUse =
Math.min(maxSubsetSize,candidateSequences.size());

        /* Compute the safety map, possibly using a subset of the sequences.
         * An alternative/preferential implementation might choose a random subset
         * of the sequences rather than just the fist numSequencesToUse that are
         * encountered.
         */

        for (int i=0; i < numSequencesToUse; i++) {
            Set<Sequence> iSafety = new HashSet<Sequence>();
            iSafety.add(fullSequenceList[i]);
            safetyMap.put(fullSequenceList[i], iSafety);
        }

        /* Create the safety map, ensuring that there is enough distance
         * between every pair of sequences such that sequences as far away
         * as the distance of error detection from one sequence and error
         * correction from the other sequence could not possibly overlap
         */
        int safeDistance = errsToCorrect + errsToDetect + 1;
        for (int i=0; i < numSequencesToUse; i++) {
            Set<Sequence> iSafety = safetyMap.get(fullSequenceList[i]);
            for (int j=i+1; j < numSequencesToUse; j++) {
                Set<Sequence> jSafety = safetyMap.get(fullSequenceList[j]);

                if (Library.minEditDistance(fullSequenceList[i],

    fullSequenceList[j])
                                                                    >=
safeDistance) {
                    iSafety.add(fullSequenceList[j]);
                    jSafety.add(fullSequenceList[i]);
                }
            }
        }

        // Perform that actual search with the safety-map in hand
        return searchCompatibleSetUsingSafetyMap(safetyMap.keySet(),setSize,
                errsToCorrect,errsToDetect,
                safetyMap,new HashSet<Sequence>(), new
HashSet<String>());
    }

    /**
     * From the set of candidates, select a set of compatible sequences that
     * can correct and detect the desired number of errors.
     *
     * This strategy uses a pre-calculated edit distance between pairs of
     * sequences to know, in advance, which sequences are compatible with
```


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```
     * each other.  This pair-wise information forms a "safety map" of
     * compatible pairs that allow more efficient forward-looking knowledge
     * of what sequences will still be compatible after other sequences
     * are added to the solution set.
     *
     * @param candidateSequences Sequence set from which to select.
     * @param setSize          The desired set size to generate.
     * @param errsToCorrect    The numbers of errors that must be able
     *                         to be corrected.
     * @param errsToDetect     The number of errors that must merely be
     *                         detected.
     * @param safetyMap        The map indicating the set of sequences
     *                         that are compatible with any given other
     *                         sequence.
     * @param selectedSequences  The current set of sequences selected in
     *                         the partial solution so far.
     * @param searchStateHistory A history of what subsets of sequences have
     *                         already been considered.
     *
     * @return A set of sequences that meet the desired criteria.
     */
    public static Set<Sequence> searchCompatibleSetUsingSafetyMap (
                    Set<Sequence> candidateSequences, int setSize,
                    int errsToCorrect, int errsToDetect,
                    Map<Sequence,Set<Sequence>> safetyMap,
                    Set<Sequence> selectedSequences,
                    Set<String> searchStateHistory) {


        String searchStateString = searchStateString(selectedSequences);
        if (searchStateHistory.contains(searchStateString)) {
                /* some other branch of the search has already explored this area
                 * so no need to search twice
                 */
                return null;
        } else {
                /*
                 * Record that we are initiating a search in the given state
                 */
                searchStateHistory.add(searchStateString);
        }

        if (selectedSequences.size() > maxReportSize) {
                // Provide intermediate reporting to show progress
                maxReportSize = selectedSequences.size();
                reportSet(selectedSequences);
        }
        if (selectedSequences.size() >= setSize) {
                return selectedSequences;
        }
```


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```
        if (selectedSequences.size() + candidateSequences.size() < setSize) {
            // If there aren't enough candidates to fill out the required set size,
            // return immediately with failure.
            return null;
        }

        /* find the candidate Sequence with the greatest number of compatible choices
of the
         * Sequences still available:
         */
        final Map<Sequence,Integer> remainingSafetyMapSize = new
HashMap<Sequence,Integer>();
        Sequence candidates[] = candidateSequences.toArray(new Sequence[0]);
        for (Sequence sequence : candidates) {
            Set<Sequence> currentSafety = new
HashSet<Sequence>(safetyMap.get(sequence));
            currentSafety.retainAll(candidateSequences);
            remainingSafetyMapSize.put(sequence,currentSafety.size());
        }

        Comparator<Sequence> candidateSorter = new Comparator<Sequence>() {
            public int compare(Sequence seq1, Sequence seq2) {
                int seq1Val = remainingSafetyMapSize.get(seq1);
                int seq2Val = remainingSafetyMapSize.get(seq2);
                if (seq1Val > seq2Val) {
                    return -1;
                } else if (seq1Val < seq2Val) {
                    return 1;
                } else {
                    return (seq1).compareTo(seq2);
                }
            }
        };

        Arrays.sort(candidates,candidateSorter);

        Set<Sequence> result = null;
        final int searchBreadth = 10;
        for (int i=0; i < candidates.length && i < searchBreadth && result == null;
i++) {
            Sequence nextCandidate = candidates[i];
            int numNextCompatible =
remainingSafetyMapSize.get(nextCandidate);
            if (numNextCompatible == 1) {
                /* the next candidate is only compatible with itself, so
                 * the search is done
                 */
                break;
            } else {
```


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```
                                Set<Sequence> nextCandidateSequences =
                                        new HashSet<Sequence>(candidateSequences);

        nextCandidateSequences.retainAll(safetyMap.get(nextCandidate));
                                nextCandidateSequences.remove(nextCandidate);
                                Set<Sequence> nextSelectedSeqs = new
HashSet<Sequence>(selectedSequences);
                                nextSelectedSeqs.add(nextCandidate);
                                result =

        searchCompatibleSetUsingSafetyMap(nextCandidateSequences,

         setSize,

         errsToCorrect,

         errsToDetect,

         safetyMap,

         nextSelectedSeqs,

         searchStateHistory);
                        }
                }
                return result;
        }


        /**
         * Generate the "error cloud" sequence sets out to the indicated number
         * of mutations of the given input sequence.
         *
         * This routine implements a breadth-first enumeration of all possible
         * mutations of a given sequence, while avoiding redundant, equivalent
         * subtrees of the search space.
         *
         * @param inputSequence
         *          The sequence to mutate.
         * @param numMutations
         *          The number of plys of mutations to generate
         * @return A list of sets of mutated sequences such that the i'th list
         *       element represents the set of mutated sequences that may
         *       derived via i mutations from the initial sequence and, further,
         *       cannot be derived by fewer than i mutations of the original
         *       sequence.
         */
        public static List<Set<Sequence>> generateErrorClouds(
                        Sequence inputSequence, int numMutations) {
```


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```
        List<Set<Sequence>> mutationPlys = new ArrayList<Set<Sequence>>();

        // The 0'th mutation ply is simply the initial sequence itself:
        Set<Sequence> initialPly = new HashSet<Sequence>();
        initialPly.add(inputSequence);
        mutationPlys.add(initialPly);

        for (int ply = 1; ply <= numMutations; ply++) {
            Set<Sequence> lastPlySequences =
                mutationPlys.get(ply - 1);
            Set<Sequence> nextPlyCandidates =
                Sequence.generateSingleMutations(lastPlySequences);
            Iterator<Sequence> candidateIter =
                nextPlyCandidates.iterator();
            /* Remove any candidates that appeared in a previous ply
             * (meaning that they are derivable via a shorter,
             *  more direct sequence of mutations).
             */
            while (candidateIter.hasNext()) {
                Sequence candidate = candidateIter.next();
                for (Set<Sequence> previousPly : mutationPlys) {
                    if (previousPly.contains(candidate)) {
                        candidateIter.remove();
                        break;
                    }
                }
            }

            // Candidates that remain at this point represent the next ply
            mutationPlys.add(nextPlyCandidates);
        }
        return mutationPlys;
    }


    /**
     * Validate the given collection of sequences to ensure that they
     * are compatible with respect to the desired number of errors
     * to correct and detect.
     *
     * Two sequences are compatible if there is no intersection of the
     * error cloud out to the correction distance of either sequence with
     * the error cloud out to the detection distance of the other sequence.
     * If all pairs of sequences in a collection of sequences are compatible,
     * then the collection itself is compatible.
     *
     * This definition of compatibility logically follows from the fact
     * that incompatibilities exist when a potentially observable sequence
     * could be derived, via mutation, from more than one sequence
     * in the collection (thereby preventing a definitive correction to be
```


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```
         * performed) and if that observable sequence is within the desired
         * error correction distance of any of those sequences.  Note that
         * mutated sequences that are within the error detection distance of
         * two sequences are not a problem as there is no expectation of being
         * able to correct such mutated sequences (only to detect that a
         * mutation has occurred).
         *
         * @param sequences          The collection of sequences to test.
         * @param errsToCorrect The desired number of errors to correct.
         * @param errsToDetect  The desired number of errors to detect.
         * @return true, if the collection of sequences are compatible,
         *       false otherwise.
         */
        public static boolean validateCollection(Set<Sequence> sequences,
                                                                    int
    errsToCorrect,
                                                                    int
    errsToDetect)
        {
            /* First generate the error clouds for each sequence and
             * collapse the separate cloud levels into two sets: those
             * sequences within the "errsToCorrect" distance of the
             * sequence center, and those within the the "errsToDetect"
             * distance from the center.
             */
            Map<Sequence,Set<Sequence>> correctLevelMap =
                    new HashMap<Sequence,Set<Sequence>>();
            Map<Sequence,Set<Sequence>> detectLevelMap =
                    new HashMap<Sequence,Set<Sequence>>();
            for (Sequence sequence: sequences) {
                List<Set<Sequence>> errorClouds =
                        generateErrorClouds(sequence, errsToDetect);
                Set<Sequence> errsToCorrectSequences = new HashSet<Sequence>();
                for (int errLevel=0; errLevel <= errsToCorrect; errLevel++) {
                    errsToCorrectSequences.addAll(errorClouds.get(errLevel));
                }
                Set<Sequence> errsToDetectSequences =
                        new HashSet<Sequence>(errsToCorrectSequences);
                for (int errLevel=errsToCorrect+1; errLevel <= errsToDetect;
                        errLevel++) {
                    errsToDetectSequences.addAll(errorClouds.get(errLevel));
                }
                correctLevelMap.put(sequence,errsToCorrectSequences);
                detectLevelMap.put(sequence,errsToDetectSequences);
            }

            /* Validate that none of the mutations out to the "errsToDetect"
             * error distance of one sequence are in common with any of the
             * mutations out to the "errsToCorrect" error distance another
             * sequence
```


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```
                */
                Sequence seqList[] = sequences.toArray(new Sequence[0]);
                boolean foundOverlap = false;

                for (int i=0; !foundOverlap && i < seqList.length; i++) {
                        for (int j=0; !foundOverlap && j < seqList.length; j++) {
                                if (i == j) {
                                        continue;
                                }
                                Set<Sequence> overlapSet =
                                        new
HashSet<Sequence>(detectLevelMap.get(seqList[i]));
                                overlapSet.retainAll(correctLevelMap.get(seqList[j]));
                                foundOverlap = !overlapSet.isEmpty();
                        }
                }

                return !foundOverlap;
        }

        /**
         * Validate the given collection of sequences to ensure that they
         * are compatible with respect to the desired number of errors
         * to correct and detect.
         *
         * Two sequences are compatible if there is no intersection of the
         * error cloud out to the correction distance of either sequence with
         * the error cloud out to the detection distance of the other sequence.
         * If all pairs of sequences in a collection of sequences are compatible,
         * then the collection itself is compatible.
         *
         * This definition of compatibility logically follows from the fact
         * that incompatibilities exist when a potentially observable sequence
         * could be derived, via mutation, from more than one sequence
         * in the collection (thereby preventing a definitive correction to be
         * performed) and if that observable sequence is within the desired
         * error correction distance of any of those sequences.  Note that
         * mutated sequences that are within the error detection distance of
         * two sequences are not a problem as there is no expectation of being
         * able to correct such mutated sequences (only to detect that a
         * mutation has occurred).
         *
         * This routine performs the calculation without creating the
         * actual error clouds, but instead uses the minimum edit distance
         * between sequences to ensure compatibility.
         *
         * @param sequences         The collection of sequences to test.
         * @param errsToCorrect The desired number of errors to correct.
         * @param errsToDetect  The desired number of errors to detect.
         * @return true, if the collection of sequences are compatible,
```


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```
     *       false otherwise.
     */
    public static boolean validateCollectionUsingDistance(
                                                    Set<Sequence> sequences,
                                                    int errsToCorrect, int errsToDetect) {
        Sequence seqList[] = sequences.toArray(new Sequence[0]);
        /* The error detection cloud and error correction cloud of two
         * sequences cannot overlap if the minimum distance between the
         * sequences is one greater than the sum of the errors.
         */
        int safeDistance = errsToCorrect + errsToDetect + 1;
        for (int i=0; i < seqList.length; i++) {
            for (int j=i+1; j < seqList.length; j++) {
                int ijDist= Library.minEditDistance(seqList[i],seqList[j]);
                if (ijDist < safeDistance) {
                    System.out.println("Validation failed, dist = "+ijDist+"
for "+seqList[i]+" vs "+seqList[j]);
                    return false;
                }
            }
        }
        return true;
    }


    /**
     * From the set of candidates, select a set of compatible sequences that
     * can correct and detect the desired number of errors.
     *
     * This strategy uses the edit distance between pairs of sequences
     * to ensure that they do not overlap in a manner that would prevent
     * error detection/correction. This technique is much more efficient
     * than explicitly enumerating and comparing the error clouds between
     * sequences.
     *
     * @param candidateSequences Sequence set from which to select.
     * @param setSize          The desired set size to generate.
     * @param errsToCorrect    The numbers of errors that must be able
     *                         to be corrected.
     * @param errsToDetect     The number of errors that must merely be
     *                         detected.
     * @param currentSequences  State of search indicating the currently
     *                         selected candidates.
     *
     * @return A set of sequences that meet the desired criteria.
     */
    public static Set<Sequence> searchCompatibleSetUsingEditDistance (
                    List<Sequence> candidateSequences, int setSize,
                    int errsToCorrect, int errsToDetect,
                    Set<Sequence> currentSequences) {
```


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```
                if (currentSequences.size() > maxReportSize) {
                        /**
                         * Provide intermediate level reporting to ensure progress
                         * is being made.
                         */
                        maxReportSize = currentSequences.size();
                        reportSet(currentSequences);
                }
                if (currentSequences.size() >= setSize) {
                        return currentSequences;
                }

                /* The error detection cloud and error correction cloud of two
                 * sequences cannot overlap if the minimum distance between the
                 * sequences is one greater than the sum of the errors.
                 */
                int safeDistance = errsToCorrect + errsToDetect + 1;

                for (int nextIdx = 0; nextIdx < candidateSequences.size(); nextIdx++) {
                        /* Check to see that nextSequence is far enough away from all the
                         * other sequences in the prefix solution.
                         */
                        Sequence nextSequence = candidateSequences.get(nextIdx);
                        boolean overlappingClouds = false;
                        for (Sequence currentSequence : currentSequences) {
                                if (Library.minEditDistance(currentSequence,nextSequence) <
safeDistance) {
                                        overlappingClouds = true;
                                        break;
                                }
                        }

                        if (!overlappingClouds) {
                                List<Sequence> remainingCandidates =
                                        candidateSequences.subList(nextIdx+1,
candidateSequences.size());
                                currentSequences.add(nextSequence);

                                Set<Sequence> solution =
                                        searchCompatibleSetUsingEditDistance(
                                                remainingCandidates,
                                                setSize, errsToCorrect, errsToDetect,
                                                currentSequences);
                                if (solution == null) {
                                        currentSequences.remove(nextSequence);
                                } else {
                                        return solution;
                                }
                        }
```


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```
            }
            return null;
        }

        /**
         * From the set of candidates, select a set of compatible sequences that
         * can correct and detect the desired number of errors.
         *
         * This strategy uses an explicit enumeration of the "error clouds"
         * surrounding the candidate sequences to ensure that they do not
         * overlap in a manner that would prevent error detection/correction.
         * This technique may not be appropriate, efficient, or even practically
         * usable for large error clouds.
         *
         * @param candidateSequences Sequence set from which to select.
         * @param setSize           The desired set size to generate.
         * @param errsToCorrect     The numbers of errors that must be able
         *                          to be corrected.
         * @param errsToDetect      The number of errors that must merely be
         *                          detected.
         * @param currentErrorClouds State of search mapping from the current
         *                          selected candidates and their corresponding
         *                          error clouds.
         * @return A set of sequences that meet the desired criteria.
         */
        public static Set<Sequence> searchCompatibleSetUsingErrorClouds(List<Sequence>
candidateSequences,
                                                                        int
setSize,
                                                                        int
errsToCorrect, int errsToDetect,

Map<Sequence, List<Set<Sequence>>> currentErrorClouds) {

            if (currentErrorClouds.size() > maxReportSize) {
                /**
                 * Provide intermediate level reporting to ensure progress
                 * is being made.
                 */
                maxReportSize = currentErrorClouds.size();
                reportSet(currentErrorClouds.keySet());
            }
            if (currentErrorClouds.size() >= setSize) {
                return currentErrorClouds.keySet();
            }

            for (int nextIdx = 0; nextIdx < candidateSequences.size(); nextIdx++) {
                Sequence nextSequence = candidateSequences.get(nextIdx);
                List<Set<Sequence>> nextErrorCloud =
                        generateErrorClouds(nextSequence, errsToDetect);
```


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```
                    /*
                     * Check to see that nextErrorCloud doesn't overlap with any of the
                     * currentErrorClouds except possibly in the errsToDetect category,
                     * where it can only overlap with other errsToDetect distant clouds
                     */
                    boolean overlappingClouds = false;
                    for (List<Set<Sequence>> currentClouds :
currentErrorClouds.values()) {
                        for (int currentErrorLevel = 0; !overlappingClouds
                                && currentErrorLevel <= errsToCorrect;
currentErrorLevel++) {
                            for (int nextErrorLevel = 0; !overlappingClouds
                                    && nextErrorLevel <= errsToDetect;
nextErrorLevel++) {
                                Set<Sequence> currentLevelErrorCloud =
currentClouds.get(currentErrorLevel);
                                for (Sequence nextErrorSequence :
nextErrorCloud.get(nextErrorLevel)) {
                                    if
(currentLevelErrorCloud.contains(nextErrorSequence)) {
                                        overlappingClouds = true;
                                        break;
                                    }
                                }
                            }
                        }
                    }
                    /*
                     * Check to see that none of the error clouds surrounding the current
                     * codes in the range of errors to merely detect overlap with the
                     * nextErrorCloud clouds in the range of errors to correct
                     */
                    if (!overlappingClouds) {
                        for (List<Set<Sequence>> currentClouds :
currentErrorClouds.values()) {
                            for (int currentErrorLevel = errsToCorrect+1;
!overlappingClouds
                                    && currentErrorLevel <= errsToDetect;
currentErrorLevel++) {
                                for (int nextErrorLevel = 0; !overlappingClouds
                                        && nextErrorLevel <=
errsToCorrect; nextErrorLevel++) {
                                    Set<Sequence> currentLevelErrorCloud
= currentClouds.get(currentErrorLevel);
                                    for (Sequence nextErrorSequence :
nextErrorCloud.get(nextErrorLevel)) {
                                        if
(currentLevelErrorCloud.contains(nextErrorSequence)) {
                                            overlappingClouds = true;
```


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```
                                                    break;
                                                }
                                            }
                                        }
                                    }
                                }

                                if (!overlappingClouds) {
                                    List<Sequence> remainingCandidates =
                                        candidateSequences.subList(nextIdx+1,
candidateSequences.size());
                                    currentErrorClouds.put(nextSequence, nextErrorCloud);

                                    Set<Sequence> solution =
searchCompatibleSetUsingErrorClouds(
                                                    remainingCandidates,
                                                    setSize, errsToCorrect, errsToDetect,
currentErrorClouds);
                                    if (solution == null) {
                                        currentErrorClouds.remove(nextSequence);
                                    } else {
                                        return solution;
                                    }
                                }
                            }
                            return null;
                        }

                        /**
                         * Generate the set of all possible flow patterns that would produce
                         * sequences of a given length, with no monomer repeats, using at most
                         * a given number of flows, and avoiding a given starting flow as the
                         * first positive flow of the pattern.
                         *
                         * @param numBases      The number of called bases that should
                         *                      be produced if the given flowgram were
                         *                      observed for a sequence.
                         * @param startFlow     The conceptual flow index of the first
                         *                      flow in the recursive call to this routine.
                         * @param maxFlow       The maximum number of flows (positive or
                         *                      negative) that may be consumed by the pattern.
                         * @param avoidStartFlow  A flow that may not be the first positive flow.
                         * @return Set of flow patterns (Strings of 0's and 1's representing
                         *      negative and positive flows that meet the desired
                         *      criteria).
                         */
                        public static Set<String> generateCandidateFlowPatterns(int numBases,
                                int startFlow, int maxFlow, int avoidStartFlow) {
                            Set<String> candidates = new HashSet<String>();
```


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```
            if (numBases > 0) {
                if (startFlow == maxFlow) {
                    return candidates;
                } else {
                    String zeroPrefix = "";
                    for (int flowSkip = 0; flowSkip < (startFlow == 0 ? 4 : 3);
flowSkip++) {
                        int nextPositiveFlow = startFlow + flowSkip;
                        if (nextPositiveFlow < maxFlow
                                && (startFlow > 0 || nextPositiveFlow !=
avoidStartFlow)) {
                            String currentPrefix = zeroPrefix + "1";
                            for (String candidateSuffix :
generateCandidateFlowPatterns(
                                    numBases - 1, nextPositiveFlow
+ 1, maxFlow,
                                    avoidStartFlow)) {
                                candidates.add(currentPrefix +
candidateSuffix);
                            }
                        }
                        zeroPrefix += "0";
                    }
                }
            } else {
                candidates.add("");
            }
            return candidates;
        }

        /**
         * Generate a set of candidate sequences of a given base content length, using
         * a maximum number of flow cycles, based on the given flow order such that
         * none of the sequences begin with a particular base.
         *
         * @param numBases   Number of bases each candidate sequence should be.
         * @param maxCycles  Maximum number of flow cycles allowed.
         * @param flowOrder  Flow order for sequencing.
         * @param avoidStartBase Base to avoid at start of sequence.
         * @return Candidate set of sequences that meet the given criteria.
         */
        public static Set<Sequence> generateCandidateSequences(int numBases, int
maxCycles,
                String flowOrder, char avoidStartBase)
        {
            Set<String> candidateFlows =
                generateCandidateFlowPatterns(numBases,
                                              0,
                                              maxCycles*4,
```


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```
flowOrder.indexOf(avoidStartBase));

                Set<Sequence> candidateSequences = new HashSet<Sequence>();
                for (String flows : candidateFlows) {
                        Flowgram f = new
Flowgram(flowOrder,Flowgram.flowValueStringToFlowValues(flows));
                        candidateSequences.add(new Sequence(f.baseCall()));
                }

                /*
                 * At this point, one might further filter the candidate sequences by some
                 * molecular biological criteria, such as propensity to form hairpin turns
                 */
                return candidateSequences;
        }


        /**
         * Produce a printed representation of a set of sequences
         * assuming a default flow oder of TACG.
         *
         * @param sequences  The set of sequences to report.
         */
        public static void reportSet(Set<Sequence> sequences) {
                reportSet(sequences, "TACG");
        }

        /**
         * Produce a printed representation of a set of sequences
         * along with their conceptual flowgrams, assuming the
         * given flow order.
         *
         * @param sequenceSet The set of sequences to report.
         * @param flowOrder   The flow order that would be used
         *                    in sequencing.
         */

        public static void reportSet(Set<Sequence> sequenceSet,String flowOrder) {
                Sequence sequences[] = sequenceSet.toArray(new Sequence[0]);
                Arrays.sort(sequences);

                for (int i = 0; i < sequences.length; i++) {
                        System.out.println("Sequence #" + (i + 1) + "\t"
                                        + new
Flowgram(flowOrder,sequences[i].getSequence()).getFlowValueString() + "\t"
                                        + sequences[i].getSequence());
                }
                System.out.println("---------");
                System.out.flush();
```


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```
        }

        /**
         * Example use of search code to generate a set of compatible
         * sequences that meet given design criteria of base composition,
         * maximum flow usage, and ability to correct and detect errors.
         *
         * @param args
         */
        public static void main(String[] args) {
                char fivePrimeAvoidBase     = 'G';
                final String flowOrder      = "TACG";
                final int   uidBaseLength   = 10;
                final int   uidMaxCycles    = 5;
                final int   errorsToCorrect = 2;
                final int   errorsToDetect  = 3;
                final int   desiredSetSize  = 12;
                System.out.println("Computation Begun");

                Set<Sequence> sequenceSet =
                        generateCandidateSequences(uidBaseLength,
                                                   uidMaxCycles,
                                                   flowOrder,
                                                   fivePrimeAvoidBase);
                System.out.println("Total candidate sequencess=" + sequenceSet.size());

                Set<Sequence> compatibleSequences =
                        searchCompatibleSet(sequenceSet,desiredSetSize,
                                            errorsToCorrect,errorsToDetect,
                                            SearchType.EditDistance);
                if (compatibleSequences == null) {
                        System.out.println("No solution");
                } else {
                        reportSet(compatibleSequences,flowOrder);
                }
        }
}
```

It will be appreciated that the foregoing computer code is provided for the purposes of example, and that numerous alternative methods and code structures may be employed. It will also be appreciated that the exemplary code provided herein is not intended to execute as a stand alone application or to run perfectly without additional computer code or modification.

Example 3- Table of computed UID sequences, cluster ID, and Flowgram script

Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127176	14	0110010101010110011010	ACAGAGTGTC	10	7
C1127176	14	0111101010010101010100	ACGTCTGAGA	10	8
C1127176	14	0101011100100110101010	AGACGCACTC	10	9
C1127176	14	0100101011001010101011	ATCTATCTCG	10	10
C1127176	14	0011010011110011111000	CGATACGCGT	10	11
C1127176	14	0011001100111001010011	CGCGCGTGCG	10	12
C1127176	14	0011110101001101010010	CGTAGATAGC	10	13
C1127176	14	0011100110101010101100	CGTGTCTCTA	10	14
C1127176	14	0010101001100111010110	CTCACACGAC	10	15
C1127176	14	1110101001001011100	TACTCATCGT	10	16
C1127176	14	1101001101001110010	TAGCGATACA	10	17
C1127176	14	1100100111011100100	TATGTAGTAT	10	18
C1127176	14	1010100100110110100	TCTGCGACTG	10	19
C1127176	14	1001011001011010010	TGACAGTCAG	10	20
C1127177	14	0110110100110101010	ACTAGCGAGA	10	21
C1127177	14	0101011101001100110	AGACGATATA	10	22
C1127177	14	0100101010010111010	ATCTGACGTC	10	23
C1127177	14	0100100110101101011	ATGTCTAGCG	10	24
C1127177	14	0011010011110011100	CGATACGCGT	10	25
C1127177	14	0011001100111001011	CGCGCGTGCG	10	26
C1127177	14	0011101001100101011	CGTCACAGAC	10	27
C1127177	14	0011100110101010110	CGTGTCTCTA	10	28
C1127177	14	1110101001010100100	TACTCAGATG	10	29
C1127177	14	1101001001101010101	TAGCACTCTC	10	30
C1127177	14	1100110011001100100	TATATACACA	10	31
C1127177	14	1010010010111010010	TCATCGTCAG	10	32
C1127177	14	1001010110010011010	TGAGTGCGAC	10	33
C1127177	14	1001100101011011000	TGTGAGTAGT	10	34
C1127178	14	0110011010100100110	ACACTCTGAC	10	35
C1127178	14	0101010101010110100	AGAGAGACTG	10	36
C1127178	14	0100111111001010100	ATACGTATCT	10	37
C1127178	14	0100101110110101010	ATCGTCGAGA	10	38
C1127178	14	0010011001011011100	CACAGTAGTA	10	39
C1127178	14	0011010011110011100	CGATACGCGT	10	40
C1127178	14	0011001100111001011	CGCGCGTGCG	10	41
C1127178	14	0011100110101010110	CGTGTCTCTA	10	42
C1127178	14	0010100111010100101	CTGTAGATCG	10	43
C1127178	14	1110100101010011001	TACTGAGCGC	10	44
C1127178	14	1101001010111100100	TAGCTCGTAT	10	45
C1127178	14	1100110011001100100	TATATACACA	10	46
C1127178	14	1011001001100110101	TCGCACACTC	10	47
C1127178	14	1010110010011001	TCTATGTGTG	10	48
C1127179	14	0110101101111100000	ACTCGACGTA	10	49
C1127179	14	0101011010011010100	AGACTGTAGA	10	50
C1127179	14	0101010101010110100	AGAGAGACTG	10	51

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127179	14	01001001101011010011	ATGTCTAGCG	10	52
C1127179	14	00100110111011001001	CACTACTATG	10	53
C1127179	14	00110100111100111000	CGATACGCGT	10	54
C1127179	14	00110011001110010011	CGCGCGTGCG	10	55
C1127179	14	00111010011001010110	CGTCACAGAC	10	56
C1127179	14	00111001101010101100	CGTGTCTCTA	10	57
C1127179	14	11110101001001010010	TACGAGCAGC	10	58
C1127179	14	11010010010010111001	TAGCATCGTG	10	59
C1127179	14	11001110011010100100	TATACACTCA	10	60
C1127179	14	10101001100110010110	TCTGTGTGAC	10	61
C1127179	14	10011101111001001000	TGTAGTACAT	10	62
C1127180	14	01101011010010101010	ACTCGATCTC	10	63
C1127180	14	01010110100111010100	AGACTGTAGA	10	64
C1127180	14	01010101010101101001	AGAGAGACTG	10	65
C1127180	14	01001001101011010011	ATGTCTAGCG	10	66
C1127180	14	00100110111011001001	CACTACTATG	10	67
C1127180	14	00110100111100111000	CGATACGCGT	10	68
C1127180	14	00110011001110010011	CGCGCGTGCG	10	69
C1127180	14	00111010011001010110	CGTCACAGAC	10	70
C1127180	14	00111001101010101100	CGTGTCTCTA	10	71
C1127180	14	11110101001001010010	TACGAGCAGC	10	72
C1127180	14	11010010010010111001	TAGCATCGTG	10	73
C1127180	14	11001110011010100100	TATACACTCA	10	74
C1127180	14	10101001100110010110	TCTGTGTGAC	10	75
C1127180	14	10011101111001001000	TGTAGTACAT	10	76
C1127181	14	01100110011100101001	ACACACGCTG	10	77
C1127181	14	01110100101001001101	ACGATCATAG	10	78
C1127181	14	01010101010101100110	AGAGAGACAC	10	79
C1127181	14	01001110110010010110	ATACTATGAC	10	80
C1127181	14	00110011001110010011	CGCGCGTGCG	10	81
C1127181	14	00111001101010101100	CGTGTCTCTA	10	82
C1127181	14	00101111011001011000	CTACGACAGT	10	83
C1127181	14	00101001110101001011	CTGTAGATCG	10	84
C1127181	14	11010010010110101100	TAGCAGTCTA	10	85
C1127181	14	11011001001100111000	TAGTGCGCGT	10	86
C1127181	14	10101100100110011001	TCTATGTGTG	10	87
C1127181	14	10101011001010100110	TCTCGCTCAC	10	88
C1127181	14	10010100111011101000	TGATACTACT	10	89
C1127181	14	10011010110101010100	TGTCTAGAGA	10	90
C1127182	14	01100101101011110000	ACAGTCTACG	10	91
C1127182	14	01010111001001101010	AGACGCACTC	10	92
C1127182	14	01010010111001001101	AGCTACATAG	10	93
C1127182	14	01011010100110010110	AGTCTGTGAC	10	94
C1127182	14	01001101010110011100	ATAGAGTGTA	10	95
C1127182	14	00110011001110010011	CGCGCGTGCG	10	96

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127182	14	00111001101010101100	CGTGTCTCTA	10	97
C1127182	14	00101110110100101001	CTACTAGCTG	10	98
C1127182	14	00101001010101110101	CTGAGACGAG	10	99
C1127182	14	11011001001100111000	TAGTGCGCGT	10	100
C1127182	14	10100111110010010100	TCACGTATGA	10	101
C1127182	14	10111010010101001010	TCGTCAGATC	10	102
C1127182	14	10101100111001100100	TCTATACACA	10	103
C1127182	14	10010100110110110010	TGATAGTCGC	10	104
C1127183	14	01110100101100111000	ACGATCGCGT	10	105
C1127183	14	01101010110010011001	ACTCTATGTG	10	106
C1127183	14	01010010011001101101	AGCACACTAG	10	107
C1127183	14	01001110010101011010	ATACAGAGTC	10	108
C1127183	14	01001100101010100111	ATATCTCACG	10	109
C1127183	14	00100101110011110010	CAGTATACGC	10	110
C1127183	14	00110011001110010011	CGCGCGTGCG	10	111
C1127183	14	00111001101010101100	CGTGTCTCTA	10	112
C1127183	14	00101111111001001000	CTACGTACAT	10	113
C1127183	14	11001111001010010100	TATACGCTGA	10	114
C1127183	14	10110110010010101010	TCGACATCTC	10	115
C1127183	14	10110010110101100100	TCGCTAGACA	10	116
C1127183	14	10010101100100110110	TGAGTGCGAC	10	117
C1127183	14	10011001010111011000	TGTGAGTAGT	10	118
C1127184	14	01100111001010100110	ACACGCTCAC	10	119
C1127184	14	01110100101100111000	ACGATCGCGT	10	120
C1127184	14	01010111010101010100	AGACGAGAGA	10	121
C1127184	14	01010010100111001110	AGCTGTATAC	10	122
C1127184	14	01001101100101001011	ATAGTGATCG	10	123
C1127184	14	00100110111001101001	CACTACACTG	10	124
C1127184	14	00110011001110010011	CGCGCGTGCG	10	125
C1127184	14	00111101011101100000	CGTAGACGAC	10	126
C1127184	14	00111001101010101100	CGTGTCTCTA	10	127
C1127184	14	11100100110010010101	TACATATGAG	10	128
C1127184	14	10101010101101100100	TCTCTCGACA	10	129
C1127184	14	10101001010100101101	TCTGAGCTAG	10	130
C1127184	14	10010101010011101010	TGAGATACTC	10	131
C1127184	14	10011110100110011000	TGTACTGTGT	10	132
C1127185	14	01100100101110101001	ACATCGTCTG	10	133
C1127185	14	01110010100111011000	ACGCTGTAGT	10	134
C1127185	14	01010101010101100110	AGAGAGACAC	10	135
C1127185	14	01011010010100111100	AGTCAGCGTA	10	136
C1127185	14	01001111001001110100	ATACGCACGA	10	137
C1127185	14	00100100100111010111	CATGTAGACG	10	138
C1127185	14	00110011001110010011	CGCGCGTGCG	10	139
C1127185	14	00111001101010101100	CGTGTCTCTA	10	140
C1127185	14	00101110010010011110	CTACATGTAC	10	141

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C1127185	14	11101110100100101000	TACTACTGCT	10	142
C1127185	14	11010101010010011001	TAGAGATGTG	10	143
C1127185	14	10100101011011010100	TCAGACTAGA	10	144
C1127185	14	10011100101101010010	TGTATCGAGC	10	145
C1127185	14	10011011111001001000	TGTCGTACAT	10	146
C1127186	14	01100100101110101001	ACATCGTCTG	10	147
C1127186	14	01110010100111011000	ACGCTGTAGT	10	148
C1127186	14	01010101010101100110	AGAGAGACAC	10	149
C1127186	14	01011010010100111100	AGTCAGCGTA	10	150
C1127186	14	01001111001001110100	ATACGCACGA	10	151
C1127186	14	00100100100111010111	CATGTAGACG	10	152
C1127186	14	00110011001110010011	CGCGCGTGCG	10	153
C1127186	14	00111001101010101100	CGTGTCTCTA	10	154
C1127186	14	00101110010010011110	CTACATGTAC	10	155
C1127186	14	11101110100100101000	TACTACTGCT	10	156
C1127186	14	11010101010010011001	TAGAGATGTG	10	157
C1127186	14	10100101011011010100	TCAGACTAGA	10	158
C1127186	14	10110010011001101010	TCGCACACTC	10	159
C1127186	14	10011100101101010010	TGTATCGAGC	10	160
C1127187	14	01100111001010100110	ACACGCTCAC	10	161
C1127187	14	01110010100111011000	ACGCTGTAGT	10	162
C1127187	14	01011010010010111010	AGTCATCGTC	10	163
C1127187	14	01011001010101100101	AGTGAGACAG	10	164
C1127187	14	01001101010110011100	ATAGAGTGTA	10	165
C1127187	14	00100110010011110101	CACATACGAG	10	166
C1127187	14	00110011001110010011	CGCGCGTGCG	10	167
C1127187	14	00111001101010101100	CGTGTCTCTA	10	168
C1127187	14	00101010110101101010	CTCTAGACTC	10	169
C1127187	14	11001110101001010100	TATACTCAGA	10	170
C1127187	14	11001011110010110000	TATCGTATCG	10	171
C1127187	14	10111110010011001000	TCGTACATAT	10	172
C1127187	14	10101001100110010110	TCTGTGTGAC	10	173
C1127187	14	10010111011100101000	TGACGACGCT	10	174
C1127188	14	01100100101110101001	ACATCGTCTG	10	175
C1127188	14	01110010011101001100	ACGCACGATA	10	176
C1127188	14	01010101110100111000	AGAGTAGCGT	10	177
C1127188	14	01011110011001101000	AGTACACACT	10	178
C1127188	14	01011010100110010110	AGTCTGTGAC	10	179
C1127188	14	00100110111011010010	CACTACTAGC	10	180
C1127188	14	00110011001110010011	CGCGCGTGCG	10	181
C1127188	14	00111001101010101100	CGTGTCTCTA	10	182
C1127188	14	00101110010110011100	CTACAGTGTA	10	183
C1127188	14	00101001110101001011	CTGTAGATCG	10	184
C1127188	14	11001011001101011000	TATCGCGAGT	10	185
C1127188	14	10110110010100100101	TCGACAGCAG	10	186

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127188	14	10101010010011110100	TCTCATACGA	10	187
C1127188	14	10010101010011001110	TGAGATATAC	10	188
C1127189	14	01100101001010110110	ACAGCTCGAC	10	189
C1127189	14	01101011010011100100	ACTCGATACA	10	190
C1127189	14	01010100110101101100	AGATAGACTA	10	191
C1127189	14	01010011001110011001	AGCGCGTGTG	10	192
C1127189	14	01001001101011010011	ATGTCTAGCG	10	193
C1127189	14	00100111110111001000	CACGTAGTAT	10	194
C1127189	14	00110110011100100101	CGACACGCAG	10	195
C1127189	14	00111001010101010110	CGTGAGAGAC	10	196
C1127189	14	00111001101010101100	CGTGTCTCTA	10	197
C1127189	14	11101100101100101000	TACTATCGCT	10	198
C1127189	14	11011001001001100101	TAGTGCACAG	10	199
C1127189	14	10110010010101111000	TCGCAGACGT	10	200
C1127189	14	10101110100110010100	TCTACTGTGA	10	201
C1127189	14	10010111101001001010	TGACGTCATC	10	202
C1127190	14	01100101011001001101	ACAGACATAG	10	203
C1127190	14	01110011001110011000	ACGCGCGTGT	10	204
C1127190	14	01010111001001101010	AGACGCACTC	10	205
C1127190	14	01010010110010110101	AGCTATCGAG	10	206
C1127190	14	01001100100110011110	ATATGTGTAC	10	207
C1127190	14	01001001110101111000	ATGTAGACGT	10	208
C1127190	14	00100110101110100110	CACTCGTCAC	10	209
C1127190	14	00111001010101010110	CGTGAGAGAC	10	210
C1127190	14	00111001101010101100	CGTGTCTCTA	10	211
C1127190	14	00101010011011011001	CTCACTAGTG	10	212
C1127190	14	11101100110010101000	TACTATATCT	10	213
C1127190	14	11001110101001010100	TATACTCAGA	10	214
C1127190	14	10110010010111100100	TCGCAGTACA	10	215
C1127190	14	10010101100100110011	TGAGTGCGCG	10	216
C1127191	14	01100101011010011010	ACAGACTGTC	10	217
C1127191	14	01010011001111100100	AGCGCGTACA	10	218
C1127191	14	01011011010100101001	AGTCGAGCTG	10	219
C1127191	14	01001110110101010010	ATACTAGAGC	10	220
C1127191	14	01001011101001111000	ATCGTCACGT	10	221
C1127191	14	00110101001001110011	CGAGCACGCG	10	222
C1127191	14	00111001010101010110	CGTGAGAGAC	10	223
C1127191	14	00111001101010101100	CGTGTCTCTA	10	224
C1127191	14	00101010010010111101	CTCATCGTAG	10	225
C1127191	14	11100110101100101000	TACACTCGCT	10	226
C1127191	14	11001001110111001000	TATGTAGTAT	10	227
C1127191	14	10110010100110011001	TCGCTGTGTG	10	228
C1127191	14	10101100111001100100	TCTATACACA	10	229
C1127191	14	10010111101001001010	TGACGTCATC	10	230
C1127192	14	01101001100101001011	ACTGTGATCG	10	231

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127192	14	01010011001111100100	AGCGCGTACA	10	232
C1127192	14	01011110100110011000	AGTACTGTGT	10	233
C1127192	14	01001110101001100110	ATACTCACAC	10	234
C1127192	14	00100110010111011100	CACAGTAGTA	10	235
C1127192	14	00110101001001110011	CGAGCACGCG	10	236
C1127192	14	00111001010101010110	CGTGAGAGAC	10	237
C1127192	14	00111001101010101100	CGTGTCTCTA	10	238
C1127192	14	00101010010010101111	CTCATCTACG	10	239
C1127192	14	10110010110010010101	TCGCTATGAG	10	240
C1127192	14	10101100111001001100	TCTATACATA	10	241
C1127192	14	10101011001100111000	TCTCGCGCGT	10	242
C1127192	14	10010111011011001000	TGACGACTAT	10	243
C1127192	14	10010100110110110010	TGATAGTCGC	10	244
C1127193	14	01101001100101001011	ACTGTGATCG	10	245
C1127193	14	01010011001111100100	AGCGCGTACA	10	246
C1127193	14	01011110100110011000	AGTACTGTGT	10	247
C1127193	14	00100110010111011100	CACAGTAGTA	10	248
C1127193	14	00110101001001110011	CGAGCACGCG	10	249
C1127193	14	00111001010101010110	CGTGAGAGAC	10	250
C1127193	14	00111001101010101100	CGTGTCTCTA	10	251
C1127193	14	00101010010010101111	CTCATCTACG	10	252
C1127193	14	11010010101001101010	TAGCTCACTC	10	253
C1127193	14	10110010110010010101	TCGCTATGAG	10	254
C1127193	14	10101100111001001100	TCTATACATA	10	255
C1127193	14	10101011001100111000	TCTCGCGCGT	10	256
C1127193	14	10010111011011001000	TGACGACTAT	10	257
C1127193	14	10010100110110110010	TGATAGTCGC	10	258
C1127194	14	01101001100101001011	ACTGTGATCG	10	259
C1127194	14	01010011001111100100	AGCGCGTACA	10	260
C1127194	14	01011100111001011000	AGTATACAGT	10	261
C1127194	14	00100100111110011001	CATACGTGTG	10	262
C1127194	14	00110101001001110011	CGAGCACGCG	10	263
C1127194	14	00111001010101010110	CGTGAGAGAC	10	264
C1127194	14	00111001101010101100	CGTGTCTCTA	10	265
C1127194	14	00101010010010101111	CTCATCTACG	10	266
C1127194	14	11100100110101001100	TACATAGATA	10	267
C1127194	14	11010010101001101010	TAGCTCACTC	10	268
C1127194	14	10110010110010010101	TCGCTATGAG	10	269
C1127194	14	10101011001100111000	TCTCGCGCGT	10	270
C1127194	14	10010111011011001000	TGACGACTAT	10	271
C1127194	14	10010100110110110010	TGATAGTCGC	10	272
C1127195	14	01101110101001010100	ACTACTCAGA	10	273
C1127195	14	01101001100101001011	ACTGTGATCG	10	274
C1127195	14	01010011001111100100	AGCGCGTACA	10	275
C1127195	14	00100100111110011001	CATACGTGTG	10	276

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127195	14	00110101001001110011	CGAGCACGCG	10	277
C1127195	14	00111001010101010110	CGTGAGAGAC	10	278
C1127195	14	00111001101010101100	CGTGTCTCTA	10	279
C1127195	14	00101010010010101111	CTCATCTACG	10	280
C1127195	14	11100100110101001100	TACATAGATA	10	281
C1127195	14	11010010101001101010	TAGCTCACTC	10	282
C1127195	14	10110010110010010101	TCGCTATGAG	10	283
C1127195	14	10101011001100111000	TCTCGCGCGT	10	284
C1127195	14	10010111011011001000	TGACGACTAT	10	285
C1127195	14	10010100110110110010	TGATAGTCGC	10	286
C1127196	14	01100101011010011010	ACAGACTGTC	10	287
C1127196	14	01101011001100101001	ACTCGCGCTG	10	288
C1127196	14	01010011001111100100	AGCGCGTACA	10	289
C1127196	14	01011100111001001001	AGTATACATG	10	290
C1127196	14	01001110010110110100	ATACAGTCGA	10	291
C1127196	14	00100111110111001000	CACGTAGTAT	10	292
C1127196	14	00110101001001110011	CGAGCACGCG	10	293
C1127196	14	00111001010101010110	CGTGAGAGAC	10	294
C1127196	14	00111001101010101100	CGTGTCTCTA	10	295
C1127196	14	00101010010010101111	CTCATCTACG	10	296
C1127196	14	11010010101001101010	TAGCTCACTC	10	297
C1127196	14	11001001100110010011	TATGTGTGCG	10	298
C1127196	14	10110100101110010100	TCGATCGTGA	10	299
C1127196	14	10010110100101001101	TGACTGATAG	10	300
C1127197	14	01100101011001001101	ACAGACATAG	10	301
C1127197	14	01101011001100101001	ACTCGCGCTG	10	302
C1127197	14	01010011001111100100	AGCGCGTACA	10	303
C1127197	14	01011100111001011000	AGTATACAGT	10	304
C1127197	14	01001110010110110100	ATACAGTCGA	10	305
C1127197	14	00100111110111001000	CACGTAGTAT	10	306
C1127197	14	00110101001001110011	CGAGCACGCG	10	307
C1127197	14	00111001010101010110	CGTGAGAGAC	10	308
C1127197	14	00111001101010101100	CGTGTCTCTA	10	309
C1127197	14	00101010010010101111	CTCATCTACG	10	310
C1127197	14	11010100110010101010	TAGATATCTC	10	311
C1127197	14	11001001100110010011	TATGTGTGCG	10	312
C1127197	14	10110100101110010100	TCGATCGTGA	10	313
C1127197	14	10011110100101001001	TGTACTGATG	10	314
C1127198	14	01100101011001001101	ACAGACATAG	10	315
C1127198	14	01101011001100101001	ACTCGCGCTG	10	316
C1127198	14	01010011001111100100	AGCGCGTACA	10	317
C1127198	14	01011100111001011000	AGTATACAGT	10	318
C1127198	14	01001110010110110100	ATACAGTCGA	10	319
C1127198	14	00100111110111001000	CACGTAGTAT	10	320
C1127198	14	00110101001001110011	CGAGCACGCG	10	321

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127198	14	00111001010101010110	CGTGAGAGAC	10	322
C1127198	14	00111001101010101100	CGTGTCTCTA	10	323
C1127198	14	00101010010010101111	CTCATCTACG	10	324
C1127198	14	11010010110100101010	TAGCTAGCTC	10	325
C1127198	14	11001001100110010011	TATGTGTGCG	10	326
C1127198	14	10110100101110010100	TCGATCGTGA	10	327
C1127198	14	10011110100101001001	TGTACTGATG	10	328
C1127199	14	01100101011001001101	ACAGACATAG	10	329
C1127199	14	01101011001100101001	ACTCGCGCTG	10	330
C1127199	14	01010011001111100100	AGCGCGTACA	10	331
C1127199	14	01011100111001011000	AGTATACAGT	10	332
C1127199	14	01001110010110110100	ATACAGTCGA	10	333
C1127199	14	00100111110111001000	CACGTAGTAT	10	334
C1127199	14	00110101001001110011	CGAGCACGCG	10	335
C1127199	14	00111001010101010110	CGTGAGAGAC	10	336
C1127199	14	00111001101010101100	CGTGTCTCTA	10	337
C1127199	14	00101010010010101111	CTCATCTACG	10	338
C1127199	14	11010010101001101010	TAGCTCACTC	10	339
C1127199	14	11001001100110010011	TATGTGTGCG	10	340
C1127199	14	10110100101110010100	TCGATCGTGA	10	341
C1127199	14	10011110100101001001	TGTACTGATG	10	342
C1127200	14	01100101011001001101	ACAGACATAG	10	343
C1127200	14	01101011001100101001	ACTCGCGCTG	10	344
C1127200	14	01010011001111100100	AGCGCGTACA	10	345
C1127200	14	01001110010110110100	ATACAGTCGA	10	346
C1127200	14	00100111110111001000	CACGTAGTAT	10	347
C1127200	14	00110101001001110011	CGAGCACGCG	10	348
C1127200	14	00111001010101010110	CGTGAGAGAC	10	349
C1127200	14	00111001101010101100	CGTGTCTCTA	10	350
C1127200	14	00101010010010101111	CTCATCTACG	10	351
C1127200	14	11010100110010101010	TAGATATCTC	10	352
C1127200	14	11010011011001011000	TAGCGACAGT	10	353
C1127200	14	11001001100110010011	TATGTGTGCG	10	354
C1127200	14	10110100101110010100	TCGATCGTGA	10	355
C1127200	14	10011110100101001001	TGTACTGATG	10	356
C1127201	14	01101011001100101001	ACTCGCGCTG	10	357
C1127201	14	01010011001111100100	AGCGCGTACA	10	358
C1127201	14	01001110010110110100	ATACAGTCGA	10	359
C1127201	14	01001010111001100110	ATCTACACAC	10	360
C1127201	14	00100111110111001000	CACGTAGTAT	10	361
C1127201	14	00110101001001110011	CGAGCACGCG	10	362
C1127201	14	00111001010101010110	CGTGAGAGAC	10	363
C1127201	14	00111001101010101100	CGTGTCTCTA	10	364
C1127201	14	00101010010010101111	CTCATCTACG	10	365
C1127201	14	11010100110010101010	TAGATATCTC	10	366

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127201	14	11010011011001011000	TAGCGACAGT	10	367
C1127201	14	11001001100110010011	TATGTGTGCG	10	368
C1127201	14	10110100101110010100	TCGATCGTGA	10	369
C1127201	14	10011110100101001001	TGTACTGATG	10	370
C1127202	14	01100101011001001101	ACAGACATAG	10	371
C1127202	14	01101011001100101001	ACTCGCGCTG	10	372
C1127202	14	01101010110010010110	ACTCTATGAC	10	373
C1127202	14	01010011001111100100	AGCGCGTACA	10	374
C1127202	14	01011100111001011000	AGTATACAGT	10	375
C1127202	14	01001110010110110100	ATACAGTCGA	10	376
C1127202	14	00100111110111001000	CACGTAGTAT	10	377
C1127202	14	00110101001001110011	CGAGCACGCG	10	378
C1127202	14	00111001010101010110	CGTGAGAGAC	10	379
C1127202	14	00111001101010101100	CGTGTCTCTA	10	380
C1127202	14	11010100110010101010	TAGATATCTC	10	381
C1127202	14	11001001100110010011	TATGTGTGCG	10	382
C1127202	14	10110100101110010100	TCGATCGTGA	10	383
C1127202	14	10011110100101001001	TGTACTGATG	10	384
C1127203	14	01100101011001001101	ACAGACATAG	10	385
C1127203	14	01101011001100101001	ACTCGCGCTG	10	386
C1127203	14	01101010110010010110	ACTCTATGAC	10	387
C1127203	14	01010011001111100100	AGCGCGTACA	10	388
C1127203	14	01011100111001011000	AGTATACAGT	10	389
C1127203	14	01001110010110110100	ATACAGTCGA	10	390
C1127203	14	00100111110111001000	CACGTAGTAT	10	391
C1127203	14	00110101001001110011	CGAGCACGCG	10	392
C1127203	14	00111001010101010110	CGTGAGAGAC	10	393
C1127203	14	00111001101010101100	CGTGTCTCTA	10	394
C1127203	14	11010010110100101010	TAGCTAGCTC	10	395
C1127203	14	11001001100110010011	TATGTGTGCG	10	396
C1127203	14	10110100101110010100	TCGATCGTGA	10	397
C1127203	14	10011110100101001001	TGTACTGATG	10	398
C1127204	14	01100101011001001101	ACAGACATAG	10	399
C1127204	14	01101011001100101001	ACTCGCGCTG	10	400
C1127204	14	01101010110010010110	ACTCTATGAC	10	401
C1127204	14	01010011001111100100	AGCGCGTACA	10	402
C1127204	14	01011100111001011000	AGTATACAGT	10	403
C1127204	14	01001110010110110100	ATACAGTCGA	10	404
C1127204	14	00100111110111001000	CACGTAGTAT	10	405
C1127204	14	00110101001001110011	CGAGCACGCG	10	406
C1127204	14	00111001010101010110	CGTGAGAGAC	10	407
C1127204	14	00111001101010101100	CGTGTCTCTA	10	408
C1127204	14	11010010101001101010	TAGCTCACTC	10	409
C1127204	14	11001001100110010011	TATGTGTGCG	10	410
C1127204	14	10110100101110010100	TCGATCGTGA	10	411

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127204	14	10011110100101001001	TGTACTGATG	10	412
C1127205	14	01100101011001001101	ACAGACATAG	10	413
C1127205	14	01101011001100101001	ACTCGCGCTG	10	414
C1127205	14	01101010110010010110	ACTCTATGAC	10	415
C1127205	14	01010011001111100100	AGCGCGTACA	10	416
C1127205	14	01001110010110110100	ATACAGTCGA	10	417
C1127205	14	00100111110111001000	CACGTAGTAT	10	418
C1127205	14	00110101001001110011	CGAGCACGCG	10	419
C1127205	14	00111001010101010110	CGTGAGAGAC	10	420
C1127205	14	00111001101010101100	CGTGTCTCTA	10	421
C1127205	14	11010100110010101010	TAGATATCTC	10	422
C1127205	14	11001011011001011000	TATCGACAGT	10	423
C1127205	14	11001001100110010011	TATGTGTGCG	10	424
C1127205	14	10110100101110010100	TCGATCGTGA	10	425
C1127205	14	10011110100101001001	TGTACTGATG	10	426
C1127206	14	01100101011001001101	ACAGACATAG	10	427
C1127206	14	01101011001100101001	ACTCGCGCTG	10	428
C1127206	14	01101010110010010110	ACTCTATGAC	10	429
C1127206	14	01010011001111100100	AGCGCGTACA	10	430
C1127206	14	01001110010110110100	ATACAGTCGA	10	431
C1127206	14	00100111110111001000	CACGTAGTAT	10	432
C1127206	14	00110101001001110011	CGAGCACGCG	10	433
C1127206	14	00111001010101010110	CGTGAGAGAC	10	434
C1127206	14	00111001101010101100	CGTGTCTCTA	10	435
C1127206	14	11010010110100101010	TAGCTAGCTC	10	436
C1127206	14	11001011011001011000	TATCGACAGT	10	437
C1127206	14	11001001100110010011	TATGTGTGCG	10	438
C1127206	14	10110100101110010100	TCGATCGTGA	10	439
C1127206	14	10011110100101001001	TGTACTGATG	10	440
C1127207	14	01100101011001001101	ACAGACATAG	10	441
C1127207	14	01101011001100101001	ACTCGCGCTG	10	442
C1127207	14	01101010110010010110	ACTCTATGAC	10	443
C1127207	14	01010011001111100100	AGCGCGTACA	10	444
C1127207	14	01001110010110110100	ATACAGTCGA	10	445
C1127207	14	00100111110111001000	CACGTAGTAT	10	446
C1127207	14	00110101001001110011	CGAGCACGCG	10	447
C1127207	14	00111001010101010110	CGTGAGAGAC	10	448
C1127207	14	00111001101010101100	CGTGTCTCTA	10	449
C1127207	14	11010100110010101010	TAGATATCTC	10	450
C1127207	14	11010011011001011000	TAGCGACAGT	10	451
C1127207	14	11001001100110010011	TATGTGTGCG	10	452
C1127207	14	10110100101110010100	TCGATCGTGA	10	453
C1127207	14	10011110100101001001	TGTACTGATG	10	454
C1127208	14	01100100110011110010	ACATATACGC	10	455
C1127208	14	01101011001100101001	ACTCGCGCTG	10	456

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127208	14	01010011001111100100	AGCGCGTACA	10	457
C1127208	14	01011110100110011000	AGTACTGTGT	10	458
C1127208	14	00100110010111011100	CACAGTAGTA	10	459
C1127208	14	00110101001001110011	CGAGCACGCG	10	460
C1127208	14	00111001010101010110	CGTGAGAGAC	10	461
C1127208	14	00111001101010101100	CGTGTCTCTA	10	462
C1127208	14	00101010111001001011	CTCTACATCG	10	463
C1127208	14	11010010110100101010	TAGCTAGCTC	10	464
C1127208	14	11001011011001011000	TATCGACAGT	10	465
C1127208	14	11001001100110010011	TATGTGTGCG	10	466
C1127208	14	10110100101110010100	TCGATCGTGA	10	467
C1127208	14	10010010011010110110	TGCACTCGAC	10	468
C1127209	14	01101011001100101001	ACTCGCGCTG	10	469
C1127209	14	01010011001111100100	AGCGCGTACA	10	470
C1127209	14	01001101101011011000	ATAGTCTAGT	10	471
C1127209	14	01001010010011100111	ATCATACACG	10	472
C1127209	14	00100111110111001000	CACGTAGTAT	10	473
C1127209	14	00110101001001110011	CGAGCACGCG	10	474
C1127209	14	00111001010101010110	CGTGAGAGAC	10	475
C1127209	14	00111001101010101100	CGTGTCTCTA	10	476
C1127209	14	00101110100101110100	CTACTGACGA	10	477
C1127209	14	11010100110010101010	TAGATATCTC	10	478
C1127209	14	11001111001001001100	TATACGCATA	10	479
C1127209	14	11001001100110010011	TATGTGTGCG	10	480
C1127209	14	10110100101110010100	TCGATCGTGA	10	481
C1127209	14	10010010011010110110	TGCACTCGAC	10	482
C1127210	14	01100101011001001101	ACAGACATAG	10	483
C1127210	14	01101011001100101001	ACTCGCGCTG	10	484
C1127210	14	01010011001111100100	AGCGCGTACA	10	485
C1127210	14	01011100111001011000	AGTATACAGT	10	486
C1127210	14	01001110010110110100	ATACAGTCGA	10	487
C1127210	14	00100111110111001000	CACGTAGTAT	10	488
C1127210	14	00110101001001110011	CGAGCACGCG	10	489
C1127210	14	00111001010101010110	CGTGAGAGAC	10	490
C1127210	14	00111001101010101100	CGTGTCTCTA	10	491
C1127210	14	00101010010010101111	CTCATCTACG	10	492
C1127210	14	11010100110010101010	TAGATATCTC	10	493
C1127210	14	11001001100110010011	TATGTGTGCG	10	494
C1127210	14	10110010101101011000	TCGCTCGAGT	10	495
C1127210	14	10101110100100100110	TCTACTGCAC	10	496
C1127211	14	01100101011001001101	ACAGACATAG	10	497
C1127211	14	01101011001100101001	ACTCGCGCTG	10	498
C1127211	14	01010011001111100100	AGCGCGTACA	10	499
C1127211	14	01011100111001011000	AGTATACAGT	10	500
C1127211	14	01001110010110110100	ATACAGTCGA	10	501

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127211	14	00100111110111001000	CACGTAGTAT	10	502
C1127211	14	00110101001001110011	CGAGCACGCG	10	503
C1127211	14	00111001010101010110	CGTGAGAGAC	10	504
C1127211	14	00111001101010101100	CGTGTCTCTA	10	505
C1127211	14	00101010010010101111	CTCATCTACG	10	506
C1127211	14	11010100110010101010	TAGATATCTC	10	507
C1127211	14	11001001100110010011	TATGTGTGCG	10	508
C1127211	14	10110010101101011000	TCGCTCGAGT	10	509
C1127211	14	10011110100101001001	TGTACTGATG	10	510
C1127212	14	01100101011001001101	ACAGACATAG	10	511
C1127212	14	01101011001100101001	ACTCGCGCTG	10	512
C1127212	14	01101010110010010110	ACTCTATGAC	10	513
C1127212	14	01010011001111100100	AGCGCGTACA	10	514
C1127212	14	01011100111001011000	AGTATACAGT	10	515
C1127212	14	01001110010110110100	ATACAGTCGA	10	516
C1127212	14	00100111110111001000	CACGTAGTAT	10	517
C1127212	14	00110101001001110011	CGAGCACGCG	10	518
C1127212	14	00111001010101010110	CGTGAGAGAC	10	519
C1127212	14	00111001101010101100	CGTGTCTCTA	10	520
C1127212	14	11010100110010101010	TAGATATCTC	10	521
C1127212	14	11001001100110010011	TATGTGTGCG	10	522
C1127212	14	10110010101101011000	TCGCTCGAGT	10	523
C1127212	14	10011110100101001001	TGTACTGATG	10	524
C1127213	14	01100111011010010010	ACACGACTGC	10	525
C1127213	14	01011100111001011000	AGTATACAGT	10	526
C1127213	14	01001110101001001011	ATACTCATCG	10	527
C1127213	14	01001011010011101100	ATCGATACTA	10	528
C1127213	14	00110101001001110011	CGAGCACGCG	10	529
C1127213	14	00111001010101010110	CGTGAGAGAC	10	530
C1127213	14	00111001101010101100	CGTGTCTCTA	10	531
C1127213	14	00101110010110011100	CTACAGTGTA	10	532
C1127213	14	00101010111100100110	CTCTACGCAC	10	533
C1127213	14	11010010101010010110	TAGCTCTGAC	10	534
C1127213	14	10100110010011010101	TCACATAGAG	10	535
C1127213	14	10101001100110010011	TCTGTGTGCG	10	536
C1127213	14	10010100110110110010	TGATAGTCGC	10	537
C1127213	14	10011011001101001001	TGTCGCGATG	10	538
C1127214	14	01100110101010011010	ACACTCTGTC	10	539
C1127214	14	01011100111001011000	AGTATACAGT	10	540
C1127214	14	01001101001110100101	ATAGCGTCAG	10	541
C1127214	14	01001011010011101100	ATCGATACTA	10	542
C1127214	14	00110101001001110011	CGAGCACGCG	10	543
C1127214	14	00111001010101010110	CGTGAGAGAC	10	544
C1127214	14	00111001101010101100	CGTGTCTCTA	10	545
C1127214	14	00101111010110011000	CTACGAGTGT	10	546

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C1127214	14	00101010111100100110	CTCTACGCAC	10	547
C1127214	14	11101001011001001010	TACTGACATC	10	548
C1127214	14	10100110010011010101	TCACATAGAG	10	549
C1127214	14	10101001100110010011	TCTGTGTGCG	10	550
C1127214	14	10010100110110110010	TGATAGTCGC	10	551
C1127214	14	10011011001101001001	TGTCGCGATG	10	552
C1127215	14	01100100111010111000	ACATACTCGT	10	553
C1127215	14	01010010101111010100	AGCTCGTAGA	10	554
C1127215	14	01011100100110010011	AGTATGTGCG	10	555
C1127215	14	01001010100101111010	ATCTGACGTC	10	556
C1127215	14	00110101001001110011	CGAGCACGCG	10	557
C1127215	14	00111001010101010110	CGTGAGAGAC	10	558
C1127215	14	00111001101010101100	CGTGTCTCTA	10	559
C1127215	14	00101111010110011000	CTACGAGTGT	10	560
C1127215	14	00101010111001100101	CTCTACACAG	10	561
C1127215	14	11100100110101001100	TACATAGATA	10	562
C1127215	14	11010011100100100110	TAGCGTGCAC	10	563
C1127215	14	10100110100110101001	TCACTGTCTG	10	564
C1127215	14	10111010010011101000	TCGTCATACT	10	565
C1127215	14	10011011001101001001	TGTCGCGATG	10	566
C1127216	14	01100100111010110010	ACATACTCGC	10	567
C1127216	14	01010010101111010100	AGCTCGTAGA	10	568
C1127216	14	01011100100110010011	AGTATGTGCG	10	569
C1127216	14	01001010100101111010	ATCTGACGTC	10	570
C1127216	14	00110101001001110011	CGAGCACGCG	10	571
C1127216	14	00111001010101010110	CGTGAGAGAC	10	572
C1127216	14	00111001101010101100	CGTGTCTCTA	10	573
C1127216	14	00101111010110011000	CTACGAGTGT	10	574
C1127216	14	00101010111001100101	CTCTACACAG	10	575
C1127216	14	11100100110101001100	TACATAGATA	10	576
C1127216	14	11010011100100100110	TAGCGTGCAC	10	577
C1127216	14	10100110100110101001	TCACTGTCTG	10	578
C1127216	14	10111010010011101000	TCGTCATACT	10	579
C1127216	14	10011011001101001001	TGTCGCGATG	10	580
C1127217	14	01100110011001101010	ACACACACTC	10	581
C1127217	14	01100100101010011101	ACATCTGTAG	10	582
C1127217	14	01110011001110011000	ACGCGCGTGT	10	583
C1127217	14	01010011010011001110	AGCGATATAC	10	584
C1127217	14	01011101100101010100	AGTAGTGAGA	10	585
C1127217	14	00110101010100110011	CGAGAGCGCG	10	586
C1127217	14	00111010010011111000	CGTCATACGT	10	587
C1127217	14	00111001101010101100	CGTGTCTCTA	10	588
C1127217	14	00101110110110101000	CTACTAGTCT	10	589
C1127217	14	00101011001101100101	CTCGCGACAG	10	590
C1127217	14	11010110101101001000	TAGACTCGAT	10	591

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127217	14	1100100101010101011010	TATGAGAGTC	10	592
C1127217	14	1001001010011101011	TGCTGTAGCG	10	593
C1127217	14	1001111100101001010	TGTACGCTGC	10	594
C1127218	14	0110010010101001101	ACATCTGTAG	10	595
C1127218	14	0111001100111001100	ACGCGCGTGT	10	596
C1127218	14	0101001101001100111	AGCGATATAC	10	597
C1127218	14	0101110110010101010	AGTAGTGAGA	10	598
C1127218	14	0011010101010011001	CGAGAGCGCG	10	599
C1127218	14	0011101001001111100	CGTCATACGT	10	600
C1127218	14	0011100110101010110	CGTGTCTCTA	10	601
C1127218	14	0010111011010101000	CTACTAGTCT	10	602
C1127218	14	0010101100110110010	CTCGCGACAG	10	603
C1127218	14	1101011010110100100	TAGACTCGAT	10	604
C1127218	14	1100110011100110010	TATATACACA	10	605
C1127218	14	1010011001010101100	TCACAGAGTA	10	606
C1127218	14	1001001010011101001	TGCTGTAGCG	10	607
C1127218	14	1001111100101001001	TGTACGCTGC	10	608
C1127219	14	0111001100111001100	ACGCGCGTGT	10	609
C1127219	14	0101010101100100111	AGAGACATAC	10	610
C1127219	14	0100110111010101000	ATAGTAGTCT	10	611
C1127219	14	0100101010010111010	ATCTGACGAG	10	612
C1127219	14	0010011100101100101	CACGCTATCG	10	613
C1127219	14	0011010101010011001	CGAGAGCGCG	10	614
C1127219	14	0011101001001111100	CGTCATACGT	10	615
C1127219	14	0011100110101010110	CGTGTCTCTA	10	616
C1127219	14	0010101001111010011	CTCACGTCAC	10	617
C1127219	14	1101001010101001011	TAGCTCTGAC	10	618
C1127219	14	1100111001001001	TATACATGTG	10	619
C1127219	14	1010011010010101	TCACTGAGTA	10	620
C1127219	14	1010110011100110010	TCTATACACA	10	621
C1127219	14	1001001111010100	TGCGTAGATG	10	622
C1127220	14	0110011001001100	ACACATATAG	10	623
C1127220	14	0111001100111001100	ACGCGCGTGT	10	624
C1127220	14	0101011100100110	AGACGCACTC	10	625
C1127220	14	0100110011111010010	ATATACGTCA	10	626
C1127220	14	0100100110101101001	ATGTCTAGCG	10	627
C1127220	14	0011010101010011001	CGAGAGCGCG	10	628
C1127220	14	0011001010110110010	CGCTCGACAG	10	629
C1127220	14	0011100110101010110	CGTGTCTCTA	10	630
C1127220	14	0010101111010100101	CTCGTAGATC	10	631
C1127220	14	1110100101010010110	TACTGAGCTA	10	632
C1127220	14	1101001101001001011	TAGCGATGAC	10	633
C1127220	14	1010110010011001	TCTATGTGTG	10	634
C1127220	14	1010101001101011001	TCTCACTCGC	10	635
C1127220	14	1001010111100101100	TGAGTACAGT	10	636

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127221	14	01100110010011001101	ACACATATAG	10	637
C1127221	14	01110011001110011000	ACGCGCGTGT	10	638
C1127221	14	01010111001001101010	AGACGCACTC	10	639
C1127221	14	01001100111110100100	ATATACGTCA	10	640
C1127221	14	01001001101011010011	ATGTCTAGCG	10	641
C1127221	14	00110101010100110011	CGAGAGCGCG	10	642
C1127221	14	00110010101101100101	CGCTCGACAG	10	643
C1127221	14	00111001101010101100	CGTGTCTCTA	10	644
C1127221	14	00101011110101001010	CTCGTAGATC	10	645
C1127221	14	11101001010100101100	TACTGAGCTA	10	646
C1127221	14	11010011010010010110	TAGCGATGAC	10	647
C1127221	14	10101100100110011001	TCTATGTGTG	10	648
C1127221	14	10101010011010110010	TCTCACTCGC	10	649
C1127221	14	10010101111001010100	TGAGTACAGA	10	650
C1127222	14	01100100110011100101	ACATATACAG	10	651
C1127222	14	01110011001110011000	ACGCGCGTGT	10	652
C1127222	14	01010111001001101010	AGACGCACTC	10	653
C1127222	14	01001001011011010011	ATGACTAGCG	10	654
C1127222	14	00100110010111011100	CACAGTAGTA	10	655
C1127222	14	00110101010100110011	CGAGAGCGCG	10	656
C1127222	14	00110010111010010110	CGCTACTGAC	10	657
C1127222	14	00111001101010101100	CGTGTCTCTA	10	658
C1127222	14	00101011001101100101	CTCGCGACAG	10	659
C1127222	14	11100100101101010010	TACATCGAGC	10	660
C1127222	14	11011110101110000000	TAGTACTCGT	10	661
C1127222	14	10101110011010100100	TCTACACTCA	10	662
C1127222	14	10101100100110011001	TCTATGTGTG	10	663
C1127222	14	10011010010101001110	TGTCAGATAC	10	664
C1127223	14	01100110011001101010	ACACACACTC	10	665
C1127223	14	01100100101010011101	ACATCTGTAG	10	666
C1127223	14	01110011001110011000	ACGCGCGTGT	10	667
C1127223	14	01010011010011001110	AGCGATATAC	10	668
C1127223	14	01011101100101010100	AGTAGTGAGA	10	669
C1127223	14	00110101010100110011	CGAGAGCGCG	10	670
C1127223	14	00111001101010101100	CGTGTCTCTA	10	671
C1127223	14	00101110110110101000	CTACTAGTCT	10	672
C1127223	14	00101011001101100101	CTCGCGACAG	10	673
C1127223	14	11010110101101001000	TAGACTCGAT	10	674
C1127223	14	11001010010010100111	TATCATCACG	10	675
C1127223	14	11001001010101011010	TATGAGAGTC	10	676
C1127223	14	10010010100111010011	TGCTGTAGCG	10	677
C1127223	14	10011111001010010010	TGTACGCTGC	10	678
C1127224	14	01100110101010100101	ACACTCTCAG	10	679
C1127224	14	01110011001110011000	ACGCGCGTGT	10	680
C1127224	14	01111101011001001000	ACGTAGACAT	10	681

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127224	14	01010110010111001100	AGACAGTATA	10	682
C1127224	14	01011100100110010011	AGTATGTGCG	10	683
C1127224	14	00110101001100100111	CGAGCGCACG	10	684
C1127224	14	00111001101010101100	CGTGTCTCTA	10	685
C1127224	14	00101111010010101010	CTACGATCTC	10	686
C1127224	14	00101010111101010100	CTCTACGAGA	10	687
C1127224	14	11011010011100100100	TAGTCACGCA	10	688
C1127224	14	11001101001001011001	TATAGCAGTG	10	689
C1127224	14	10111010100101001010	TCGTCTGATC	10	690
C1127224	14	10101001010011001101	TCTGATATAG	10	691
C1127224	14	10010010011011111000	TGCACTACGT	10	692
C1127225	14	01100101101100100110	ACAGTCGCAC	10	693
C1127225	14	01110011001110011000	ACGCGCGTGT	10	694
C1127225	14	01010110100110010101	AGACTGTGAG	10	695
C1127225	14	01011100111001001001	AGTATACATG	10	696
C1127225	14	00100110111011010010	CACTACTAGC	10	697
C1127225	14	00110101001001110011	CGAGCACGCG	10	698
C1127225	14	00111001101010101100	CGTGTCTCTA	10	699
C1127225	14	00101111001101001100	CTACGCGATA	10	700
C1127225	14	00101010010110011011	CTCAGTGTCG	10	701
C1127225	14	11001011001010100101	TATCGCTCAG	10	702
C1127225	14	11001001110110010100	TATGTAGTGA	10	703
C1127225	14	10110010010011110100	TCGCATACGA	10	704
C1127225	14	10010101010011001110	TGAGATATAC	10	705
C1127225	14	10011011010101101000	TGTCGAGACT	10	706
C1127226	14	01100100111011001001	ACATACTATG	10	707
C1127226	14	01110011001110011000	ACGCGCGTGT	10	708
C1127226	14	01011101010011011000	AGTAGATAGT	10	709
C1127226	14	01001001100101110110	ATGTGACGAC	10	710
C1127226	14	00100101010010111110	CAGATCGTAC	10	711
C1127226	14	00110101001001110011	CGAGCACGCG	10	712
C1127226	14	00111001101010101100	CGTGTCTCTA	10	713
C1127226	14	00101111001101001100	CTACGCGATA	10	714
C1127226	14	00101010010110011011	CTCAGTGTCG	10	715
C1127226	14	11010110011010010100	TAGACACTGA	10	716
C1127226	14	11001010110100111000	TATCTAGCGT	10	717
C1127226	14	10111100100101010100	TCGTATGAGA	10	718
C1127226	14	10101011001010100110	TCTCGCTCAC	10	719
C1127226	14	10010010110011101010	TGCTATACTC	10	720
C1127227	14	01100101101100100110	ACAGTCGCAC	10	721
C1127227	14	01110011001110011000	ACGCGCGTGT	10	722
C1127227	14	01011100110101100100	AGTATAGACA	10	723
C1127227	14	01001001011011100101	ATGACTACAG	10	724
C1127227	14	00100111110101001001	CACGTAGATG	10	725
C1127227	14	00110101010100110101	CGAGAGCGAG	10	726

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C1127227	14	00111010010011111000	CGTCATACGT	10	727
C1127227	14	00111001101010101100	CGTGTCTCTA	10	728
C1127227	14	00101010011100101011	CTCACGCTCG	10	729
C1127227	14	11110100101001101000	TACGATCACT	10	730
C1127227	14	11010010010010011101	TAGCATGTAG	10	731
C1127227	14	11001110010100110010	TATACAGCGC	10	732
C1127227	14	10110101010011001010	TCGAGATATC	10	733
C1127227	14	10101001100110010011	TCTGTGTGCG	10	734
C1127228	14	01100101101100100110	ACAGTCGCAC	10	735
C1127228	14	01110011001110011000	ACGCGCGTGT	10	736
C1127228	14	01010110100101011010	AGACTGAGTC	10	737
C1127228	14	01001010111001010101	ATCTACAGAG	10	738
C1127228	14	00100111110101001001	CACGTAGATG	10	739
C1127228	14	00110101010100110101	CGAGAGCGAG	10	740
C1127228	14	00111010010011111000	CGTCATACGT	10	741
C1127228	14	00111001101010101100	CGTGTCTCTA	10	742
C1127228	14	00101010011100101011	CTCACGCTCG	10	743
C1127228	14	11110100101001101000	TACGATCACT	10	744
C1127228	14	11010010010010011101	TAGCATGTAG	10	745
C1127228	14	11001111001001001100	TATACGCATA	10	746
C1127228	14	10110101010011001010	TCGAGATATC	10	747
C1127228	14	10101001100110010011	TCTGTGTGCG	10	748
C1127229	14	01100110110010101001	ACACTATCTG	10	749
C1127229	14	01110011001110011000	ACGCGCGTGT	10	750
C1127229	14	01010011010011001110	AGCGATATAC	10	751
C1127229	14	01011010101101110000	AGTCTCGACG	10	752
C1127229	14	01001110010101011010	ATACAGAGTC	10	753
C1127229	14	00100111100101110010	CACGTGACGC	10	754
C1127229	14	00110101010100110101	CGAGAGCGAG	10	755
C1127229	14	00111001101010101100	CGTGTCTCTA	10	756
C1127229	14	00101010110111010100	CTCTAGTAGA	10	757
C1127229	14	11011010010111001000	TAGTCAGTAT	10	758
C1127229	14	11001100111001100100	TATATACACA	10	759
C1127229	14	10101011001010100110	TCTCGCTCAC	10	760
C1127229	14	10101001100110010011	TCTGTGTGCG	10	761
C1127229	14	10010101001011111000	TGAGCTACGT	10	762
C1127230	14	01110011001110010100	ACGCGCGTGA	10	763
C1127230	14	01101001110101010010	ACTGTAGAGC	10	764
C1127230	14	01010101011001001110	AGAGACATAC	10	765
C1127230	14	01001111100100101010	ATACGTGCTC	10	766
C1127230	14	00100110111001101001	CACTACACTG	10	767
C1127230	14	00110101010100110011	CGAGAGCGCG	10	768
C1127230	14	00111010010011111000	CGTCATACGT	10	769
C1127230	14	00111001101010101100	CGTGTCTCTA	10	770
C1127230	14	00101010010110011101	CTCAGTGTAG	10	771

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127230	14	11010100110110011000	TAGATAGTGT	10	772
C1127230	14	11001011011100100100	TATCGACGCA	10	773
C1127230	14	10101111010011001000	TCTACGATAT	10	774
C1127230	14	10101100101010010011	TCTATCTGCG	10	775
C1127230	14	10010010011010110110	TGCACTCGAC	10	776
C1127231	14	01110011001110010100	ACGCGCGTGA	10	777
C1127231	14	01010111001001101010	AGACGCACTC	10	778
C1127231	14	01011101010111001000	AGTAGAGTAT	10	779
C1127231	14	01001011100101100101	ATCGTGACAG	10	780
C1127231	14	01001001011011010011	ATGACTAGCG	10	781
C1127231	14	00100110011010011101	CACACTGTAG	10	782
C1127231	14	00110101010100110011	CGAGAGCGCG	10	783
C1127231	14	00111010010011111000	CGTCATACGT	10	784
C1127231	14	00111001101010101100	CGTGTCTCTA	10	785
C1127231	14	11011010011100100100	TAGTCACGCA	10	786
C1127231	14	11001010110101001010	TATCTAGATC	10	787
C1127231	14	10100111010011100100	TCACGATACA	10	788
C1127231	14	10101100100110011001	TCTATGTGTG	10	789
C1127231	14	10010010010110110110	TGCAGTCGAC	10	790
C1127232	14	01110011001110010100	ACGCGCGTGA	10	791
C1127232	14	01101001010111101000	ACTGAGTACT	10	792
C1127232	14	01010100101111001010	AGATCGTATC	10	793
C1127232	14	01001110101010100101	ATACTCTCAG	10	794
C1127232	14	01001001111001010011	ATGTACAGCG	10	795
C1127232	14	00110101010100110011	CGAGAGCGCG	10	796
C1127232	14	00110010010111001101	CGCAGTATAG	10	797
C1127232	14	00111001101010101100	CGTGTCTCTA	10	798
C1127232	14	00101111011001001100	CTACGACATA	10	799
C1127232	14	11010101011010011000	TAGAGACTGT	10	800
C1127232	14	11010011100100100110	TAGCGTGCAC	10	801
C1127232	14	10111010110101001000	TCGTCTAGAT	10	802
C1127232	14	10101100100110011001	TCTATGTGTG	10	803
C1127232	14	10101010011010110010	TCTCACTCGC	10	804
C1127233	14	01100101101100100110	ACAGTCGCAC	10	805
C1127233	14	01101001011001011001	ACTGACAGTG	10	806
C1127233	14	01010100110101101100	AGATAGACTA	10	807
C1127233	14	01010011001011100101	AGCGCTACAG	10	808
C1127233	14	01001010110010101011	ATCTATCTCG	10	809
C1127233	14	00110101010100110011	CGAGAGCGCG	10	810
C1127233	14	00111010010011111000	CGTCATACGT	10	811
C1127233	14	00111001101010101100	CGTGTCTCTA	10	812
C1127233	14	00101111100101100100	CTACGTGACA	10	813
C1127233	14	11011110100100101000	TAGTACTGCT	10	814
C1127233	14	11001010101001010110	TATCTCAGAC	10	815
C1127233	14	10100101010111010100	TCAGAGTAGA	10	816

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C1127233	14	10110010100110011001	TCGCTGTGTG	10	817
C1127233	14	10010011011101001010	TGCGACGATC	10	818
C1127234	14	01100110011010011001	ACACACTGTG	10	819
C1127234	14	01110010110101001100	ACGCTAGATA	10	820
C1127234	14	01101001100100111010	ACTGTGCGTC	10	821
C1127234	14	01001111001001110100	ATACGCACGA	10	822
C1127234	14	00110101010100110011	CGAGAGCGCG	10	823
C1127234	14	00110010011110100110	CGCACGTCAC	10	824
C1127234	14	00111010010011111000	CGTCATACGT	10	825
C1127234	14	00111001101010101100	CGTGTCTCTA	10	826
C1127234	14	00101110110110101000	CTACTAGTCT	10	827
C1127234	14	11100100101101010010	TACATCGAGC	10	828
C1127234	14	11011001110011100000	TAGTGTATAC	10	829
C1127234	14	10101100100101100101	TCTATGACAG	10	830
C1127234	14	10010100111001101010	TGATACACTC	10	831
C1127234	14	10011011010110010100	TGTCGAGTGA	10	832
C1127235	14	01110100101010010101	ACGATCTGAG	10	833
C1127235	14	01101011001100101001	ACTCGCGCTG	10	834
C1127235	14	01011100110101100100	AGTATAGACA	10	835
C1127235	14	01001110101001001011	ATACTCATCG	10	836
C1127235	14	01001001100101111010	ATGTGACGTC	10	837
C1127235	14	00100111110111001000	CACGTAGTAT	10	838
C1127235	14	00110101010100110011	CGAGAGCGCG	10	839
C1127235	14	00110010011110100110	CGCACGTCAC	10	840
C1127235	14	00111010010011111000	CGTCATACGT	10	841
C1127235	14	00111001101010101100	CGTGTCTCTA	10	842
C1127235	14	11010100110010101010	TAGATATCTC	10	843
C1127235	14	11010010011101011000	TAGCACGAGT	10	844
C1127235	14	11001101100110010100	TATAGTGTGA	10	845
C1127235	14	10101010100101001110	TCTCTGATAC	10	846
C1127236	14	01100100101010111001	ACATCTCGTG	10	847
C1127236	14	01110010100101100101	ACGCTGACAG	10	848
C1127236	14	01010111001001101010	AGACGCACTC	10	849
C1127236	14	01011110110010011000	AGTACTATGT	10	850
C1127236	14	01001011010101011100	ATCGAGAGTA	10	851
C1127236	14	00100101001110011110	CAGCGTGTAC	10	852
C1127236	14	00110101010100110011	CGAGAGCGCG	10	853
C1127236	14	00111001101010101100	CGTGTCTCTA	10	854
C1127236	14	00101010011001110110	CTCACACGAC	10	855
C1127236	14	11100101010011010010	TACAGATAGC	10	856
C1127236	14	11011010011100100100	TAGTCACGCA	10	857
C1127236	14	10101110100100101010	TCTACTGCTC	10	858
C1127236	14	10010011001110111000	TGCGCGTCGT	10	859
C1127236	14	10011100101001010101	TGTATCAGAG	10	860
C1127237	14	01101010110010100110	ACTCTATCAC	10	861

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C1127237	14	01101001010011011001	ACTGATAGTG	10	862
C1127237	14	01010111001001101010	AGACGCACTC	10	863
C1127237	14	01011101100101010100	AGTAGTGAGA	10	864
C1127237	14	00100101001110011110	CAGCGTGTAC	10	865
C1127237	14	00110101010100110011	CGAGAGCGCG	10	866
C1127237	14	00111001101010101100	CGTGTCTCTA	10	867
C1127237	14	00101010101101010101	CTCTCGAGAG	10	868
C1127237	14	11100101011101100000	TACAGACGAC	10	869
C1127237	14	11011101010010101000	TAGTAGATCT	10	870
C1127237	14	11001010011010010011	TATCACTGCG	10	871
C1127237	14	10101110011001001100	TCTACACATA	10	872
C1127237	14	10010100100111001101	TGATGTATAG	10	873
C1127237	14	10010011001110111000	TGCGCGTCGT	10	874
C1127238	14	01101010110010100110	ACTCTATCAC	10	875
C1127238	14	01101001010011011001	ACTGATAGTG	10	876
C1127238	14	01010111001001101010	AGACGCACTC	10	877
C1127238	14	01011101100101010100	AGTAGTGAGA	10	878
C1127238	14	00100101001110011110	CAGCGTGTAC	10	879
C1127238	14	00110101010100110011	CGAGAGCGCG	10	880
C1127238	14	00111001101010101100	CGTGTCTCTA	10	881
C1127238	14	00101010101101010101	CTCTCGAGAG	10	882
C1127238	14	11100110100100101001	TACACTGCTG	10	883
C1127238	14	11100101011101100000	TACAGACGAC	10	884
C1127238	14	11011101010010101000	TAGTAGATCT	10	885
C1127238	14	10101110011001001100	TCTACACATA	10	886
C1127238	14	10010100100111001101	TGATGTATAG	10	887
C1127238	14	10010011001110111000	TGCGCGTCGT	10	888
C1127239	14	01110010010010101110	ACGCATCTAC	10	889
C1127239	14	01101011001100101001	ACTCGCGCTG	10	890
C1127239	14	01010110100110011010	AGACTGTGTC	10	891
C1127239	14	01001100111100100110	ATATACGCAC	10	892
C1127239	14	00100111110110010100	CACGTAGTGA	10	893
C1127239	14	00110101010100110011	CGAGAGCGCG	10	894
C1127239	14	00111011001001010110	CGTCGCAGAC	10	895
C1127239	14	00111001101010101100	CGTGTCTCTA	10	896
C1127239	14	00101010111001001011	CTCTACATCG	10	897
C1127239	14	11100101010011010010	TACAGATAGC	10	898
C1127239	14	11011010100101100100	TAGTCTGACA	10	899
C1127239	14	10101100101101011000	TCTATCGAGT	10	900
C1127239	14	10010100110011101001	TGATATACTG	10	901
C1127239	14	10010011001110111000	TGCGCGTCGT	10	902
C1127240	14	01101011100110010100	ACTCGTGTGA	10	903
C1127240	14	01101001011001111000	ACTGACACGT	10	904
C1127240	14	01010010011011101010	AGCACTACTC	10	905
C1127240	14	01001110010101001110	ATACAGATAC	10	906

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127240	14	0100110010011010 1010	ATATGTCGTC	10	907
C1127240	14	0011010101010011 0011	CGAGAGCGCG	10	908
C1127240	14	0011101100100101 0110	CGTCGCAGAC	10	909
C1127240	14	0011100110101010 1100	CGTGTCTCTA	10	910
C1127240	14	0010101011111110 01000	CTCTACGTAT	10	911
C1127240	14	1101101001110010 0100	TAGTCACGCA	10	912
C1127240	14	1010011001101101 0100	TCACACTAGA	10	913
C1127240	14	1010110010101001 0011	TCTATCTGCG	10	914
C1127240	14	1001010010011100 1101	TGATGTATAG	10	915
C1127240	14	1001001100111011 1000	TGCGCGTCGT	10	916
C1127241	14	0110101110011001 0100	ACTCGTGTGA	10	917
C1127241	14	0110100100101010 0111	ACTGCTCACG	10	918
C1127241	14	0101110011100101 1000	AGTATACAGT	10	919
C1127241	14	0100111001011110 0100	ATACAGTACA	10	920
C1127241	14	0100110110110100 1010	ATAGTCGATC	10	921
C1127241	14	0010011101001110 1010	CACGATACTC	10	922
C1127241	14	0011010101010011 0011	CGAGAGCGCG	10	923
C1127241	14	0011101100100101 0110	CGTCGCAGAC	10	924
C1127241	14	0011100110101010 1100	CGTGTCTCTA	10	925
C1127241	14	0010101011111110 01000	CTCTACGTAT	10	926
C1127241	14	1100101011010011 0010	TATCTAGCGC	10	927
C1127241	14	1100100101010100 1101	TATGAGATAG	10	928
C1127241	14	1010011001101001 0101	TCACACTGAG	10	929
C1127241	14	1001001100111011 1000	TGCGCGTCGT	10	930
C1127242	14	0110101110011001 0100	ACTCGTGTGA	10	931
C1127242	14	0110100100101010 0111	ACTGCTCACG	10	932
C1127242	14	0101110011100101 1000	AGTATACAGT	10	933
C1127242	14	0100110110110100 1010	ATAGTCGATC	10	934
C1127242	14	0010011101001110 1010	CACGATACTC	10	935
C1127242	14	0011010101010011 0011	CGAGAGCGCG	10	936
C1127242	14	0011101100100101 0110	CGTCGCAGAC	10	937
C1127242	14	0011100110101010 1100	CGTGTCTCTA	10	938
C1127242	14	0010101011111110 01000	CTCTACGTAT	10	939
C1127242	14	1100101011010011 0010	TATCTAGCGC	10	940
C1127242	14	1100100101010100 1101	TATGAGATAG	10	941
C1127242	14	1010011001101101 0100	TCACACTAGA	10	942
C1127242	14	1010010111001001 1001	TCAGTATGTG	10	943
C1127242	14	1001001100111011 1000	TGCGCGTCGT	10	944
C1127243	14	0110010011101010 0110	ACATACTCAC	10	945
C1127243	14	0111001001110100 1100	ACGCACGATA	10	946
C1127243	14	0110100110011001 0101	ACTGTGTGAG	10	947
C1127243	14	0101110011100101 1000	AGTATACAGT	10	948
C1127243	14	0100111111001001 0010	ATACGTATGC	10	949
C1127243	14	0011010101010011 0011	CGAGAGCGCG	10	950
C1127243	14	0011101100100101 0110	CGTCGCAGAC	10	951

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127243	14	00111001101010101100	CGTGTCTCTA	10	952
C1127243	14	00101010111001001011	CTCTACATCG	10	953
C1127243	14	11100110100100101001	TACACTGCTG	10	954
C1127243	14	11001001010101101010	TATGAGACTC	10	955
C1127243	14	10100101001111100100	TCAGCGTACA	10	956
C1127243	14	10101011001100111000	TCTCGCGCGT	10	957
C1127243	14	10010110110111001000	TGACTAGTAT	10	958
C1127244	14	01110010110101101000	ACGCTAGACT	10	959
C1127244	14	01011011100101010100	AGTCGTGAGA	10	960
C1127244	14	01001100101001001111	ATATCATACG	10	961
C1127244	14	00100100110111011001	CATAGTAGTG	10	962
C1127244	14	00110101010101001110	CGAGAGATAC	10	963
C1127244	14	00111001101010101100	CGTGTCTCTA	10	964
C1127244	14	00101011001110011010	CTCGCGTGTC	10	965
C1127244	14	00101010111100100101	CTCTACGCAG	10	966
C1127244	14	11100110011001001100	TACACACATA	10	967
C1127244	14	11101001100111001000	TACTGTGTAT	10	968
C1127244	14	11010010101010110010	TAGCTCTCGC	10	969
C1127244	14	10101101010010110100	TCTAGATCGA	10	970
C1127244	14	10010110010100110011	TGACAGCGCG	10	971
C1127244	14	10010101111001011000	TGAGTACAGT	10	972
C1127245	14	01110101100100111000	ACGAGTGCGT	10	973
C1127245	14	01110010101101100100	ACGCTCGACA	10	974
C1127245	14	01010111001001101010	AGACGCACTC	10	975
C1127245	14	01010010011010011101	AGCACTGTAG	10	976
C1127245	14	01001100101100110101	ATATCGCGAG	10	977
C1127245	14	01001010010101100111	ATCAGACACG	10	978
C1127245	14	00100100110111011001	CATAGTAGTG	10	979
C1127245	14	00110101010101001110	CGAGAGATAC	10	980
C1127245	14	00111001101010101100	CGTGTCTCTA	10	981
C1127245	14	00101011001110011010	CTCGCGTGTC	10	982
C1127245	14	11101001010100101100	TACTGAGCTA	10	983
C1127245	14	11011100101001010010	TAGTATCAGC	10	984
C1127245	14	10101010110010010011	TCTCTATGCG	10	985
C1127245	14	10010100111111010100	TGATACGTCT	10	986
C1127246	14	01100110100111001100	ACACTGTATA	10	987
C1127246	14	01100101001101111000	ACAGCGACGT	10	988
C1127246	14	01100100111010100110	ACATACTCAC	10	989
C1127246	14	01001011001100101101	ATCGCGCTAG	10	990
C1127246	14	01001001110011011010	ATGTATAGTC	10	991
C1127246	14	00110110010010111001	CGACATCGTG	10	992
C1127246	14	00110101010101001110	CGAGAGATAC	10	993
C1127246	14	00111001101010101100	CGTGTCTCTA	10	994
C1127246	14	00101010111101010100	CTCTACGAGA	10	995
C1127246	14	11101101010010101000	TACTAGATCT	10	996

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C1127246	14	11010100100110010101	TAGATGTGAG	10	997
C1127246	14	10101001101001010011	TCTGTCAGCG	10	998
C1127246	14	10010011001110011010	TGCGCGTGTC	10	999
C1127246	14	10011011111001001000	TGTCGTACAT	10	1000
C1127247	14	01100110100111001100	ACACTGTATA	10	1001
C1127247	14	01010110011010111000	AGACACTCGT	10	1002
C1127247	14	01001011001100101101	ATCGCGCTAG	10	1003
C1127247	14	01001001110011011010	ATGTATAGTC	10	1004
C1127247	14	00110101010101001110	CGAGAGATAC	10	1005
C1127247	14	00111010100101010011	CGTCTGAGCG	10	1006
C1127247	14	00111001101010101100	CGTGTCTCTA	10	1007
C1127247	14	00101111101101100000	CTACGTCGAC	10	1008
C1127247	14	11101101001010100100	TACTAGCTCA	10	1009
C1127247	14	11010100100110010101	TAGATGTGAG	10	1010
C1127247	14	10100101101001110010	TCAGTCACGC	10	1011
C1127247	14	10101110010101011000	TCTACAGAGT	10	1012
C1127247	14	10010011001110011010	TGCGCGTGTC	10	1013
C1127247	14	10011011111001001000	TGTCGTACAT	10	1014
C1127248	14	01101010101101100100	ACTCTCGACA	10	1015
C1127248	14	01010100111001101001	AGATACACTG	10	1016
C1127248	14	01001111110010101000	ATACGTATCT	10	1017
C1127248	14	01001001100101111010	ATGTGACGTC	10	1018
C1127248	14	00100111011010010101	CACGACTGAG	10	1019
C1127248	14	00110101010101001110	CGAGAGATAC	10	1020
C1127248	14	00110010011110111000	CGCACGTCGT	10	1021
C1127248	14	00111001101010101100	CGTGTCTCTA	10	1022
C1127248	14	00101001110011010011	CTGTATAGCG	10	1023
C1127248	14	11010100100110011100	TAGATGTGTA	10	1024
C1127248	14	11001010010110100110	TATCAGTCAC	10	1025
C1127248	14	10110110111010100000	TCGACTACTC	10	1026
C1127248	14	10111101001001010100	TCGTAGCAGA	10	1027
C1127248	14	10010101001100110011	TGAGCGCGCG	10	1028
C1127249	14	01100101001011100101	ACAGCTACAG	10	1029
C1127249	14	01010010101010011011	AGCTCTGTCG	10	1030
C1127249	14	01001111100100101010	ATACGTGCTC	10	1031
C1127249	14	01001001110011111000	ATGTATACGT	10	1032
C1127249	14	00100111010110011001	CACGAGTGTG	10	1033
C1127249	14	00110101010101001110	CGAGAGATAC	10	1034
C1127249	14	00111001101010101100	CGTGTCTCTA	10	1035
C1127249	14	00101010011111010100	CTCACGTAGA	10	1036
C1127249	14	11010110011010010100	TAGACACTGA	10	1037
C1127249	14	11001010110101001100	TATCTAGATA	10	1038
C1127249	14	10100100110010110011	TCATATCGCG	10	1039
C1127249	14	10101001100110010110	TCTGTGTGAC	10	1040
C1127249	14	10010011101101011000	TGCGTCGAGT	10	1041

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C1127249	14	10011011001001100110	TGTCGCACAC	10	1042
C1127250	14	01100110011001111000	ACACACACGT	10	1043
C1127250	14	01101010101101001010	ACTCTCGATC	10	1044
C1127250	14	01010011001110011001	AGCGCGTGTG	10	1045
C1127250	14	01001001011011010011	ATGACTAGCG	10	1046
C1127250	14	00110101010101001110	CGAGAGATAC	10	1047
C1127250	14	00111010010010010111	CGTCATGACG	10	1048
C1127250	14	00111001101010101100	CGTGTCTCTA	10	1049
C1127250	14	00101111101010010010	CTACGTCTGC	10	1050
C1127250	14	11100101001100101100	TACAGCGCTA	10	1051
C1127250	14	11011010010111001000	TAGTCAGTAT	10	1052
C1127250	14	10100110100111010100	TCACTGTAGA	10	1053
C1127250	14	10101001100100110011	TCTGTGCGCG	10	1054
C1127250	14	10010100111010011010	TGATACTGTC	10	1055
C1127250	14	10011011001001100110	TGTCGCACAC	10	1056
C1127251	14	01100110011001111000	ACACACACGT	10	1057
C1127251	14	01101010101101001010	ACTCTCGATC	10	1058
C1127251	14	01010011001110011001	AGCGCGTGTG	10	1059
C1127251	14	01001001011011010011	ATGACTAGCG	10	1060
C1127251	14	00110101010101001110	CGAGAGATAC	10	1061
C1127251	14	00111010010010010111	CGTCATGACG	10	1062
C1127251	14	00111001101010101100	CGTGTCTCTA	10	1063
C1127251	14	00101111101010010010	CTACGTCTGC	10	1064
C1127251	14	11100101001100101100	TACAGCGCTA	10	1065
C1127251	14	11011010010111001000	TAGTCAGTAT	10	1066
C1127251	14	10110100100111010100	TCGATGTAGA	10	1067
C1127251	14	10101001100100110011	TCTGTGCGCG	10	1068
C1127251	14	10010100111010011010	TGATACTGTC	10	1069
C1127251	14	10011011001001100110	TGTCGCACAC	10	1070
C1127252	14	01100110011001111000	ACACACACGT	10	1071
C1127252	14	01101010101101001010	ACTCTCGATC	10	1072
C1127252	14	01010011001110011001	AGCGCGTGTG	10	1073
C1127252	14	01001001011011010011	ATGACTAGCG	10	1074
C1127252	14	00110101010101001110	CGAGAGATAC	10	1075
C1127252	14	00111010010010010111	CGTCATGACG	10	1076
C1127252	14	00111001101010101100	CGTGTCTCTA	10	1077
C1127252	14	00101111101010010010	CTACGTCTGC	10	1078
C1127252	14	11100101001100101100	TACAGCGCTA	10	1079
C1127252	14	11011010010111001000	TAGTCAGTAT	10	1080
C1127252	14	10101100110011010100	TCTATATAGA	10	1081
C1127252	14	10101001100100110011	TCTGTGCGCG	10	1082
C1127252	14	10010100111010011010	TGATACTGTC	10	1083
C1127252	14	10011011001001100110	TGTCGCACAC	10	1084
C1127253	14	01100110011001111000	ACACACACGT	10	1085
C1127253	14	01101010101101001010	ACTCTCGATC	10	1086

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Cluster Id	Member Count	Flowgram TACGTACGTACGTACGTACG (SEQ ID NO: 6)	UID	UID Length	SEQ ID NO
C1127253	14	01010011001110011001	AGCGCGTGTG	10	1087
C1127253	14	01001001011011010011	ATGACTAGCG	10	1088
C1127253	14	00110101010101001110	CGAGAGATAC	10	1089
C1127253	14	00111010010010010111	CGTCATGACG	10	1090
C1127253	14	00111001101010101100	CGTGTCTCTA	10	1091
C1127253	14	00101111101010010010	CTACGTCTGC	10	1092
C1127253	14	11100101001100101100	TACAGCGCTA	10	1093
C1127253	14	11011010010111001000	TAGTCAGTAT	10	1094
C1127253	14	11001100110011010100	TATATATAGA	10	1095
C1127253	14	10101001100100110011	TCTGTGCGCG	10	1096
C1127253	14	10010100111010011010	TGATACTGTC	10	1097
C1127253	14	10011011001001100110	TGTCGCACAC	10	1098

Example 4- Exemplary computer code for representing and manipulating nucleotide sequences for UID identification

```
package com.fourfivefour.amplicons;

import java.util.HashSet;
import java.util.Set;

/**
 * Code to implement common operations on Nucleotide Sequences
 *
 *
 *
 */
public class Sequence implements Comparable<Sequence> {
        private String sequence;
        static final char possibleBases[] = { 'A', 'C', 'T', 'G' };

        public Sequence(String sequence) {
                this.sequence = sequence.toUpperCase();
        }

        public String getSequence() {
                return sequence;
        }

        public int hashCode() {
                return sequence.hashCode();
        }

        public boolean equals(Object obj) {
                return ((this == obj) ||
```


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```
                ((obj instanceof Sequence) &&
                 sequence.equals(((Sequence) obj).sequence)));
        }

        public int compareTo(Sequence obj) {
                return sequence.compareTo(obj.sequence);
        }

        public String toString() {
                return sequence;
        }


        /**
         * Generate the set of all single base insertions for the
         * Sequence.
         *
         * @return          A set of Sequences representing all single base
         *          insertions of the Sequence.
         */
        public Set<Sequence> generateSingleInsertions() {
                Set<Sequence> insertions = new HashSet<Sequence>();

                int seqLen = sequence.length();
                for (int insertIdx = 0; insertIdx <= seqLen; insertIdx++) {
                        String prefixString = sequence.substring(0, insertIdx);
                        String suffixString = sequence.substring(insertIdx,seqLen);
                        for (char insertBase : possibleBases) {
                                insertions.add(new Sequence(prefixString + insertBase +
suffixString));
                        }
                }
                return insertions;
        }

        /**
         * Generate the set of all single base substitutions for the
         * Sequence.
         *
         * @return          A set of Sequences representing all single base
         *          substitutions of the Sequence.
         */
        public Set<Sequence> generateSingleSubstitutions() {
                Set<Sequence> substitutions = new HashSet<Sequence>();

                int seqLen = sequence.length();
                for (int substBaseIdx = 0; substBaseIdx < seqLen; substBaseIdx++) {
                        String prefixString =
                                sequence.substring(0, substBaseIdx);
                        String suffixString =
```


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```
                        sequence.substring(substBaseIdx + 1, seqLen);
                    char originalBase =
                        sequence.charAt(substBaseIdx);
                    for (char substBase : possibleBases) {
                        if (substBase != originalBase) {
                            substitutions.add(
                             new Sequence(prefixString + substBase + suffixString)
                            );
                        }
                    }
                }
                return substitutions;
            }

            /**
             * Generate the set of all single base deletions for the
             * Sequence.
             *
             * @return              A set of sequences representing all single base
             *          deletions of the Sequence.
             */
            public Set<Sequence> generateSingleDeletions() {
                Set<Sequence> deletions = new HashSet<Sequence>();

                int seqLen = sequence.length();
                for (int deleteBaseIdx = 0; deleteBaseIdx < seqLen; deleteBaseIdx++) {
                    String prefixString =
                        sequence.substring(0, deleteBaseIdx);
                    String suffixString =
                        sequence.substring(deleteBaseIdx + 1, seqLen);
                    deletions.add(new Sequence(prefixString + suffixString));
                }
                return deletions;
            }

            /**
             * Generate all 1-base mutations starting from each of the sequences in
             * the input set of sequences.
             *
             * @param inputSeqs  The input set of sequences.
             * @return      A set of sequences that are exactly one mutation
             *          away from each of the sequences in the input set
             *          of sequences.
             */
            public static Set<Sequence> generateSingleMutations(Set<Sequence> inputSeqs) {
                Set<Sequence> mutatedSequences = new HashSet<Sequence>();
                for (Sequence inputSeq : inputSeqs) {
                    mutatedSequences.addAll(inputSeq.generateSingleDeletions());
                    mutatedSequences.addAll(inputSeq.generateSingleInsertions());
                    mutatedSequences.addAll(inputSeq.generateSingleSubstitutions());
```


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```
            }
            return mutatedSequences;
        }
}
```

As stated previously, it will be appreciated that the foregoing computer code is provided for the purposes of example, and that numerous alternative methods and code structures may be employed. It will also be appreciated that the exemplary code provided herein is not intended to execute as a stand alone application or to run perfectly without additional computer code or modification.

Having described various embodiments and implementations, it should be apparent to those skilled in the relevant art that the foregoing is illustrative only and not limiting, having been presented by way of example only. Many other schemes for distributing functions among the various functional elements of the illustrated embodiment are possible. The functions of any element may be carried out in various ways in alternative embodiments.

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CLAIMS

What is claimed is:

1. An identifier element for identifying an origin of a template nucleic acid molecule, comprising:

a nucleic acid element comprising a sequence composition that enables detection of an introduced error in sequence data generated from the nucleic acid element and correction of the introduced error, wherein the nucleic acid element is constructed to couple with the end of a template nucleic acid molecule and identifies an origin of the template nucleic acid molecule.

2. The identifier element of claim 1, wherein:

the sequence composition enables detection of up to three of the introduced errors and correction for up to two of the introduced errors.

3. The identifier element of claim 1, wherein:

The sequence composition comprises 10 sequence positions.

4. The identifier element of claim 1, wherein:

the introduced error is selected from the group consisting of an insertion error, a deletion error, and a substitution error.

5. The identifier element of claim 1, wherein:

the sequence composition comprises a design based upon a set of parameters selected from the group consisting of minimum sequence length, minimum number of flow cycles, sequence distinctiveness, and monomer repeats.

6. The identifier element of claim 1, wherein:

the sequence composition comprises a design based upon a set of parameters selected from the group consisting of melting temperature, Gibbs free energy, hairpin formation, and dimer formation.

7. The identifier element of claim 1, wherein:

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the nucleic acid element is incorporated into an adaptor comprising a primer element, wherein the adaptor couples with the end of the template nucleic acid molecule.

8. The identifier element of claim 7, wherein:
the nucleic acid element is in a known position relative to the primer element.

9. The identifier element of claim 7, wherein:
the primer element is selected from the group consisting of an amplification primer, a sequencing primer, or a bipartite amplification – sequencing primer.

10. The identifier element of claim 7, wherein:
the adaptor comprises a quality control element.

11. The identifier element of claim 7, wherein:
the nucleic acid element is in a known position relative to the quality control element.

12. The identifier element of claim 1, wherein:
the origin of the template nucleic acid molecule comprises an experimental sample or diagnostic sample.

13. The identifier element of claim 1, wherein:
the nucleic acid element belongs to a set comprising a plurality of compatible nucleic acid elements each comprising a distinctive sequence composition, wherein the detection of the introduced error is relative to the sequence composition of the compatible nucleic acid elements of the set.

14. The identifier element of claim 13, wherein:
the set comprises 14 of the compatible nucleic acid elements.

15. A method for identifying an origin of a template nucleic acid molecule, comprising the steps of:
identifying a first identifier sequence from sequence data generated from a template nucleic acid molecule;

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detecting an introduced error in the first identifier sequence;

correcting the introduced error in the first identifier sequence;

associating the corrected first identifier sequence with a first identifier element coupled to the template molecule; and

identifying an origin of the template molecule using the association of the corrected first identifier sequence with the first identifier element.

16. The method of claim 15, further comprising:

sequencing a template nucleic acid molecule to generate the sequence data.

17. The method of claim 15, wherein:

the template nucleic acid molecule is included in a multiplex sample comprising a plurality of template molecules from a plurality of different origins.

18. The method of claim 15, further comprising:

detecting up to three of the introduced errors in the first identifier sequence; and

correcting up to two of the introduced errors in the first identifier sequence.

19. The method of claim 15, wherein:

the introduced error is selected from the group consisting of an insertion error, a deletion error, and a substitution error.

20. The method of claim 15, wherein the step of detecting comprises:

measuring one or more characteristics of sequence composition in one or more sequence regions that flank the identifier sequence; and

detecting the introduced error using one or more assumptions derived from the measured characteristics.

21. The method of claim 15, wherein:

the first identifier element is incorporated into an adaptor comprising a primer element, wherein the adaptor is coupled to the template nucleic acid molecule.

22. The method of claim 21, wherein:

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the first identifier element is in a known position relative to the primer element.

23. The method of claim 21, wherein:

the primer element is selected from the group consisting of an amplification primer, a sequencing primer, or a bipartite amplification – sequencing primer.

24. The method of claim 21, wherein:

the adaptor comprises a quality control element.

25. The method of claim 21, wherein:

the first identifier element is in a known position relative to the quality control element.

26. The method of claim 15, wherein:

the origin of the template nucleic acid molecule comprises an experimental sample or diagnostic sample.

27. The method of claim 15, further comprising the steps of:

identifying a second identifier sequence from the sequence data generated from the template nucleic acid molecule;

detecting an introduced error in the second identifier sequence;

correcting the introduced error in the second identifier sequence;

associating the corrected second identifier sequence with a second identifier element coupled with the template nucleic acid molecule; and

identifying an origin of the template nucleic acid molecule using the association of the corrected second identifier sequence with the second identifier element combinatorially with the association of the corrected first identifier sequence with the first identifier element.

28. The method of claim 27, further comprising:

detecting up to three of the introduced errors in the second identifier sequence; and

correcting up to two of the introduced errors in the second identifier sequence.

29. The method of claim 15, wherein:

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the introduced error is selected from the group consisting of an insertion error, a deletion error, and a substitution error.

30. The method of claim 15, wherein:

the first identifier belongs to at least one set of compatible identifiers of a plurality of sets of identifiers.

31. The method of claim 15, wherein:

the set of compatible identifiers comprise 14 identifiers that enable the detection and the correction of the introduced error.

32. A kit for identifying an origin of a template nucleic acid molecule comprising:

a set of nucleic acid elements each comprising a distinctive sequence composition that enables detection of an introduced error in sequence data generated from each nucleic acid element and correction of the introduced error, wherein each of the nucleic acid elements is constructed to couple with the end of a template nucleic acid molecule and identifies the origin of the template nucleic acid molecule.

34. The kit of claim 32, wherein:

the distinctive sequence composition enables detection of up to three of the introduced errors and correction for up to two of the introduced errors.

35. The kit of claim 32, wherein:

the introduced error is selected from the group consisting of an insertion error, a deletion error, and a substitution error.

36. The kit of claim 32, wherein:

each nucleic acid element is incorporated into an adaptor comprising a primer element, wherein the adaptor couples with the end of the template nucleic acid molecule.

37. The kit of claim 36, wherein:

the nucleic acid element is in a known position relative to the primer element.

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38. The kit of claim 36, wherein:

the primer element is selected from the group consisting of an amplification primer, a sequencing primer, or a bipartite amplification – sequencing primer.

39. The kit of claim 36, wherein:

the adaptor comprises a quality control element.

40. The kit of claim 36, wherein:

the nucleic acid element is in a known position relative to the quality control element.

41. The kit of claim 32, wherein:

the detection of the introduced error in each of the nucleic acid elements is relative to the distinctive sequence composition of the other nucleic acid elements of the set.

42. The kit of claim 41, wherein:

the set comprises 14 of the nucleic acid elements.

43. A computer, comprising executable code stored thereon, wherein the executable code performs a method for identifying an origin of a template nucleic acid molecule, comprising the steps of:

identifying an identifier sequence from sequence data generated from a template nucleic acid molecule;

detecting an introduced error in the identifier sequence;

correcting the introduced error in the identifier sequence;

associating the corrected identifier sequence with an identifier element coupled with the template molecule; and

identifying an origin of the template molecule using the association of the corrected identifier sequence with the identifier element.

44. The method of claim 43, wherein:

the template nucleic acid molecule is included in a multiplex sample comprising a plurality of template molecules from a plurality of different origins.

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45. The method of claim 43, further comprising:

detecting up to three of the introduced errors in the first identifier sequence; and

correcting up to two of the introduced errors in the first identifier sequence.

46. The method of claim 43, wherein:

the introduced error is selected from the group consisting of an insertion error, a deletion error, and a substitution error.

48. The method of claim 43, wherein the step of identifying further comprises:

determining a position for the identifier sequence using a known positional relationship of one or more elements in the sequence data.

49. The method of claim 48, wherein:

the one or more elements include a primer sequence.

50. The method of claim 43, wherein the step of detecting further comprises:

measuring one or more characteristics of sequence composition in one or more sequence regions that flank the identifier sequence; and

detecting the introduced error using one or more assumptions derived from the measured characteristics.

51. The method of claim 43, further comprising:

identifying a second identifier sequence from the sequence data generated from the template nucleic acid molecule;

detecting an introduced error in the second identifier sequence;

correcting the introduced error in the second identifier sequence;

associating the corrected second identifier sequence with a second identifier element coupled with the template molecule; and

identifying an origin of the template molecule using the association of the corrected second identifier sequence with the second identifier element combinatorially with the association of the corrected first identifier sequence with the first identifier element.

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FIGURE 1

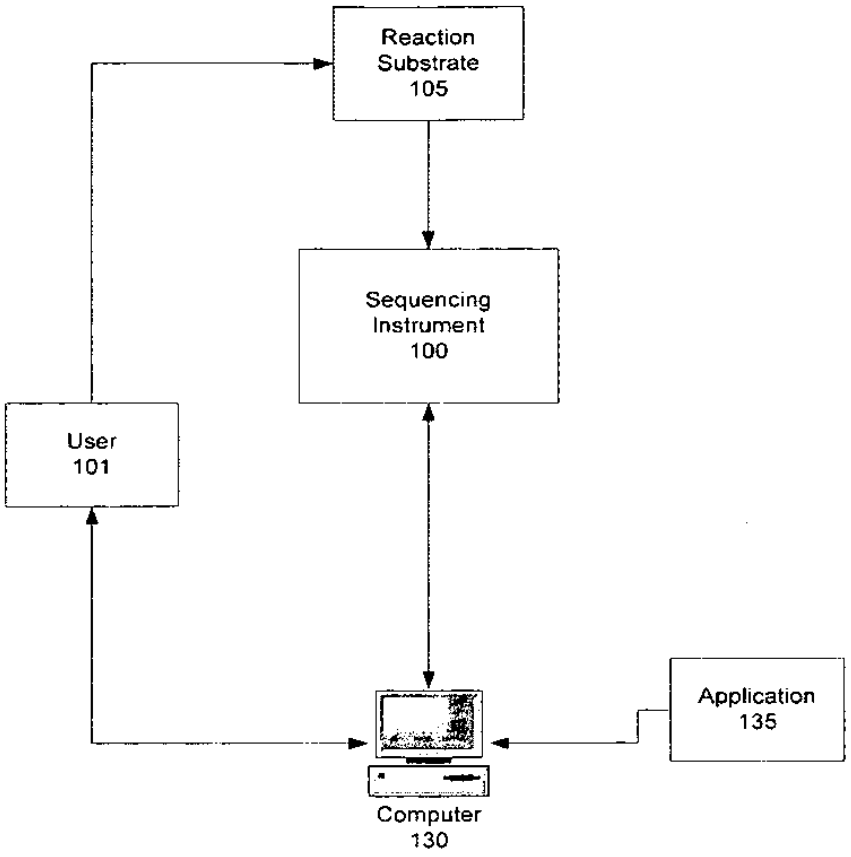

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FIGURE 2A

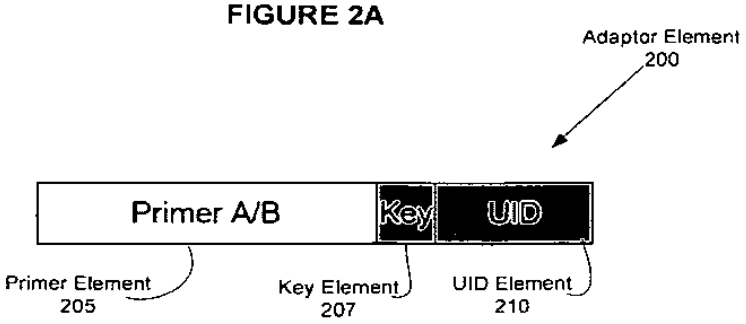

FIGURE 2B

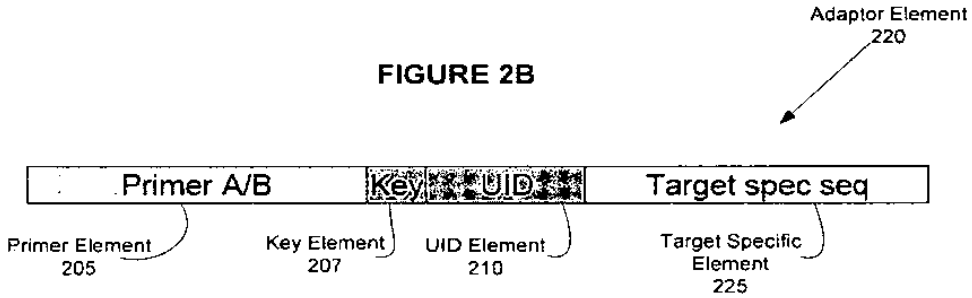

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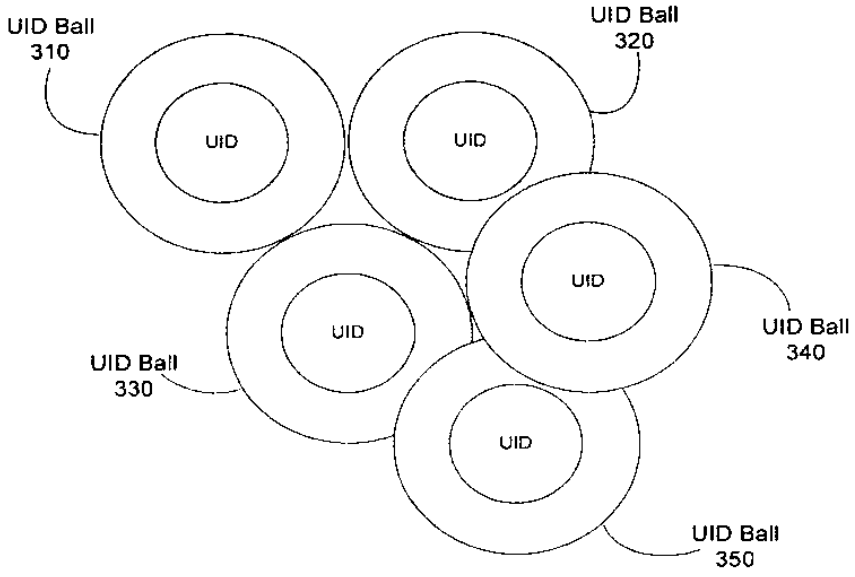
FIGURE 3



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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/06822

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C12Q 1/68 (2008.04)
USPC - 435/6
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 435/6

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 435/91.2; 536/23.1; 536/25.32; 536/25.4; 536/26.6

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST(PGPB,USPT,USOC,EPAB,JPAB), Google Scholar: (sequencing adaptors origin identify error, "Patrick S. Schnable" origin, "Daniel A. Ashlock" algorithm, sequencing adaptors quality control element error, sequencing adaptors "quality control" element error, sequencing adaptors primer "quality control element" error)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	QIU et al. DNA Sequence-Based "Bar Codes" for Tracking the Origins of Expressed Sequence Tags from a Maize cDNA Library Constructed Using Multiple mRNA Sources. Plant Physiology, 2003, vol 133, pp 475-481; Abstract; pg 475, col 2 para 3; pg 476, col 1 para 1, ln 1-8, para 3; col 2 para 1, ln 1-2; pg 480, col 1, para 3, ln 5-11,14-17, col 2 para 2, ln 7-13, para 3, 6, ln 2-3, para 7, ln 4-5; pg 481, col 1, para 2, 4, 8, ln 1-6	1-8, 12-22, 26-31, 43-46, 48-51 --- 9-11, 23-25, 32, 34-42
Y	US 2007/00772208 A1 (DRMANAC) 29 Mar 2007 (29.03.2007); para [0015], [0053]	9-11, 23-25, 32, 34-42
Y	US 2005/0221341 A1 (SHIMKETS et al) 6 Oct 2005 (06.10.2005); para [0050], [0053]	10-11, 24-25, 39-40

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01 September 2008 (01.09.2008)	08 SEP 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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CONFIRMATION NO. 9317

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
13/859,450	04/09/2013 RULE	435	1634	CGLC-020CON2

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**** CONTINUING DATA ***************************

This application is a CON of 13/622,872 09/19/2012
which is a CON of 13/387,343 02/15/2012 PAT 8298767
which is a 371 of PCT/IB2010/002243 08/13/2010
which claims benefit of 61/288,792 12/21/2009
and claims benefit of 61/235,595 08/20/2009

/NKB/

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** ** SMALL ENTITY **** /NKB/
05/16/2013

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged /NARAYAN KAMESHWAR BHAT/ Examiner's Signature ☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
	UNITED KINGDOM	13	13	1

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UNITED STATES

TITLE

Compositions and Methods for Intramolecular Nucleic Acid Rearrangement

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	17083	brenner.in. or mikawa.in. or osborne.in. or slater.in. or population.as.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 12:39
S2	658	S1 and ("multiplex identifier" or mid or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 13:01
S3	0	S2 and ("multiplex identifier" or mid or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token) near5 (plurality or multiple) near3 (segment or section or region) near5 (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 13:05
S4	19	S2 and ("multiplex identifier" or mid or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token) same (plurality or multiple) same (segment or section or region) same (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 13:06
S5	271	("multiplex identifier" or mid or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token) same (plurality or multiple) same (segment or section or region) same (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:09
S6	5	S5 and ("multiplex identifier" or mid or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token) near5 (plurality or multiple) near5 (segment or section or region) near5 (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:10
S7	10	S5 and "single locus"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:12
S8	189	S5 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:14
S9	177	S5 and ("multiplex identifier" or "bar code" or barcode or "unique identifier"	US-PGPUB; USPAT;	OR	ON	2013/08/06 14:15

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		or "zip code" or zipcode or token) same (plurality or multiple) same (segment or section or region) same (nucleic or dna)	FPRS; EPO; JPO; DERWENT; IBM_TDB			
S10	45	S9 and (composition or kit).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:15
S11	15	"6225064"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:26
S12	5	S9 and "single locus"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:38
S13	63	S9 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token) same (plurality or multiple) same (segment or section or region) same (nucleic or dna) same first	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:39
S14	49	S13 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token) same (plurality or multiple) same (segment or section or region) same (nucleic or dna) same second	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:40
S15	15	"7208295"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 14:42
S16	73	"6150516"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:08
S17	54	S16 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:09
S18	4	S17 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token) near5 (composition or kit or reagent)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:10
S19	61175	("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip	US-PGPUB; USPAT;	OR	ON	2013/08/06 15:40

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		code" or zipcode or token or "tag sequnce" tagsequnce).clm.	FPRS; EPO; JPO; DERWENT; IBM_TDB			
S20	4	S19 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (multiple or plurality or distinct or different)same (section or segment or region) same (nucleic or dna)near5 first	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:42
S21	37	("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (multiple or plurality or distinct or different)same (section or segment or region) same (nucleic or dna)near5 first	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:44
S22	25	S21 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (multiple or plurality or distinct or different)same (section or segment or region) same (nucleic or dna)near5 second	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:45
S23	140	("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (multiple or plurality or distinct or different)same (nucleic or dna)near5 second	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:52
S24	126	S23 and first same (nucleic or dna)near5 second	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:53
S25	43	S24 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (composition or kit)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/06 15:55
S26	9	"886607".ap.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/08/06 16:41

8/9/2013 6:00:35 PM
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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	51	("20070020640" | "7544473" | "20060008799" | "7700325" | "20120208724" | "8101346" | "20070238113" | "20040224331" | "20090155780" | "20130059310" | "8298767" | "8318460" | "20120316074" | "20100086914" | "20070259357" | "20110287435" | "6723513" | "20100120098" | "20100113296").PN.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:01
L2	20	l1 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:03
L3	15	l2 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (append$3 or coupl$3 or attach$3 or linked or incorporat$3 or includ$3 or join$3 or fus$3 or conjugat$3) same (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:05
L4	36	(brenner.in. or mikawa.in. or osborne.in. or slater.in. or population.as.) and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (append$3 or coupl$3 or attach$3 or linked or incorporat$3 or includ$3 or join$3 or fus$3 or conjugat$3) same (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:09
L5	2	l4 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (append$3 or coupl$3 or attach$3 or linked or incorporat$3 or includ$3 or join$3 or fus$3 or conjugat$3) same (nucleic or dna).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:10
L6	3175	("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (append$3 or coupl$3 or attach$3 or linked or incorporat$3 or includ$3 or join$3 or fus$3 or conjugat$3) same (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:12
L7	55	l6 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or	US-PGPUB; USPAT;	OR	ON	2013/08/09 18:14

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		"zip code" or zipcode or token or "tag sequnce" tagsequnce)same (plurality or multiple) near5 (section or segment or fragment) same (single or one)	FPRS; EPO; JPO; DERWENT; IBM_TDB			
L8	363175	"435"/$.ccls. or "536"/$.ccls.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:20
L9	55	l8 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (plurality or multiple) near5 (section or segment or fragment) same (single or one)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/08/09 18:21

8/9/2013 6:28:24 PM
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EAST Search History

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L10	557	("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (plurality or multiple) near5 (section or segment or fragment) same (single or one)	USPAT; UPAD	OR	ON	2013/08/09 18:22
L11	11	l10 and ("multiplex identifier" or "bar code" or barcode or "unique identifier" or "zip code" or zipcode or token or "tag sequnce" tagsequnce)same (append$3 or coupl$3 or attach$3 or linked or incorporat$3 or includ$3 or join$3 or fus$3 or conjugat$3) same (nucleic or dna)	USPAT; UPAD	OR	ON	2013/08/09 18:27

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13859450	BRENNER ET AL.
	Examiner	Art Unit
	NARAYAN BHAT	1634

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original									
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	32	-								
	33	-								

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13859450	BRENNER ET AL.
	Examiner	Art Unit
	NARAYAN BHAT	1634

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner
435	6.1, 91.1, 91.2, 91.32 and 287.2	8/8/13	Bhat N.
536	23.1	8/8/13	Bhat N.

SEARCH NOTES		
Search Notes	Date	Examiner
Searched for the invntors and the assignee in PALM for the ODP.	8/8/13	Bhat N.
Searched for the arts in the filed IDS.	8/8/13	Bhat N.
Searched for the topics in EAST, Pubmed and Google scholar. Search histories are enclosed.	8/8/13	Bhat N.
Reviewed the parent and the provisonal application for the support for the instant pending claims. Reviewed the search report in the parent allowed claims.	8/8/13	Bhat N.

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
	Searched for the key words in EAST. Search history is enclosed.	8/8/13	Bhat N.

/NARAYAN BHAT/ Examiner.Art Unit 1634	

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13859450	BRENNER ET AL.
	Examiner	Art Unit
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CPC					
Symbol				Type	Version
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CPC Combination Sets							
Symbol				Type	Set	Ranking	Version
		/					
		/					

		Total Claims Allowed:	
(Assistant Examiner)	(Date)	11	
/NARAYAN BHAT/ Examiner.Art Unit 1634 (Primary Examiner)	08/10/2013 (Date)	O.G. Print Claim(s) 21	O.G. Print Figure None

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13859450	BRENNER ET AL.
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	NARAYAN BHAT	1634

US ORIGINAL CLASSIFICATION					
CLASS			SUBCLASS		
435			91.1		
CROSS REFERENCE(S)					
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
435	6.1	91.1	91.2	91.32	287.2
536	23.1				

INTERNATIONAL CLASSIFICATION																
CLAIMED					NON-CLAIMED											
C	1	2	P	19 / 34 (2006.01.01)												
C	1	2	M	1 / 34 (2006.01.01)												
C	1	2	M	3 / 00 (2006.01.01)												
C	0	7	H	21 / 02 (2006.01.01)												
C	0	7	H	21 / 04 (2006.01.01)												

(Assistant Examiner)	(Date)	Total Claims Allowed: 11	
/NARAYAN BHAT/ Examiner.Art Unit 1634	08/10/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	21	None

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	13859450	BRENNER ET AL.
	Examiner	Art Unit
	NARAYAN BHAT	1634

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	21														
	22														
	23														
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	25														
	26														
	27														
	28														
	29														
	30														
	31														

(Assistant Examiner)	(Date)	Total Claims Allowed: 11	
/NARAYAN BHAT/ Examiner.Art Unit 1634	08/10/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	21	None

U.S. Patent and Trademark Office

Part of Paper No. 20130808

EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	16872	brenner.in. or mikawa.in. or osborne.in. or slater.in. or population.as.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:01
S3	36	S1 and (pcr or amplif$3)near5 genomic near2 (dna or nucleic) and (primer oligonucleotide or adapt$3 or linker) near3 (barcode or zipcode or unique or "multiplex identifier" or tag$4 or token or address$3 or identifier or locat$4 or encoded)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:06
S4	3	S3 and (pcr or amplif$3)near5 genomic near2 (dna or nucleic) same (multiple or pluralit$3)same (barcode or zipcode or unique or "multiplex identifier" or tag$4 or token or address$3 or identifier or locat$4 or encoded)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:07
S5	403	(pcr or amplif$3)near5 genomic near2 (dna or nucleic) same (multiple or pluralit$3)same (barcode or zipcode or unique or "multiplex identifier" or tag$4 or token or address$3 or identifier or locat$4 or encoded)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:10
S6	1	S5 and (pcr or amplif$3)near5 genomic near2 (dna or nucleic) near5 different near5 (part or section or segment or region or area or location) same locus	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:12
S7	1	S5 and (pcr or amplif$3)near5 genomic near2 (dna or nucleic) near5 different near5 (part or section or segment or region or area or location)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:13
S8	70	S5 and (pcr or amplif$3)near5 genomic near2 (dna or nucleic) near5 (part or section or segment or region or area or location)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:13
S9	54	S8 and (barcode or zipcode or "multiplex identifier" or tag$4 or token)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:17
S10	8	S9 and (barcode or zipcode or	US-PGPUB;	OR	ON	2013/06/21

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		"multiplex identifier" or token)	USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB			10:18
S11	772	genomic near2 (dna or nucleic) near5 locus same (pcr or amplif$4)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:21
S12	6	S11 and (primer oligonucleotide or adapt$3 or linker) near3 (barcode or zipcode or "multiplex identifier" or token)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:22
S13	5238	(composition or kit)near5 genomic near5 (dna or nucleic)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:25
S14	9	S13 and (barcode or zipcode or "multiplex identifier" or token).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:26
S15	43	"7544473"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/06/21 10:48
S16	17	S15 and (barcode or zipcode or "multiplex identifier" or token).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/21 10:51
S17	2	"6103474".pn.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	OFF	2013/06/21 16:49
S18	9	"067166".ap.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 18:59
S19	6	(pna or "peptide nucleic") near5 (bind$3 or associat$5 or interact$4 or aggregat$3 or complx$3) near5 nanoparticle	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:18
S20	76	(pna or "peptide nucleic") near5	US-PGPUB;	OR	ON	2013/06/22

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		(bind$3 or associat$5 or interact$4 or aggregat$3 or complx$3) same nanoparticle	USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB			19:20
S21	7	S20 and (negative$3 or anion$3) near5 nanoparticle	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:21
S22	2074	(negative$3 near3 charg$3 or anion$3) near5 nanoparticle	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:23
S23	2	S22 and (negative$3 near3 charg$3 or anion$3) near5 nanoparticle same (pna or "peptide nucleic") near5 (bind$3 or associat$5 or interact$4 or aggregat$3 or complx$3)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:24
S24	35	S22 and (pna or "peptide nucleic") near5 (bind$3 or associat$5 or interact$4 or aggregat$3 or complx$3)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:25
S25	43	S22 and (pna or "peptide nucleic") near5 (bind$3 or associat$5 or interact$4 or aggregat$3 or complex$3)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:26
S26	7	S25 and (pna or "peptide nucleic") near5 (bind$3 or associat$5 or interact$4 or aggregat$3 or complex$3) same nanoparticle	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:26
S27	16	(pna or "peptide nucleic") near5 (bind$3 or associat$5 or interact$4 or aggregat$3 or complex$3) near5 (nanoparticle or nanobead or nanotube or nanosphere or nanoraod)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:27
S28	75	(pna or "peptide nucleic") same aggregat$3 same (nanoparticle or nanobead or nanotube or nanosphere or nanoraod)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:29
S29	45	S28 and (nanoparticle or nanobead or nanotube or nanosphere or nanoraod)near5(metal$4 or gold or silver or cobalt)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:30
S30	250	(morpholino or neutral or "peptide	US-PGPUB;	OR	ON	2013/06/22

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		nucleic") same aggregat$3 same (nanoparticle or nanobead or nanotube or nanosphere or nanoraod)	USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB			19:36
S31	250	S30 (morpholino or neutral or "peptide nucleic") near5 aggregat$3 near5(nanoparticle or nanobead or nanotube or nanosphere or nanoraod)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:37
S32	13	S30 and (morpholino or neutral or "peptide nucleic") near5 aggregat$3 near5(nanoparticle or nanobead or nanotube or nanosphere or nanoraod)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:37
S33	47	(morpholino or "peptide nucleic") near5 aggregat$3	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:44
S34	256	(morpholino or "peptide nucleic" or pna) near5 aggregat$3	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:44
S35	33	S34 and (nanoparticle or nanobead or nanotube or nanosphere or nanoraod)near5(metal$4 or gold or silver or cobalt)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/06/22 19:45
S36	766250	(composition or kit or polynucleotide).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:30
S37	406	(pcr or amplif$3)near5 genomic near2 (dna or nucleic) same (multiple or pluralit$3)same (barcode or zipcode or unique or "multiplex identifier" or tag$4 or token or address$3 or identifier or locat$4 or encoded)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:31
S38	71	S37 and (pcr or amplif$3)near5 genomic near2 (dna or nucleic) near5 (part or section or segment or region or area or location)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:31
S39	8	S38 and (barcode or zipcode or "multiplex identifier" or tag$4 or token or "unique identifier").clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:31
S40	7838	S36 and (barcode or zipcode or	US-PGPUB;	OR	ON	2013/07/24

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		"multiplex identifier" or tag$4 or token or "unique identifier").clm.	USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB			12:32
S41	953	S36 and (barcode or zipcode or "multiplex identifier" or tag$4 or token or "unique identifier") near5 (dna or nucleic or polynucleotide).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:34
S42	96	S41 and (barcode or zipcode or "multiplex identifier" or tag$4 or token or "unique identifier") near5 (dna or nucleic or polynucleotide) near5 (multiple or pluralit$3).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:35
S43	15	S42 and (barcode or zipcode or "multiplex identifier" or token or "unique identifier") near5 (dna or nucleic or polynucleotide) near5 (multiple or pluralit$3).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:36
S44	51	(composition or kit or polynucleotide)same (barcode or zipcode or "multiplex identifier" or token or "unique identifier") same (dna or nucleic or polynucleotide).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:45
S45	27	S44 and (composition or kit)same (barcode or zipcode or "multiplex identifier" or token or "unique identifier") same (dna or nucleic or polynucleotide).clm.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 12:48
S46	0	(pcr or amplif$3)near5 genomic near2 (dna or nucleic) near5 (multiple or pluralit$3)near5 (barcode or zipcode or "unique identifier" or "multiplex identifier")	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:23
S47	12	(pcr or amplif$3)near5 genomic near2 (dna or nucleic) near5 (barcode or zipcode or "unique identifier" or "multiplex identifier")	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:23
S48	15	(pcr or amplif$3)same genomic near2 (dna or nucleic or target or analyte) same (barcode or zipcode or "unique identifier" or "multiplex identifier") same (composition or kit)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:26
S49	78169	(pcr or amplif$3)same genomic near2 (dna or nucleic or target or analyte)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:29
S50	3	S49 and (pcr or amplif$3)same	US-PGPUB;	OR	ON	2013/07/24

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		genomic near2 (dna or nucleic or target or analyte)near5 (tag$3 or label$3) near5 (barcode or zipcode or "unique identifier" or "multiplex identifier")	USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB			13:31
S51	37	S49 and (pcr or amplif$3)same genomic near2 (dna or nucleic or target or analyte)same (tag$3 or label$3) near5 (barcode or zipcode or "unique identifier" or "multiplex identifier")	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:34
S52	35	S51 and (composition or kit or polynucleotide)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:37
S53	0	S51 and (composition or kit) near5 amplifi$5 near5 (nucleic or dna)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:38
S54	19065	(composition or kit) same amplifi$5 near5 (nucleic or dna polynucleotide)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:38
S55	20	S54 and amplifi$5 near5 (nucleic or dna polynucleotide)same (tag$3 or label$3) near5 (barcode or zipcode or "unique identifier" or "multiplex identifier")	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:39
S56	12	"8101346"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 13:48
S57	9	"387343".ap.	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 15:04
S58	2394	"single nucleic acid molecule"	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 15:13
S59	451	S58 and amplifi$5 near5 (region or segment or section)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 15:15
S60	1	S59 and (region or segment or section)	US-PGPUB;	OR	ON	2013/07/24

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		near5 (tag$3 or label$3) near5 (barcode or zipcode or "unique identifier" or "multiplex identifier")	USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB			15:16
S61	5	S59 and (region or segment or section) same (tag$3 or label$3) same (barcode or zipcode or "unique identifier" or "multiplex identifier")	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 15:17
S62	741	single near3 strand$3 near3 (nucleic or dna) same amplifi$5 near5 (region or segment or section)	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 15:26
S63	2	S62 and (region or segment or section) same (tag$3 or label$3) same (barcode or zipcode or "unique identifier" or "multiplex identifier")	US-PGPUB; USPAT; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2013/07/24 15:27

8/9/2013 5:59:46 PM
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2

CONFIRMATION NO. 9317

93726
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

PUBLICATION NOTICE

OC000000063499178

Title:COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

Publication No.US-2013-0220812-A1
Publication Date:08/29/2013

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Office of Public Records. The Office of Public Records can be reached by telephone at (703) 308-9726 or (800) 972-6382, by facsimile at (703) 305-8759, by mail addressed to the United States Patent and Trademark Office, Office of Public Records, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently http://pair.uspto.gov/. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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FILED ELECTRONICALLY

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

93726 7590 08/23/2013
EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2	9317

TITLE OF INVENTION: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	11/25/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
BHAT, NARAYAN KAMESHWAR	1634	435-091100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 James S. Keddie
2 Bozicevic, Field & Francis, LLP
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: Population Genetics Technologies Ltd

(B) RESIDENCE: (CITY and STATE OR COUNTRY): Cambridge, United Kingdom

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☒ Payment by credit card. ~~Form PTO-2038 attached~~.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 50-0815 (enclose an extra copy of this form).

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5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☐ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /James S. Keddie, Reg. No. 48,920/ Date September 6, 2013

Typed or printed name James S. Keddie Registration No. 48,920

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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AMENDMENT UNDER 37 C.F.R. §1.312 Address to: Mail Stop Issue Fee Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	CGLC-020CON2
	Confirmation No.	9317
	First Named Inventor	Brenner, Sydney
	Application Number	13/859,450
	Filing Date	April 9, 2013
	Group Art Unit	1634
	Examiner Name	Bhat, Narayan Kameshwar
	Title "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"	

Sir:

This amendment is responsive to the Notice of Allowance and Fees Due dated November 23, 2013. Applicants submit that the amendments set forth below raise no new issues and entry of these amendments is thus respectfully requested.

AMENDMENTS TO THE CLAIMS

1-20. (Cancelled)

21. (**Currently Amended**) A composition comprising a mixture of:

a) a first plurality of different segments of a first nucleic acid molecule of a contiguous region in genomic DNA, wherein said contiguous region in genomic DNA is represented by a plurality of nucleic acid molecules, and wherein each of said first plurality of segments is appended to a first multiplex identifier (MID) sequence; and

b) a second plurality of different segments of a second nucleic acid molecule of said contiguous region, wherein each of said second plurality of segments is appended to a second MID sequence and said first MID sequence and said second MID sequence are different,

wherein, in said composition, all of the segments of each of the nucleic acid molecules of the contiguous region ~~comprises~~ **comprise** a unique MID sequence that uniquely identifies each of the nucleic acid molecules.

22. (Previously Presented) The composition of claim 21, wherein said genomic DNA is mammalian genomic DNA.

23. (Previously Presented) The composition of claim 22, wherein said mammalian genomic DNA is human genomic DNA.

24. (Previously Presented) The composition of claim 21, wherein the segments of a) and b) are in the range of 100 to 5,000 bp in length.

25. (Previously Presented) The composition of claim 21, wherein the segments of a) and b) are 400 bp or less in length.

26. (Previously Presented) The composition of claim 21, wherein:

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the different segments of said first nucleic acid molecule are distributed along said first nucleic acid molecule; and

the different segments of said second nucleic acid molecule are distributed along said second nucleic acid molecule.

27. (Previously Presented) The composition of claim 26, wherein:

the different segments of said first nucleic acid molecule are distributed along said first nucleic acid molecule at intervals in the range of 250 bp to 5kb; and

the different segments of said second nucleic acid molecule are distributed along said second nucleic acid molecule at intervals in the range of 250 bp to 5kb.

28. (Previously Presented) The composition of claim 21, wherein:

substantially all of said first nucleic acid molecule of said contiguous region is represented in said first plurality of segments; and

substantially all of said second nucleic acid molecule of said contiguous region is represented in said second plurality of segments.

29. (Previously Presented) The composition of claim 21, wherein said contiguous region is up to 30kb in length.

30. (Previously Presented) The composition of claim 21, wherein said genomic DNA is genomic DNA from a virus or a bacterium.

31. (Previously Presented) The composition of claim 21, further comprising a third plurality of different segments of a third nucleic acid molecule of said contiguous region, wherein each of said third plurality of segments is appended to a third MID sequence and said third MID sequence is different to said first and second MID sequences.

32-33. (Cancelled)

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REMARKS

Formal Matters

Claims 21-31 are pending.

Claim 21 is amended to correct a typographical error. No new matter is added.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of $3,000.00 beyond that authorized on the credit card, but not more than $3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number CGLC-020CON2.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Date: September 9, 2013

By: /James S. Keddie, Reg. No. 48,920/
James S. Keddie
Registration No. 48,920

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Parse Biosciences, Inc. v. 10x Genomics, Inc.
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Electronic Patent Application Fee Transmittal

Application Number:	13859450
Filing Date:	09-Apr-2013
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Filer:	James Samuel Keddie
Attorney Docket Number:	CGLC-020CON2

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	2501	1	890	890
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	1190

Electronic Acknowledgement Receipt	
EFS ID:	16787210
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	09-SEP-2013
Filing Date:	09-APR-2013
Time Stamp:	17:21:28
Application Type:	Utility under 35 USC 111(a)

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Payment Type	Credit Card
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1	Issue Fee Payment (PTO-85B)	CGLC-020CON2-Issue_Fee_Trans-.pdf	252772	no	2
Warnings:					
Information:					
2		CGLC-020CON2-1-312-Amend.pdf	32800	yes	4

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment after Notice of Allowance (Rule 312)	1	1
	Claims	2	3
	Applicant Arguments/Remarks Made in an Amendment	4	4

Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	31693	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	317265		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/859,450	04/09/2013	SYDNEY BRENNER	CGLC-020CON2	9317

95726 7590 09/19/2013

EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

EXAMINER	
BHAT, NARAYAN KAMESHWAR	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
09/19/2013	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com
zuehlke@bozpat.com

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00531

Response to Rule 312 Communication	Application No.	Applicant(s)
	13/859,450	BRENNER ET AL.
	Examiner	Art Unit
	NARAYAN BHAT	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ The amendment filed on *09 September 2013* under 37 CFR 1.312 has been considered, and has been:

a) ☐ entered.

b) ☒ entered as directed to matters of form not affecting the scope of the invention.

c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

d) ☐ disapproved. See explanation below.

e) ☐ entered in part. See explanation below.

The claim amendments do not introduce any new matter.

/Narayan K. Bhat/
Primary Examiner, Art Unit 1634

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00532

OK TO ENTER: /N.B./

Filed Electronically

AMENDMENT UNDER 37 C.F.R. §1.312 Address to: Mail Stop Issue Fee Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450		
	Attorney Docket	CGLC-020CON2
	Confirmation No.	9317
	First Named Inventor	Brenner, Sydney
	Application Number	13/859,450
	Filing Date	April 9, 2013
	Group Art Unit	1634
	Examiner Name	Bhat, Narayan Kameshwar
	Title "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"	

Sir:

This amendment is responsive to the Notice of Allowance and Fees Due dated November 23, 2013. Applicants submit that the amendments set forth below raise no new issues and entry of these amendments is thus respectfully requested.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
13/859,450	10/22/2013	8563274	CGLC-0200CON2	9317

93726 7590 10/02/2013

EPA - Bozicevic Field & Francis LLP
Bozicevic, Field & Francis
1900 University Ave
Suite 200
East Palo Alto, CA 94303

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

SYDNEY BRENNER, ELy, UNITED KINGDOM;
GI MIKAWA, Great Shelford, UNITED KINGDOM;
ROBERT OSBORNE, Great Chesterford, UNITED KINGDOM;
ANDREW SLATTER, London, UNITED KINGDOM;
Population Genetics Technologies Ltd, Cambridge, UNITED KINGDOM, Assignee (with 37 CFR 1.172 Interest);

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

PTO/SB/47 (03-09)
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"FEE ADDRESS" INDICATION FORM

Address to:
Mail Stop M Correspondence
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Fax to:
571-273-6500

- OR -

INSTRUCTIONS: The issue fee must have been paid for application(s) listed on this form. In addition, only an address represented by a Customer Number can be established as the fee address for maintenance fee purposes (hereafter, fee address). A fee address should be established when correspondence related to maintenance fees should be mailed to a different address than the correspondence address for the application. **When to check the first box below:** If you have a Customer Number to represent the fee address. **When to check the second box below:** If you have no Customer Number representing the desired fee address, in which case a completed Request for Customer Number (PTO/SB/125) must be attached to this form. For more information on Customer Numbers, see the Manual of Patent Examining Procedure (MPEP) § 403.

For the following listed application(s), please recognize as the "Fee Address" under the provisions of 37 CFR

1.363 the address associated with:

☒ Customer Number: **00197**

OR

☐ The attached Request for Customer Number (PTO/SB/125) form.

PATENT NUMBER (if known)	APPLICATION NUMBER
8,563,274	**13/859,450**

Completed by (check one):

☐ Applicant/Inventor

☒ Attorney or Agent of record **48,920** (Reg. No.)

☐ Assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

☐ Assignee recorded at Reel _____ Frame _____

/James S. Keddie, Reg. No. 48,920/
Signature

James S. Keddie
Typed or printed name

(650) 833-7723
Requester's telephone number

February 5, 2014
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more that one signature is required, see below*.

☒ * Total of **1** forms are submitted.

This collection of information is required by 37 CFR 1.363. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 5 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop M Correspondence, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	18115673
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	05-FEB-2014
Filing Date:	09-APR-2013
Time Stamp:	17:02:10
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Post Allowance Communication - Incoming	CGLC-020CON2_Fee_Address_Ind.pdf	25444 9b2dde4cef04ecd803d4910bd1506c3b663c5792	no	1

Warnings:

Information:

Total Files Size (in bytes):	25444

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Filed Electronically

CHANGE OF CORRESPONDENCE ADDRESS		
	Attorney Docket	CGLC-020CON2
	First Named Inventor	Brenner, Sydney
	Application Number	13/859,450
	Confirmation No.	9317
	Filing Date	04/09/2013
	Group Art Unit	1634
Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Examiner Name	Bhat, Narayan Kameshwar
	Title: "Compositions and Methods for Intramolecular Nucleic Acid Rearrangement"	

Please change the Correspondence Address for the above-identified application to:

☒ **The address associated with Customer Number 43850**

Firm Name	Morgan, Lewis & Bockius LLP		
Individual Name			
Address	One Market, Spear Street Tower		
City, State, Zip	San Francisco, California 94105		
Country	U.S.A.		
Telephone	(415) 442-1000	Facsimile	(415) 442-1001

SIGNATURE OF ATTORNEY/AGENT OF RECORD

Name/Reg. No.	James S. Keddie, 48,920	Date	
Signature	/James S. Keddie, Reg. No. 48,920/	Date	07-27-2016

Electronic Acknowledgement Receipt

EFS ID:	26471760
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	93726
Filer:	James Samuel Keddie
Filer Authorized By:	
Attorney Docket Number:	CGLC-020CON2
Receipt Date:	27-JUL-2016
Filing Date:	09-APR-2013
Time Stamp:	19:25:06
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Change of Address	CGLC-020CON2-Change_Corresp.pdf	20101 cc005e81f9f34e9e24ab676d7136dccbda9b6323	no	1

Warnings:

Information:	
Total Files Size (in bytes):	20101

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/80 (07-12)
Approved for use through 11/30/2014. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

■ Practitioners associated with Customer Number: 43850

OR

☐ Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignments documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

■ The address associated with Customer Number: 43850

OR

☐

Firm or Individual Name			
Address			
City		State	Zip
Country			
Telephone		Email	

Assignee Name and Address: 10X Genomics, Inc.
7068 Koll Center Parkway, Suite 401
Pleasanton, CA 94566

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be Filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of The practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record
The individual whose signature and title is supplied below is authorized to act on behalf of the assignee

Signature	[signature]	Date	8/13/2015
Name	Matthew Murphy	Telephone	(925) 401-7495
Title	Vice President, General Counsel		

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	28637537
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	43850
Filer:	Gargi Talukder/Sheila Gloss
Filer Authorized By:	Gargi Talukder
Attorney Docket Number:	104371-5016-US02
Receipt Date:	15-MAR-2017
Filing Date:	09-APR-2013
Time Stamp:	19:58:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		US02_POA.pdf	205252 3f5c55ac76f37b02b7c5c44a9f859a406d3d1f4a	yes	2

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Assignee showing of ownership per 37 CFR 3.73	1	1
	Power of Attorney	2	2
Warnings:			
Information:			
	Total Files Size (in bytes):	205252	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
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National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
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PTO/SB/96 (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: 10X GENOMICS, INC.

Application No./Patent No.: 8,563,274 Filed/Issue Date: October 22, 2013

Titled: COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT

10X GENOMICS, INC., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.

states that it is:

1. ☒ the assignee of the entire right, title, and interest in;

2. ☐ an assignee of less than the entire right, title, and interest in (The extent (by percentage) of its ownership interest is _____ %); or

3. ☐ the assignee of an undivided interest in the entirety of (a complete assignment from one of the joint inventors was made)

the patent application/patent identified above, by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 039162, Frame 0376, or for which a copy therefore is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

1. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at

Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(b)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (*i.e.*, a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Gargi Talukder — Signature — 3/15/17 — Date

Gargi Talukder — Printed or Typed Name — Attorney of record — Title

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/859,450	04/09/2013	SYDNEY BRENNER	104371-5016-US02

CONFIRMATION NO. 9317

POWER OF ATTORNEY NOTICE

43850
MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

Date Mailed: 03/23/2017

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/15/2017.

- The Power of Attorney to you in this application has been revoked by the applicant. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mabebe/

10x Genomics, Inc. Exhibit 2002
Parse Biosciences, Inc. v. 10x Genomics, Inc.
IPR2023-00958
Page 00545

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
13/859,450	04/09/2013	SYDNEY BRENNER	104371-5016-US02

CONFIRMATION NO. 9317

43850
MORGAN, LEWIS & BOCKIUS LLP (SF)
One Market, Spear Street Tower, Suite 2800
San Francisco, CA 94105

POA ACCEPTANCE LETTER

OC000000090077919

Date Mailed: 03/23/2017

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/15/2017.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/mabebe/

PTO/SB/123 (04-15)
Approved for use through 01/31/2018. OMB 0651-0035
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CHANGE OF CORRESPONDENCE ADDRESS
Patent

Address to:
Mail Stop Post Issue
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Patent Number	8,563,247
Issue Date	October 22, 2013
Application Number	13/859,450
Filing Date	April 9, 2013
First Named Inventor	Sydney BRENNER
Attorney Docket Number	104371-5016-US02

Please change the Correspondence Address for the above-identified patent to:

☒ The address associated with Customer Number: 156830

OR

☐ **Firm *or* Individual Name**

Address

City | **State** | **ZIP**

Country

Telephone | **Email**

This form cannot be used to change the data associated with a Customer Number. To change the data associated with an existing Customer Number use "Request for Customer Number Data Change" (PTO/SB/124).

This form will not affect any "fee address" provided for the above-identified patent. To change a "fee address" use the "Fee Address Indication Form" (PTO/SB/47).

I am the:

☐ Patentee.

☐ Assignee of record of the entire interest. See 37 CFR 3.71.
Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96).

☒ Attorney or agent of record. Registration Number 61,368.

Signature /Gargi Talukder/

Typed or Printed Name Gargi Talukder

Date August 10, 2018 | Telephone 415.442.1000

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☐ *Total of _____ forms are submitted.

This collection of information is required by 37 CFR 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Mail Stop Post Issue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Electronic Acknowledgement Receipt

EFS ID:	33437663
Application Number:	13859450
International Application Number:	
Confirmation Number:	9317
Title of Invention:	COMPOSITIONS AND METHODS FOR INTRAMOLECULAR NUCLEIC ACID REARRANGEMENT
First Named Inventor/Applicant Name:	SYDNEY BRENNER
Customer Number:	43850
Filer:	Gargi Talukder/Sheila Gloss
Filer Authorized By:	Gargi Talukder
Attorney Docket Number:	104371-5016-US02
Receipt Date:	10-AUG-2018
Filing Date:	09-APR-2013
Time Stamp:	17:13:37
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Change of Address	104371-5016-US02_Corr.pdf	64127 a3e3be40238cf6a7afaaeb2e57daf876f8819c9	no	1

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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
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New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY.DOCKET NO./TITLE	REQUEST ID
13/859,450	04/09/2013	SYDNEY BRENNER	104371-5016-US02	136623

Acknowledgement of Loss of Entitlement to Entity Status Discount

The entity status change request below filed through Private PAIR on 04/13/2021 has been accepted.

CERTIFICATIONS:

Change of Entity Status:

X Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be notification of loss of entitlement to small or micro entity status, as applicable.

This portion must be completed by the signatory or signatories making the entity status change in accordance with 37 CFR 1.4(d)(4).

Signature:	/Louis T. Nguyen/
Name:	Louis T. Nguyen
Registration Number:	58729