



ORAL ARGUMENT FOR IPR2024-01504

U.S. Patent No. 11,098,357

Patent Owner's Hearing Demonstratives

January 22, 2026

Key Points

➤ The challenged claims require the identifier and target sequence to be used in combination

➤ ***Petitioner's ground 1 fails***

- **Kivioja** does not use the target sequence with the identifier to identify duplicates
- **Kivioja** does not teach removal of a duplicate read from the sequencing reads (Claim 2)
- Petitioner has failed to provide sufficient evidence to establish a motivation to combine **lafrate** and **Kivioja**

➤ ***Petitioner's grounds 2 and 3 fail***

- **Bielas** identifies duplicate sequences based only on Cypher sequences
- **Bielas** is similar to Samuels, cited and overcome during prosecution

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➤ *Petitioner's grounds 2 and 3 fail*

- **Bielas** identifies duplicate sequences based only on Cypher sequences
- **Bielas** is similar to Samuels, cited and overcome during prosecution

Claim Construction – “identifying sequence reads with identical identifier and target sequences as duplicates”

 US011098357B2	
(12) United States Patent Amorese et al.	(10) Patent No.: US 11,098,357 B2 (45) Date of Patent: *Aug. 24, 2021
(54) COMPOSITIONS AND METHODS FOR IDENTIFICATION OF A DUPLICATE SEQUENCING READ	2,035,996 A 7/10/01 Hinkley 5,043,575 A 8/19/01 Hinkley 5,082,830 A 10/02/01 Hinkley et al. 5,095,551 A 2/19/02 Long 6,130,258 A 7/10/03 Vohde et al. 6,169,796 A 12/19/02 Schuster et al. 6,171,534 A 12/19/02 Smith et al. 6,164,370 A 1/16/03 Kevlinger et al. 6,216,131 A 6/10/03 Kerner 6,224,807 A 8/19/03 Boun et al. 6,235,033 A 8/19/03 Summerton et al. 6,242,754 A 9/10/03 Whitely et al. 6,384,424 A 11/01/03 Gales 6,388,623 A 11/01/03 Sanghera et al. 6,400,491 A 7/10/03 Kocian et al. 6,409,818 A 4/10/03 Davey et al. 6,418,149 A 5/10/03 Gelland et al. 6,425,771 A 6/10/03 Chan et al. 6,437,929 A 6/10/03 Ricchetti et al. 6,480,784 A 11/09/03 Kasian et al. 6,494,810 A 4/10/04 Huang et al. 6,500,169 A 4/10/04 Dequay et al. 6,508,178 A 4/10/04 Wain et al. 6,510,270 A 4/10/04 Fedor et al. 6,525,471 A 6/10/04 Zeng 6,545,522 A 8/19/04 Van Oelst et al. 6,554,516 A 9/10/04 Kocian et al. 6,554,517 A 9/10/04 Davey et al. 6,556,787 A 9/10/04 Lockhart et al. 6,565,340 A 10/10/04 Choudhry et al. 6,572,917 A 11/10/04 Kuznetsov et al. 6,578,832 A 11/10/04 Torkelson et al. 6,580,339 A 12/10/04 Hampton et al. 6,602,249 A 2/10/07 De Montaudou et al. (Continued)
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days. This patent is subject to a terminal disclaimer.	
(21) Appl. No. 16/743,604	
(22) Filed: Jan. 15, 2020	
(65) Prior Publication Data US 2020/0239953 A1 Jul. 30, 2020	
Related U.S. Application Data	
(60) Continuation of application No. 15/405,002, filed on Jan. 15, 2017, now Pat. No. 10,570,448, which is a division of application No. 14/540,917, filed on Nov. 13, 2014, now Pat. No. 9,546,399.	FOREIGN PATENT DOCUMENTS CA 2444926 A1 11/2002 CN 1661102 A 8/2005 (Continued)
(69) Provisional application No. 61/903,826, filed on Nov. 13, 2013.	OTHER PUBLICATIONS Thermin publication No. 770-7108-011, Multiplexed Sequencing with the Thermo Sequencing System, pp. 1-4 (Year 2018). Vadi et al., Next generation sequencing for molecular diagnosis of cardiovascular disease, Asia Neurosurg., vol. 124, pp. 273-283 plus supplemental material (p. 1-10) (Year 2017). Amos, 2006, DNA pooling in mutation detection with reference to sequence analysis, Am. J. Hum. Genet. 66:1089-1097. Hefoss, 2014, cavaSeq: detecting copy number variation in long-range targeted sequencing data, Nucleic Acids Res. 42:1016-1028. Jezewski, 2013, Constant, Next-Gen Sequencing, vol. 124, pp. 273-283 plus supplemental material (p. 1-10) (Year 2017). Dismukes, 2013, Targeted RNA-Sequencing with Competitive Multiplex-PCR Amplification Libraries, PLOS ONE 8(11):e79140. Todi, 2013, Comparison of commercially available target enrichment methods for next-generation sequencing, J. Biomol. Tech. 24:73-86. (Continued)
(51) Int. Cl. C12Q 1/6874 (2018.01) C12Q 1/6869 (2018.01)	
(52) U.S. Cl. CPC C12Q 1/6874 (2013.01); C12Q 1/6869 (2013.01); C12Q 2325/179 (2013.01); C12Q 2325/191 (2013.01)	
(58) Field of Classification Search CPC C12Q 1/6869; C12Q 2325/179; C12Q 2325/191; C12Q 2325/192 See application file for complete search history.	
(56) References Cited U.S. PATENT DOCUMENTS 4,362,867 A 12/1982 Paldanius 4,418,066 A 7/1984 Candiani et al. 4,469,063 A 9/1984 Jo et al. 4,582,977 A 4/1986 Panchuk et al. 4,876,187 A 10/1989 Duke et al. 4,925,505 A 6/1990 Sogahata 4,935,357 A 7/1990 Chiruk 4,942,124 A 1/1991 Lankford et al. 4,958,617 A 2/1991 Heller et al. 4,996,143 A 2/1991 Duke et al. 5,011,769 A 7/1991 Summerton et al. 5,024,506 A	
IDT Exhibit 1004.0001	

The invention claimed is:

1. A method for detecting duplicate sequencing reads, the method comprising:

ligating an adaptor to each of a plurality of nucleic acid fragments, wherein each adaptor comprises a unique identifier having from about 1 to about 8 nucleotides, an indexing site unique to a subset of the adaptors, and a primer binding site;

amplifying the adaptor-ligated fragments into amplicons; sequencing the amplicons to produce sequence reads that include identifier and target sequences; and

identifying sequence reads with identical identifier and target sequences as duplicates.

Tecan's Construction

“identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence”

Petitioner's Construction

“identifying sequence reads with identical identifier and target sequences as duplicates”

This limitation requires the entire “target sequence” and does not require a single “step.”

Prosecution History is Critical Intrinsic Evidence



The prosecution history is often of critical significance in determining the meaning of the claims because it contains . . . any express representations made by the applicant regarding the scope of the claims.

Genentech, Inc. v. Iancu, 809 F. App'x 781, 783 (Fed. Cir. 2020).



Nonetheless, the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be.

Phillips v. AWH Corp., 415 F.3d 1303, 1317 (Fed. Cir. 2005).

The Prosecution History of the '357 Patent

Dec. 28, 2015, Amendment/Response to Office Action

Attorney Docket No. NUGN-001/01US 301735-2003

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: AMORESE, Douglas, Confirmation No.: 7076
et al.

Application No.: 14/540,917 Group Art Unit: 1637

Filed: November 13, 2014 Examiner: Teresa E. Strzelecka

For: COMPOSITIONS AND METHODS FOR IDENTIFICATION OF A DUPLICATE
SEQUENCING READ

Filed via EFS
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT/RESPONSE TO OFFICE ACTION

In response to the Final Office Action dated September 28, 2015, this paper is timely filed within the 3-month period for reply ending December 28, 2015. Please amend the above-identified patent application in the following manner:

Amendments to the Claims are reflected in the listing of the claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

125135876 v1

1

1. (Currently Amended) A method for detecting a duplicate sequencing read from a population of sample sequencing reads comprising:
 - a) ligating an adaptor to a 5' end of each nucleic acid fragment of a plurality of nucleic acid fragments from one or more samples, wherein the adaptor comprises:
 - (i) an indexing primer binding site;
 - (ii) an indexing site;
 - (iii) an identifier site consisting of comprising at least between 1 and 8 nucleotides; and
 - (iv) a target sequence primer binding site;
 - b) amplifying the adapter-nucleic acid fragment ligated products;
 - c) generating a population of sequencing reads from amplified adapter-nucleic acid fragment ligated products; and
 - d) ~~detecting~~ identifying a duplicate sequencing read as the population of sequencing reads comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads a sequencing read with a duplicate identifier site and target sequence;

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125153876 v1

1

Dec. 28, 2015, Amendment/Response to Office Action

Samuels *et al.* do not teach (1) the active step of “identifying a duplicate sequencing read
as the sequencing read comprising the same identifier site and nucleic acid fragment as another
sequencing read in the population of sequencing reads;” (emphasis added); or (2) adaptors

EX1018.0797-798

purposes of comparing the instant claims with the disclosure of McCloskey *et al.* However, the
instant invention relies on the indexing site for batch identification of samples, and the sequence
of the identifier site and the sequence of the fragment that is amplified are used in combination to
discern duplication. This is very different than the method disclosed in McCloskey *et al.*

EX1018.0798

The Prosecution History of the '357 Patent

Application/Control Number: 16/743,604
Art Unit: 1637

Page 2

DETAILED ACTION

Notice of Pre-AIA or AIA Status

1. The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.
2. Claims 22-32 are pending and under consideration.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on July 22, 2020 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Interpretation

4. Applicant defined the term “adaptor” in paragraph [0027] as follows:

“An adapter refers to an oligonucleotide sequence, the ligation of which to a target polynucleotide or a target polynucleotide strand of interest enables the generation of amplification-ready products of the target polynucleotide or the target polynucleotide strand of interest.”

Therefore, since any oligonucleotide can perform such function, any oligonucleotide is considered to anticipate this term.

5. Applicant defined the term “identifier site” in paragraph [0030] as follows:

“An identifier site is a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.”

6. Applicant defined the term “universal primer” in paragraph [0035] as follows:

IDT Exhibit 1019.0399

Mar. 5, 2021, Amendment/Response to Office Action

This is obviated in the claimed methods by using the identifier and fragment sequence to identify duplicate reads. Moreover, because the fragment sequence is used in conjunction with the identifier to find duplicates, the identifier can be less complex than the “barcode” in McCloskey. The lower complexity of adaptors comprising fewer nucleotides proves more cost-

EX.1019.0453

Example 5 of the '357 Patent

Forward adaptor 5'

AATGATACGGCGACCACCGAGATCTACACTCTTTCCCTACACGACGCT (SEQ ID NO: 4)

CTTCCGATCTNNNNNNNN,

Reverse adaptor 1) 5'

CAAGCAGAAGACGGCATACGAGATTCCTTGTGACTGGAGTTCAGACG (SEQ ID NO: 5)

TGTGCTCTTCCGATCTNNNNNNNN,

Reverse adaptor 2) 5'

CAAGCAGAAGACGGCATACGAGATTGAAGGTGACTGGAGTTCAGACG (SEQ ID NO: 6)

TGTGCTCTTCCGATCTNNNNNNNN, and

Common partner 5' NNNNNNNNAGATCGGAAGAGC (SEQ ID NO: 7)



Identifier Site



Index Site



Sequencing Primer Binding Site

Coralville, Iowa). The reverse adaptors each contain a unique identifier (underlined) that enables libraries made with these adaptors to be distinguished. In this case N represents an equimolar mixture of A, C, G, and T. A mixture of 5 uM forward, 5 uM reverse, and 10 uM common in 10

* * *

GAllx, MiSeq, or Hi Seq sequencing instruments (Illumina Inc., San Diego, Calif.). The following series is run: 50 base first read, 6 base second read. A third read is not required for counting purposes or duplication analysis.

Data Analysis: The sequencer output was processed in accordance with manufacturer's recommendation. The 6 bases of the index read is used for standard library parsing, separating the data files from the two sample types. The first 50 bases of the target sequence read are compared to each other. Any read that has identical sequence to any other read is identified as a duplicate and removed from the population, thus, only a single copy is retained within the file. Once the

EX1004.0021, 20:19-23; 20:51-62

Expert Testimony Supports Tecan's Construction



**Carlos Bustamante,
Ph.D.**
Tecan's Expert

84. It is my opinion that based on the claim language, specification, and prosecution history, a POSA would understand the term “identifying sequence reads with identical identifier and target sequences as duplicates” to mean “identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence.” In my opinion, this construction is consistent with how “identifying sequence reads with identical identifier and target sequences as duplicates” is used by the '357 patent.

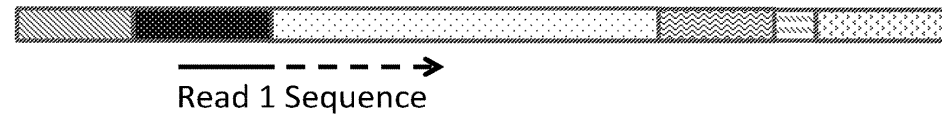
85. For example, Example 5 of the '357 patent describes a process of identifying duplicate sequencing reads. Example 5 is an experiment wherein “[t]otal

EX2035.¶¶84-85

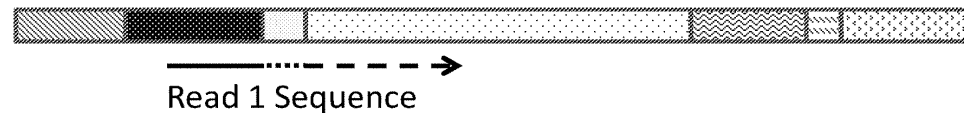
Claims Require Use of a Portion of the Target Sequence

DNA Sequencing With Duplicate Recognition at the insert junction

- Traditional library, sequence read 1 (forward read)

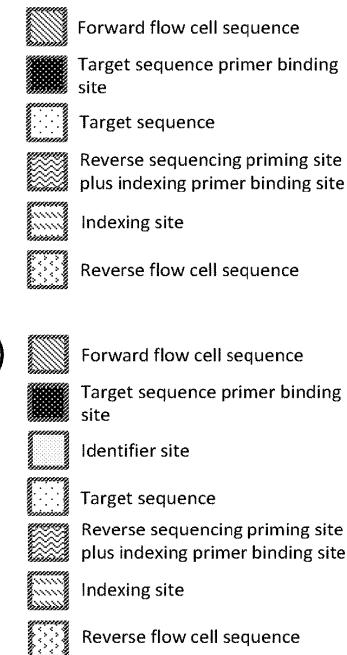


- Duplicate recognition library, sequence read 1 (forward read)



Read 1 initially records the approximately 8 random bases of the identifier site appended to the library sequences, followed by the target sequence

Figure 4



U.S. Patent

Aug. 24, 2021

Sheet 5 of 6

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Key Points

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Petitioner's ground 1 fails

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- Petitioner has failed to provide sufficient evidence to establish a motivation to combine **lafrate** and **Kivioja**

Petitioner's grounds 2 and 3 fail

- **Bielas** identifies duplicate sequences based only on Cypher sequences
- **Bielas** is similar to Samuels, cited and overcome during prosecution

Kivioja Does Not Use the Target Sequence to Identify Duplicates

BRIEF COMMUNICATIONS

Counting absolute numbers of molecules using unique molecular identifiers

Teemu Kivioja^{1,2,3,5}, Anna Vähärautio^{1,3,5}, Kasper Karlsson⁴, Martin Bonke⁴, Martin Enge³, Sten Linnarsson⁴ & Jussi Taipale³

Counting individual RNA or DNA molecules is difficult because they are hard to copy quantitatively for detection. To overcome this limitation, we applied unique molecular identifiers (UMIs), which make each molecule in a population distinct, to genome-scale human karyotyping and mRNA sequencing in *Drosophila melanogaster*. Use of this method can improve accuracy of almost any next-generation sequencing method, including chromatin immunoprecipitation–sequencing, genome assembly, diagnostics and manufacturing-process control and monitoring.

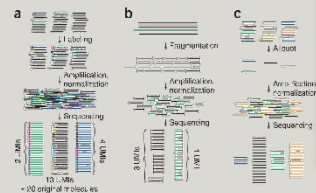
Determining the relative abundance of two different molecular species or the absolute number of molecules in a single sample is challenging. We describe an absolute counting method that can use amplification but does not require detecting each original molecule or keeping track of the number of copies made. In this method, each molecule in a population is first made unique. This can be accomplished by adding a random DNA sequence label, by fragmenting or by taking an aliquot of a complex mixture that is small enough to contain only distinct molecules (Fig. 1a–c). Any combination of these manipulations can be used to generate a library in which each molecule has a distinct identifying

sequence. We designate the resulting sequences that can be used to uniquely identify copies derived from each molecule unique molecular identifiers (UMIs; Fig. 1).

As long as the complexity of the library of molecules is maintained, the library can be amplified, normalized or otherwise processed without loss of information about the original molecule count because the number of UMIs in the library acts as a molecular memory of the number of molecules in the starting sample (Supplementary Fig. 1). Upon deep sequencing, each UMI will be observed multiple times, and the number of original DNA molecules can be determined simply by counting each UMI only once. However, long before all UMIs are observed, increasingly precise estimates of the absolute molecule number can be made (Online Methods). This is in contrast to other counting methods such as direct single-molecule sequencing^{1–3}, which require that all counted molecules are observed directly. In addition, many existing digital molecule counting methods such as digital PCR⁴, digital microarray profiling⁵ and direct single-molecule sequencing^{1–3} cannot be effectively multiplexed and are thus generally not applicable to measuring one or few molecular species from many samples, or many species from a single sample. Counting methods that introduce random tags to make molecules unique before amplification have been suggested^{6,7} and applied to analysis of RNA–protein interactions^{8,9}. In addition, three recent publications applied such labeling methods to the analysis of selected target genes by using either microarrays⁸ or sequencing^{9–11}. Here we apply the idea more generally and show that it can be used for absolute quantification.

The UMI method is very effective on simulated data (Supplementary Fig. 1). To assess whether it can be used to improve experimental measurements, we applied UMI counting to digital karyotyping and mRNA sequencing (mRNA seq).

Figure 1 | UMIs can be generated by adding oligonucleotide labels, fragmenting, taking a small enough aliquot or a combination thereof. (a) Three different DNA species (green, blue and black lines) are labeled with a collection of random labels (colored filled circles). Two green molecules are originally present (top), corresponding to two different UMIs (red, blue) among the sequenced molecules (green; bottom). Information about the original number of molecules (top) is preserved in the number of different UMIs detected by sequencing a sample of this amplified and normalized library (bottom). Even if some UMIs are not observed, the original number of molecules can be estimated using count statistics. (b) The original molecule is randomly fragmented, and a short unique sequence from the resulting fragments constitutes each UMI; here only the fragment adjacent to the poly(A) sequence (red vertical bars) is amplified. (c) An aliquot is taken from a sample that has many identical molecules such that on average, less than one copy of each molecule remains.



¹Genome-Scale Biology Program, Institute of Biocenter, University of Helsinki, Helsinki, Finland. ²Department of Computer Science, University of Helsinki, Helsinki, Finland. ³Science for Life Laboratory, Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. ⁴Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden. ⁵These authors contributed equally to this work. Correspondence should be addressed to T.K. (teemu.kivioja@helsinki.fi) or J.T. (jussi.taipale@helsinki.fi).

RECEIVED 10 MARCH; ACCEPTED 27 SEPTEMBER; PUBLISHED ONLINE 20 NOVEMBER 2011; DOI:10.1038/NMETH.1778

72 | VOL.9 NO.1 | JANUARY 2012 | NATURE METHODS
IDT Exhibit 1012.0001

amplification cycles, respectively. Total read count of a gene is the number of accepted reads mapped to its reference sequence.

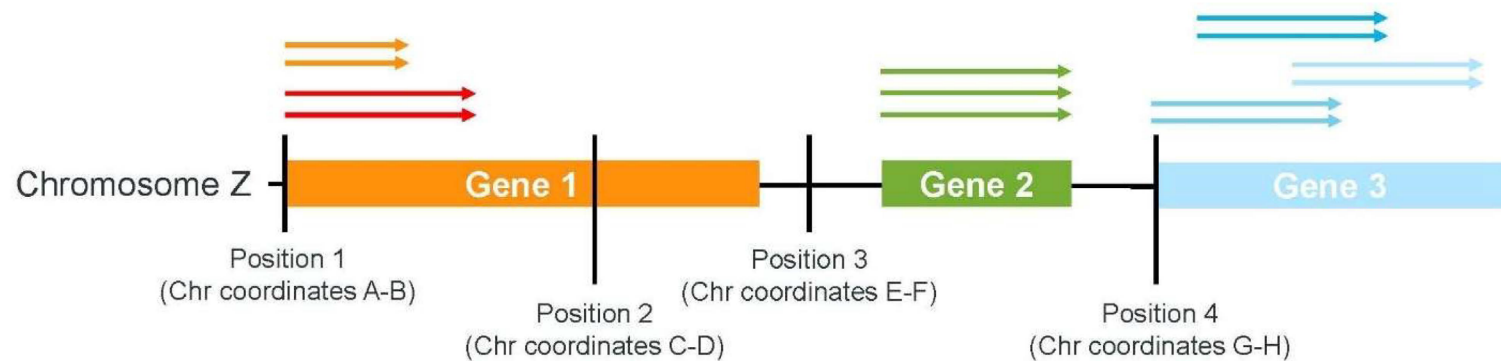
The mapped reads with the same gene, position and label were collected to one UMI and the number of such reads was recorded as the copy number of that UMI. Average copy numbers were 10.7 and 17.0 for samples taken after 15 and 25 PCR cycles, respectively. Sequence errors introduced by library preparation, amplification and sequencing can produce false UMIs with a low

EX1012.0005

Kivioja Does Not Use the Target Sequence to Identify Duplicates

Bustamante Decl.

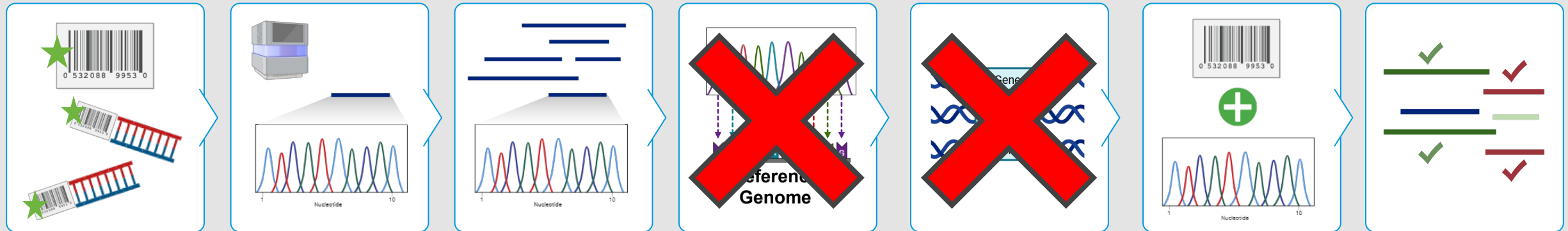
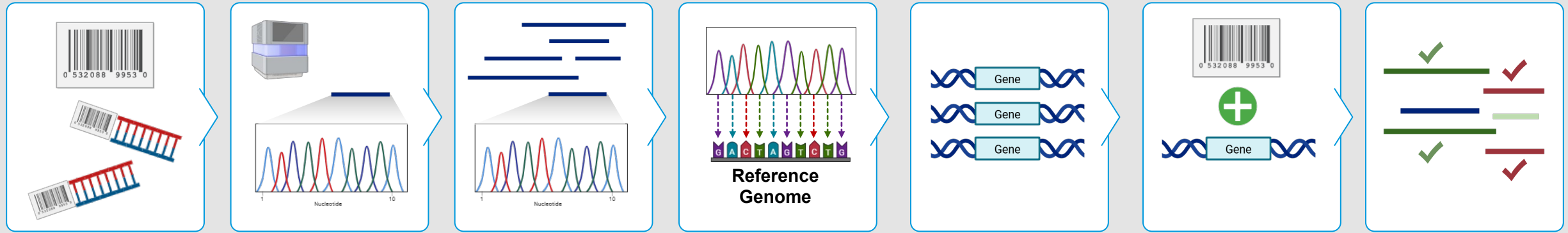
representation of this process is depicted in the below figure. Reads (depicted as colored arrows) are shown aligned to a reference genome, indicating the sequence of the reads match or closely match that sequence of the reference genome.



EX2035.¶113

Kivioja Does Not Use the Target Sequence to Identify Duplicates

Kivioja Method



'357 Patent Method

Kivioja Fig. 1 Does Not Show Use of the Target Sequence

BRIEF COMMUNICATIONS

Counting of molecules

Teemu Kivioja
Kasper Karlsson
Sten Linnarsson

Counting individual molecules is a hard task, but this limitation, which makes each scale human karyotyping almost a next-generation sequencing challenge. We use amplification of molecules or keep method, each molecule can be amplified by fragmenting or is small enough. Any combination of a library in

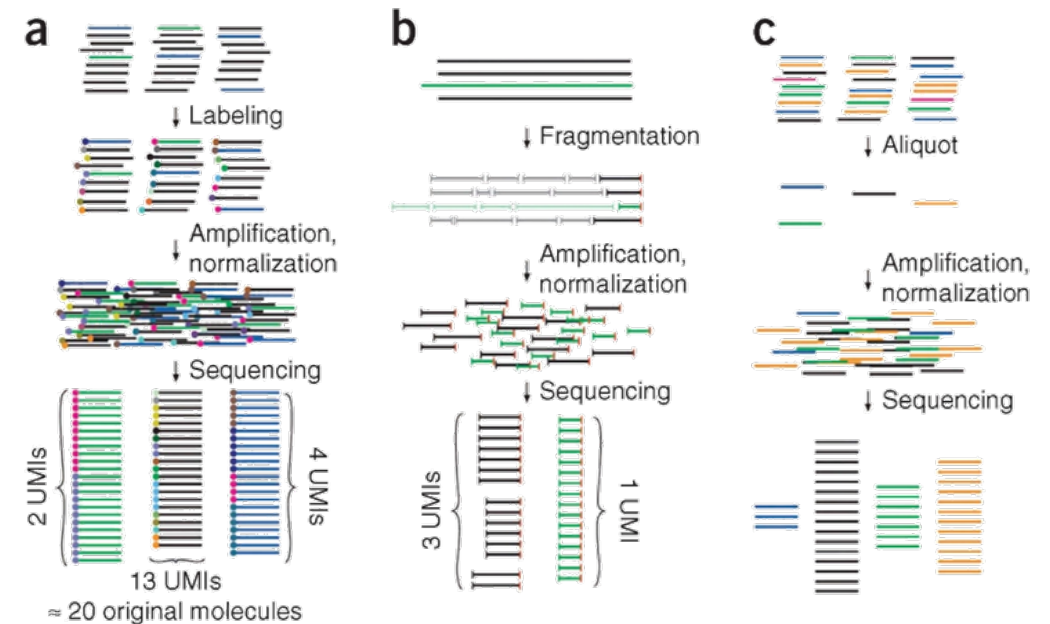
Figure 1 | UMIs can be generated by adding oligonucleotide labels, fragmenting, taking a small enough aliquot or a combination thereof. (a) Three different DNA species (green, blue and black lines) are labeled with a collection of random labels (colored filled circles). Two green molecules are originally present (top), corresponding to two different UMIs (red, blue) among the sequenced molecules (green; bottom). Information about the original number of molecules (top) is preserved in the number of different UMIs detected by sequencing a sample of the amplified and normalized library (bottom). Even if some UMIs are not observed, the original number of molecules can be estimated using count statistics. (b) The original molecule is randomly fragmented, and a short unique sequence from the resulting fragments constitutes each UMI; here only the fragment adjacent to the poly(A) sequence (red vertical bars) is amplified. (c) An aliquot is taken from a sample that has many identical molecules such that on average, less than one copy of each molecule remains.

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72 | VOL.9 NO.1 | JANUARY 2012 | NATURE METHODS

IDT Exhibit 1012.0001



EX1012.0001

Claim 2: Kivioja Does Not Remove Duplicate Reads

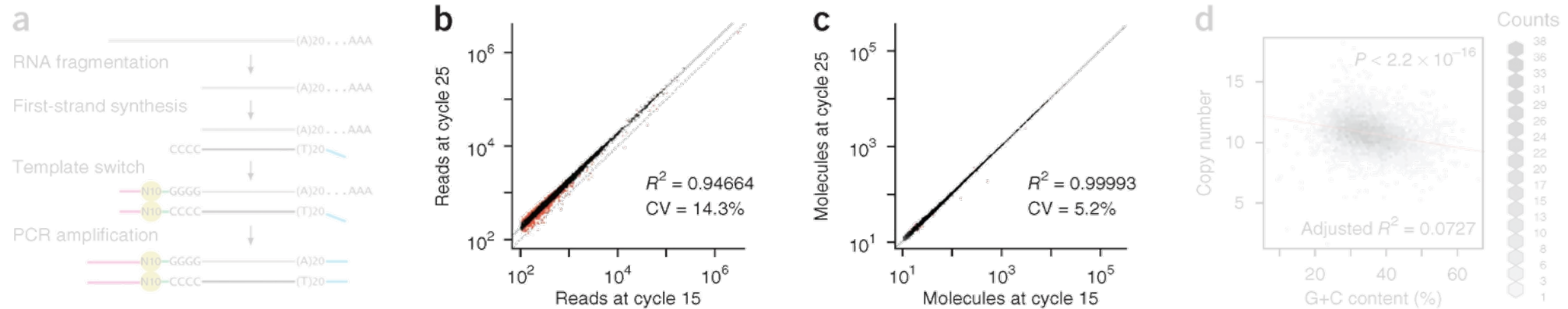


Figure 3 | Accuracy of mRNA-seq can be improved by the UMI method. (a) mRNA-seq libraries were generated by fragmenting total RNA and reverse-transcribing it to cDNA using an oligo(dT) primer with an Illumina linker (blue) and a 5' template switch adaptor containing another Illumina linker (magenta), a 10-base-pair random label (N10) and an index sequence (green). The combination of label sequence and the 5' mapped position of the RNA fragment forms the UMI. (b,c) Measurements of expression of the same set of genes after 15 (x axes) and 25 (y axes) PCR amplification cycles were obtained using total read counts (b) or the UMI method (c). Most individual transcript total read counts obtained in the two measurements are far from each other and from diagonal (dashed gray line), and this effect is corrected by the UMI method (c). Genes whose mean in the two measurements deviated more than 5% from the fitted line (gray, solid) are in red. (d) A density plot shows average copy number of UMIs after 15 PCR cycles as a function of the average G+C content of the fragments for each measured gene from b and c. Red line in d indicates a least-squares fit, for which a P value and adjusted R^2 value are given.

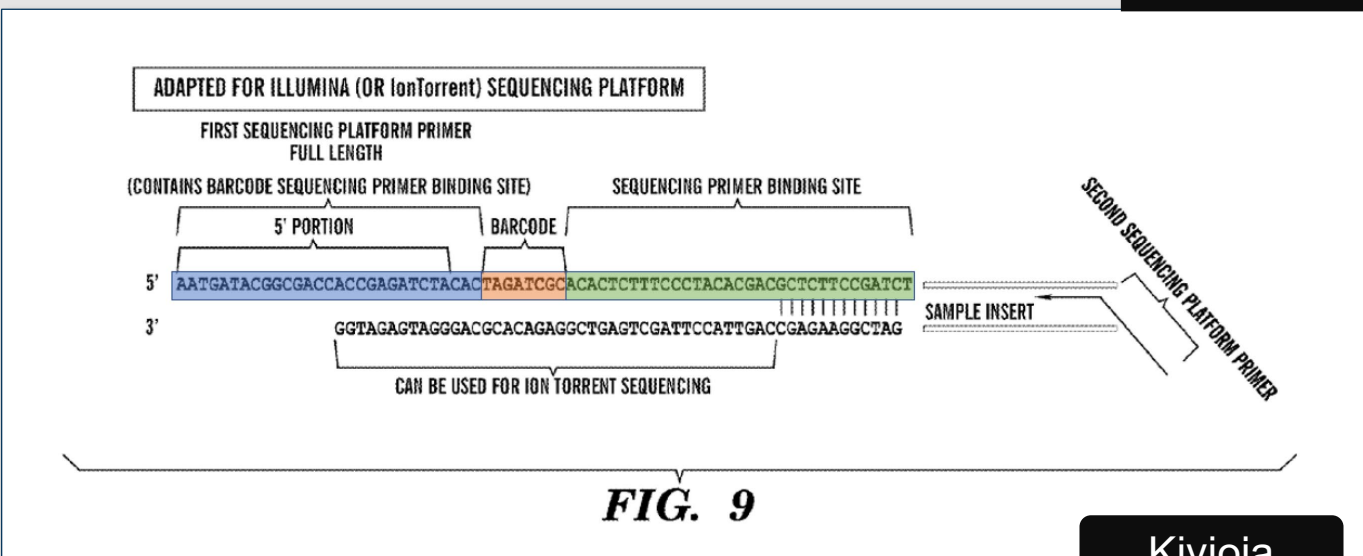
amplification cycles, respectively. Total read count of a gene is the number of accepted reads mapped to its reference sequence.

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EX1012.0002, -0005

Petitioner Fails to Show a Motivation to Combine lafrate and Kivioja

lafrate



Kivioja

Supplementary Table 1. Sequences for oligomers used in mRNA-seq. Sequences in square brackets and parentheses represent an index sequence that was used to enable multiplexed sequencing, and a random ten base DNA sequence label, respectively. dU and rG represent deoxyuridine and guanine ribonucleotide, respectively.

Oligomer	Sequence (5'-3')
Oligo-dT adapter	CAAGCAGAAGACGGCATACGAGCTCTTCCGATCTTTTTTTTTTTTTTTTTTTTTTVN
5'-adapter	ACACTCTTTCCCTACACGACGCTCTTCCGATCT (NNN) dU (NNNN) dU (NNN) [GACTT] rGrGrGrG
Paired-end compatible oligo-dT adapter	CTCGGCATTCTGCTGAACCGCTCTTCCGATCTTTTTTTTTTTTTTTTTTTTTTVN

Key Points



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Petitioner's ground 1 fails

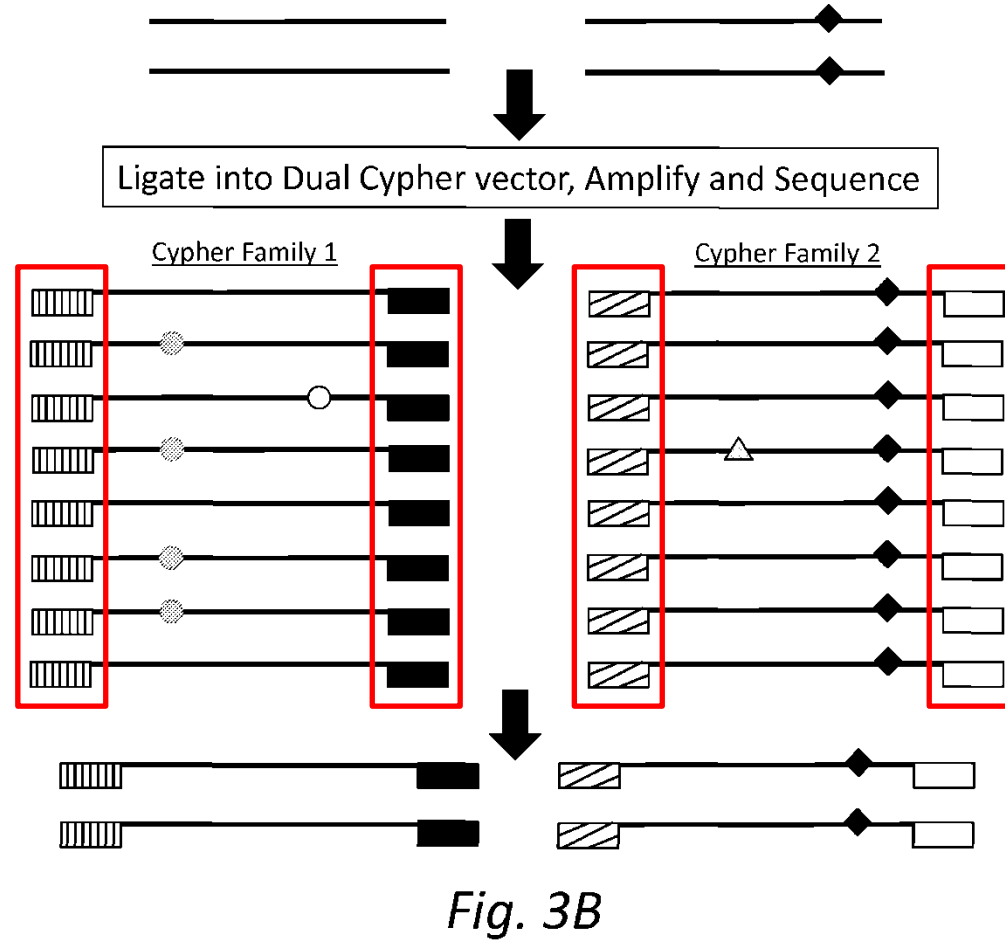
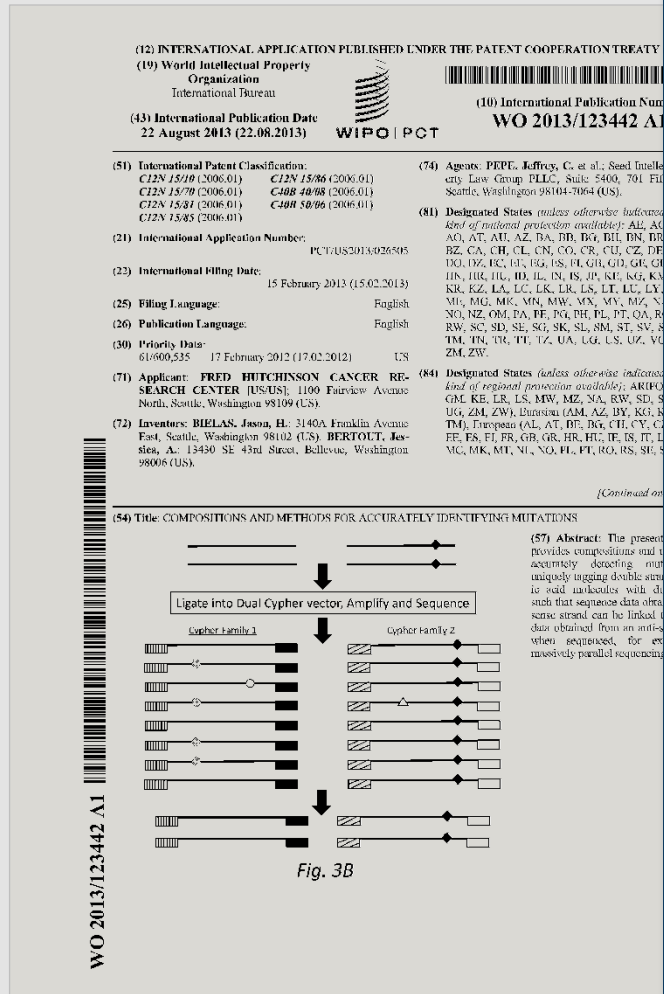
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Bielas Uses Only Cyphers to Group Reads



Bielas Uses Only Cyphers to Group Reads

amplified and sequenced. All sequencing reads having identical cypher pairs, along with their reverse complements, were grouped into families. Comparison of family

The unique cypher tags are used to computationally deconvolute the sequencing data and map all sequence reads to single molecules (*i.e.*, distinguish PCR and sequencing errors from real mutations). Base calling and sequence alignment will be

TP53 Exon 4 DNA from a dual cypher vector library produced in *E. coli* was sequenced with a depth of over a million, and all sequencing reads with identical cypher pairs and their reverse complements were grouped into families to create a consensus sequence. As illustrated in Figure 3B, errors introduced during library preparation

EX1013.0006, -0027, -0031

Bielas Groups Reads in the Same Way as Samuels

Bielas

Samuels

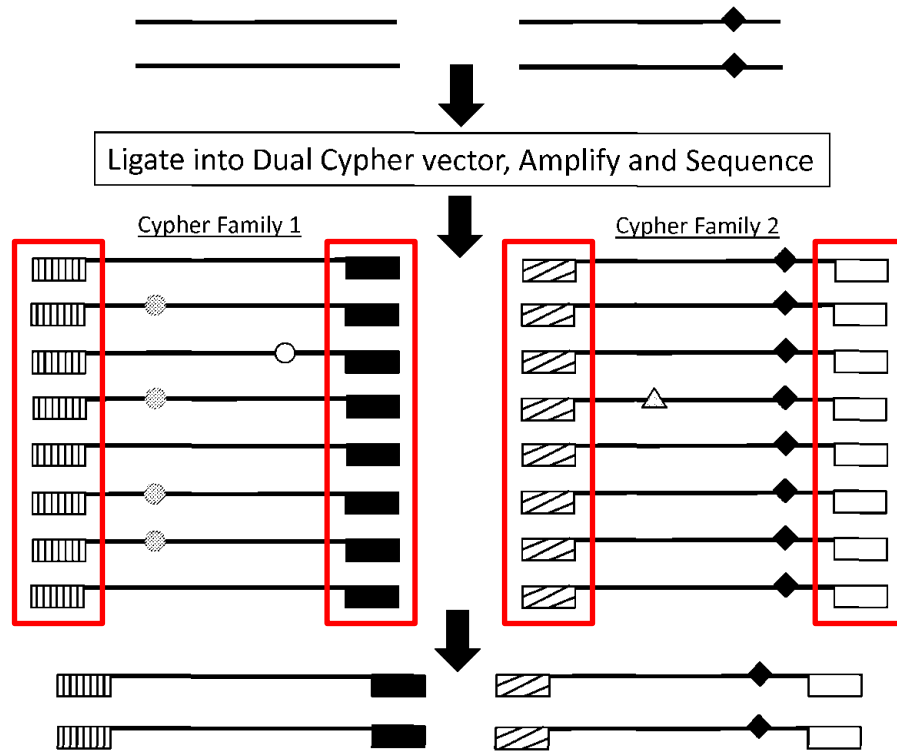


Fig. 3B

EX1013.0043

Figure 43 High Accuracy Sequencing Method

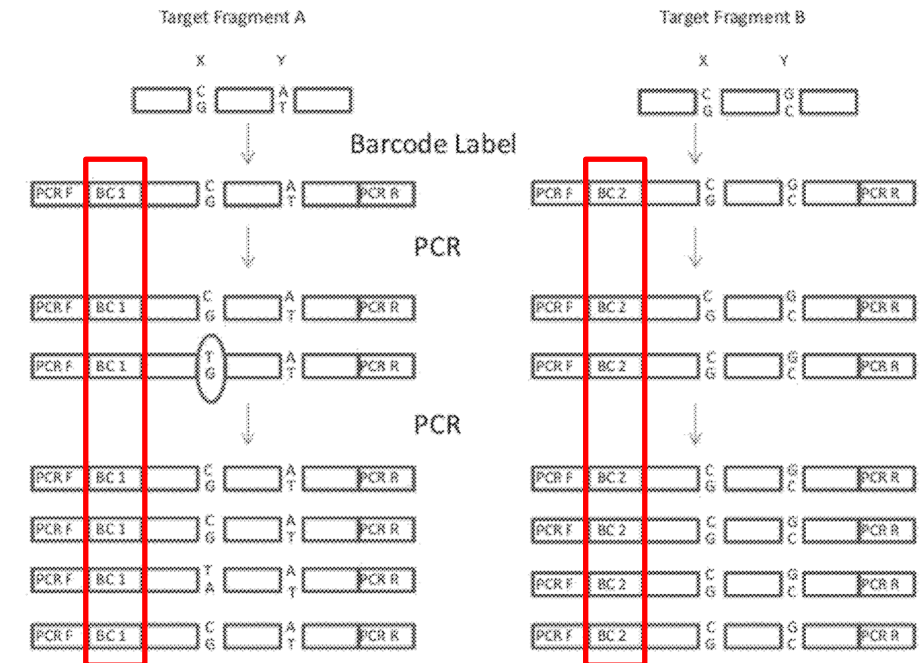


Figure 44 Sequencing Error Revealed by BC1

Barcode	Site X - C	Site X - T	Site Y - A	Site Y - G
BC1	3	1	4	
BC2	4			4

EX1033.0044-45

“Computationally Deconvolute” Has No Established Meaning

The unique cypher tags are used to computationally deconvolute the sequencing data and map all sequence reads to single molecules (*i.e.*, distinguish PCR and sequencing errors from real mutations). Base calling and sequence alignment will be

EX1013.0027

Q. Deconvolute can mean something other than de-duplication, right?

A. **The word "deconvolute" can be used in different ways in different contexts in different applications. My interpretation is that, in this context, deconvolute refers to the de-duplication process described in Bielas.**

EX2016.0126:5-11

Petitioner Has Failed to Show Bielas's Consensus Sequence Meets the Identifying Duplicates Limitation



**Carlos Bustamante,
Ph.D.**

A. It can. There are lots of ways to create consensus sequence and lots of decisions one might make about including or not including quality, whether or not the unique identifier is part of the consensus sequence comparison or not.

EX1124.0171:22-172:2



Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

PAR Pharm., Inc. v. TWI Pharms., Inc., 773 F.3d 1186, 1195 (Fed. Cir. 2014).

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **PATENT OWNER'S HEARING DEMONSTRATIVES** were served on January 16, 2026 and January 20, 2026 via email to Petitioner by serving the correspondence addresses of record as follows:

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January 20, 2026

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