targeting an oncogene rearrangement product if the presence of the oncogene rearrangement is detected.

[0092] In some embodiments, a subject is in need of treatment for lung cancer. In some embodiments, *e.g.* when the sample is obtained from a subject in need of treatment for lung cancer, the known target sequence can comprise a sequence from a gene selected from the group of ALK, ROS1, and RET. Accordingly, in some embodiments, gene rearrangements result in fusions involving the ALK, ROS1, or RET. Non-limiting examples of gene arrangements involving ALK, ROS1, or RET are described in, *e.g.*, Soda et al. Nature 2007 448561-6: Rikova et al. Cell 2007 131:1190-1203; Kohno et al. Nature Medicine 2012 18:375-7; Takouchi et al. Nature Medicine 2012 18:378-81; which are incorporated by reference herein in their entireties. However, it should be appreciated that the precise location of a gene rearrangement, and the identity of the second gene involved in the rearrangement may not be known in advance. Accordingly, in methods described herein, the presence and identity of such rearrangements can be detected without having to know the location of the rearrangement or the identity of the second gene involved in the gene rearrangement.

[0093] In some embodiments, the known target sequence can comprise sequence from a gene selected from the group of: ALK, ROS1, and RET.

[0094] In some embodiments, the presence of a gene rearrangement of ALK in a sample obtained from a tumor in a subject can indicate that the tumor is susceptible to treatment with a treatment selected from the group consisting of: an ALK inhibitor; crizotinib (PF-02341066); AP26113; LDK378; 3-39; AF802; IPI-504; ASP3026; AP-26113; X-396; GSK-1838705A; CH5424802; diamino and aminopyrimidine inhibitors of ALK kinase activity such as NVP-TAE684 and PF-02341066 (see, *e.g.* Galkin et al, Proc Natl Acad Sci USA, 2007, 104:270-275; Zou et al. Cancer Res, 2007, 67:4408-4417; Hallberg and Palmer F1000 Med Reports 2011 3:21; and Sakamoto et al. Cancer Cell 2011 19:679-690) and molecules disclosed in WO 04/079326. All of the foregoing references are incorporated by reference herein in their entireties. An ALK inhibitor can include any agent that reduces the expression and/or kinase activity of ALK or a portion thereof, including, *e.g.* oligonucleotides, small molecules, and/or peptides that reduce the expression and/or activity of ALK or a portion thereof. As used herein "anaplastic lymphoma kinase" or "ALK" refers to a transmembrane tyROS1ine kinase typically involved in neuronal regulation in the wildtype form. The nucleotide sequence of the ALK gene and mRNA are known for a number of species, including human (*e.g.* SEQ ID NO: 2 (mRNA), NCBI Gene ID: 238).

[0095] In some embodiments, the presence of a gene rearrangement of ROS1 in a sample obtained from a tumor in a subject can indicate that the tumor is susceptible to treatment with a

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treatment selected from the group consisting of: a ROS1 inhibitor and an ALK inhibitor as described herein above (*e.g.* crizotinib). A ROS1 inhibitor can include any agent that reduces the expression and/or kinase activity of ROS1 or a portion thereof, including, *e.g.* oligonucleotides, small molecules, and/or peptides that reduce the expression and/or activity of ROS1 or a portion thereof. As used herein "c-ros oncogene 1" or "ROS1" (also referred to in the art as ros-1) refers to a transmembrane tyrosine kinase of the sevenless subfamily and which interacts with PTPN6. Nucleotide sequences of the ROS1 gene and mRNA are known for a number of species, including human (*e.g.* SEQ ID NO: 1 (mRNA), NCBI Gene ID: 238).

[0096] In some embodiments, the presence of a gene rearrangement of RET in a sample obtained from a tumor in a subject can indicate that the tumor is susceptible to treatment with a treatment selected from the group consisting of: a RET inhibitor; DP-2490, DP-3636, SU5416; BAY 43-9006, BAY 73-4506 (regorafenib), ZD6474, NVP-AST487, sorafenib, RPI-1, XL184, vandetanib, sunitinib, imatinib, pazopanib, axitinib, motesanib, gefitinib, and withaferin A (see, *e.g.* Samadi et al. Surgery 2010 148:1228-36; Cuccuru et al. JNCI 2004 13:1006-1014; Akeno-Stuart et al. Cancer Research 2007 67:6956; Grazma et al. J Clin Oncol 2010 28:15s 5559; Mologni e tal. J Mol Endocrinol 2006 37:199-212; Calmomagno et al. Journal NCI 2006 98:326-334; Mologni. Curr Med Chem 2011 18:162-175 and the compounds disclosed in WO 06/034833; US Patent Publication 2011/0201598 and US Patent 8,067,434). All of the foregoing references are incorporated by reference herein in their entireties. A RET inhibitor can include any agent that reduces the expression and/or kinase activity of RET or a portion thereof, including, *e.g.* oligonucleotides, small molecules, and/or peptides that reduce the expression and/or activity of RET or a portion thereof. As used herein "rearranged during transfection" or "RET" refers to a receptor tyrosine kinase of the cadherein superfamily which is involved in neural crest development and recognizes glial cell line-derived neurotrophic factor family signaling molecules. Nucleotide sequences of the ROS1 gene and mRNA are known for a number of species, including human (*e.g.* SEQ ID NOs: 3-4 (mRNA), NCBI Gene ID: 5979).

[0097] Further non-limiting examples of applications of methods described herein include detection of hematological malignancy markers and panels thereof (*e.g.* including those to detect genomic rearrangements in lymphomas and leukemias), detection of sarcoma-related genomic rearrangements and panels thereof; and detection of IGH/TCR gene rearrangements and panels thereof for lymphoma testing.

[0098] In some embodiments, methods described herein relate to treating a subject having or diagnosed as having, *e.g.* cancer with a treatment for cancer. Subjects having cancer can be identified by a physician using current methods of diagnosing cancer. For example, symptoms and/or complications of lung cancer which characterize these conditions and aid in diagnosis are

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well known in the art and include but are not limited to, weak breathing, swollen lymph nodes above the collarbone, abnormal sounds in the lungs, dullness when the chest is tapped, and chest pain. Tests that may aid in a diagnosis of, *e.g.* lung cancer include, but are not limited to, x-rays, blood tests for high levels of certain substances (*e.g.* calcium), CT scans, and tumor biopsy. A family history of lung cancer, or exposure to risk factors for lung cancer (*e.g.* smoking or exposure to smoke and/or air pollution) can also aid in determining if a subject is likely to have lung cancer or in making a diagnosis of lung cancer.

[0099] Cancer can include, but is not limited to, carcinoma, including adenocarcinoma, lymphoma, blastoma, melanoma, sarcoma, leukemia, squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, Hodgkin's and non Hodgkin's lymphoma, pancreatic cancer, glioblastoma, basal cell carcinoma, biliary tract cancer, bladder cancer, brain cancer including glioblastomas and medulloblastomas; breast cancer, cervical cancer, choriocarcinoma; colon cancer, colorectal cancer, endometrial carcinoma, endometrial cancer; esophageal cancer, gastric cancer; various types of head and neck cancers, intraepithelial neoplasms including Bowen's disease and Paget's disease; hematological neoplasms including acute lymphocytic and myelogenous leukemia; Kaposi's sarcoma, hairy cell leukemia; chromic myelogenous leukemia, AIDS-associated leukemias and adult T-cell leukemia lymphoma; kidney cancer such as renal cell carcinoma, T-cell acute lymphoblastic leukemia/lymphoma, lymphomas including Hodgkin's disease and lymphocytic lymphomas; liver cancer such as hepatic carcinoma and hepatoma, Merkel cell carcinoma, melanoma, multiple myeloma; neuroblastomas; oral cancer including squamous cell carcinoma; ovarian cancer including those arising from epithelial cells, sarcomas including leiomyosarcoma, rhabdomyosarcoma, liposarcoma, fibROS1arcoma, and osteosarcoma; pancreatic cancer; skin cancer including melanoma, stromal cells, germ cells and mesenchymal cells; pROS1tate cancer, rectal cancer; vulval cancer, renal cancer including adenocarcinoma; testicular cancer including germinal tumors such as seminoma, non-seminoma (teratomas, choriocarcinomas), stromal tumors, and germ cell tumors; thyroid cancer including thyroid adenocarcinoma and medullar carcinoma; esophageal cancer, salivary gland carcinoma, and Wilms' tumors. In some embodiments, the cancer can be lung cancer.

[00100] In some embodiments, methods described herein comprise administering an effective amount of compositions described herein, *e.g.* a treatment for cancer to a subject in order to alleviate a symptom of a cancer. As used herein, "alleviating a symptom of a cancer" is ameliorating any condition or symptom associated with the cancer. As compared with an equivalent untreated control, such reduction is by at least 5%, 10%, 20%, 40%, 50%, 60%, 80%, 90%, 95%, 99% or more as measured by any standard technique. A variety of means for administering the compositions described herein to subjects are known to those of skill in the art.

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Such methods can include, but are not limited to oral, parenteral, intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), pulmonary, cutaneous, topical, injection, or intratumoral administration. Administration can be local or systemic. The term "effective amount" as used herein refers to the amount of a treatment needed to alleviate at least one or more symptom of the disease or disorder, and relates to a sufficient amount of pharmacological composition to provide the desired effect. The term "therapeutically effective amount" therefore refers to an amount that is sufficient to effect a particular anti-cancer effect when administered to a typical subject. An effective amount as used herein, in various contexts, would also include an amount sufficient to delay the development of a symptom of the disease, alter the course of a symptom disease (for example but not limited to, slowing the progression of a symptom of the disease), or reverse a symptom of the disease. Thus, it is not generally practicable to specify an exact "effective amount". However, for any given case, an appropriate "effective amount" can be determined by one of ordinary skill in the art using only routine experimentation. The effects of any particular dosage can be monitored by a suitable bioassay. The dosage can be determined by a physician and adjusted, as appropriate, to suit observed effects of the treatment.

[00101] Non-limiting examples of a treatment for cancer can include radiation therapy, surgery, gemcitabine, cisplastin, paclitaxel, carboplatin, bortezomib, AMG479, vorinostat, rituximab, temozolomide, rapamycin, ABT-737, PI-103; alkylating agents such as thiotepa and CYTOXAN® cyclosphosphamide; alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, trietylenephosphoramide, triethiylenethiophosphoramide and trimethylolomelamine; acetogenins (especially bullatacin and bullatacinone); a camptothecin (including the synthetic analogue topotecan); bryostatin; callystatin; CC-1065 (including its adozelesin, carzelesin and bizelesin synthetic analogues); cryptophycins (particularly cryptophycin 1 and cryptophycin 8); dolastatin; duocarmycin (including the synthetic analogues, KW-2189 and CB1-TM1); eleutherobin; pancratistatin; a sarcodictyin; spongistatin; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, and ranimnustine; antibiotics such as the enediyne antibiotics (*e.g.*, calicheamicin, especially calicheamicin gamma1 and calicheamicin omega1 (see, *e.g.*, Agnew, Chem. Intl. Ed. Engl., 33: 183-186 (1994)); dynemicin, including dynemicin A; bisphosphonates, such as clodronate; an esperamicin; as well as neocarzinostatin chromophore and related chromoprotein enediyne

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antiobiotic chromophores), aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, carabicin, caminomycin, carzinophilin, chromomycinis, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, ADRIAMYCIN® doxorubicin (including morpholino-doxorubicin, cyanomorpholino-doxorubicin, 2-pyrrolino-doxorubicin and deoxydoxorubicin), epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins such as mitomycin C, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine; androgens such as calusterone, dromostanolone propionate, epitiostanol, mepitiostane, testolactone; anti-adrenals such as aminoglutethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglatone; aldophosphamide glycoside; aminolevulinic acid; eniluracil; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elformithine; elliptinium acetate; an epothilone; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidainine; maytansinoids such as maytansine and ansamitocins; mitoguazone; mitoxantrone; mopidanmol; nitraerine; pentostatin; phenamet; pirarubicin; losoxantrone; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK® polysaccharide complex (JHS Natural Products, Eugene, Oreg.); razoxane; rhizoxin; sizofuran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; trichothecenes (especially T-2 toxin, verracurin A, roridin A and anguidine); urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxoids, *e.g.*, TAXOL® paclitaxel (Bristol-Myers Squibb Oncology, Princeton, N.J.), ABRAXANE® Cremophor-free, albumin-engineered nanoparticle formulation of paclitaxel (American Pharmaceutical Partners, Schaumberg, Ill.), and TAXOTERE® doxetaxel (Rhone-Poulenc Rorer, Antony, France); chloranbucil; GEMZAR® gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin, oxaliplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitoxantrone; vincristine; NAVELBINE.RTM. vinorelbine; novantrone; teniposide; edatrexate; daunomycin; aminopterin; xeloda; ibandronate; irinotecan (Camptosar, CPT-11) (including the treatment regimen of irinotecan with 5-FU and leucovorin); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO); retinoids such as retinoic acid; capecitabine; combretastatin; leucovorin (LV); oxaliplatin, including the oxaliplatin treatment regimen (FOLFOX); lapatinib

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(Tykerb.RTM.); inhibitors of PKC-alpha, Raf, H-Ras, EGFR (*e.g.*, erlotinib (Tarceva®)) and VEGF-A that reduce cell proliferation and pharmaceutically acceptable salts, acids or derivatives of any of the above. In addition, methods of treatment can further include the use of radiation or radiation therapy. Further, methods of treatment can further include the use of surgical treatments.

[00102] In some embodiments, methods described herein can be applicable for resequencing, *e.g.* for confirming particularly relevant, low-quality, and/or complex sequences obtained by non-directed sequencing of a large amount of nucleic acids. By way of non-limiting examples, methods described herein can allow the directed and/or targeted resequencing of targeted disease gene panels (*e.g.* 10-100 genes), resequencing to confirm variants obtained in large scale sequencing projects, whole exome resequencing, and/or targeted resequencing for detection of single nucleotide variants, multiple nucleotide variants, insertions, deletions, copy number changes, and methylation status.

[00103] In some embodiments, methods described herein can allow microbiota sequencing, ancient sample sequencing, and/or new variant virus genotyping.

[00104] For convenience, the meaning of some terms and phrases used in the specification, examples, and appended claims, are provided below. Unless stated otherwise, or implicit from context, the following terms and phrases include the meanings provided below. The definitions are provided to aid in describing particular embodiments, and are not intended to limit the claimed invention, because the scope of the invention is limited only by the claims. 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. If there is an apparent discrepancy between the usage of a term in the art and its definition provided herein, the definition provided within the specification shall prevail.

[00105] For convenience, certain terms employed herein, in the specification, examples and appended claims are collected here.

[00106] The terms "decrease", "reduced", "reduction", or "inhibit" are all used herein generally to mean a decrease by a statistically significant amount. However, for avoidance of doubt, "reduced", "reduction", "decrease", or "inhibit" means a decrease by at least 10% as compared to a reference level, for example a decrease by at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% decrease (*e.g.* absent level or non-detectable level as compared to a reference level), or any decrease between 10-100% as compared to a reference level. In the context of a marker or symptom is meant a statistically

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significant decrease in such level. The decrease can be, for example, at least 10%, at least 20%, at least 30%, at least 40% or more, and is preferably down to a level accepted as within the range of normal for an individual without such disorder.

[00107] The terms "increased" ,"increase", "enhance", or "activate" are all used herein to generally mean an increase by a statically significant amount; for the avoidance of doubt, the terms "increased", "increase", "enhance", or "activate" mean an increase of at least 10% as compared to a reference level, for example an increase of at least about 20%, or at least about 30%, or at least about 40%, or at least about 50%, or at least about 60%, or at least about 70%, or at least about 80%, or at least about 90% or up to and including a 100% increase or any increase between 10-100% as compared to a reference level, or at least about a 2-fold, or at least about a 3-fold, or at least about a 4-fold, or at least about a 5-fold or at least about a 10-fold increase, or any increase between 2-fold and 10-fold or greater as compared to a reference level.

[00108] As used herein, a "subject" means a human or animal. Usually the animal is a vertebrate such as a primate, rodent, domestic animal or game animal. Primates include chimpanzees, cynomologous monkeys, spider monkeys, and macaques, *e.g.*, Rhesus. Rodents include mice, rats, woodchucks, ferrets, rabbits and hamsters. Domestic and game animals include cows, horses, pigs, deer, bison, buffalo, feline species, *e.g.*, domestic cat, canine species, *e.g.*, dog, fox, wolf, avian species, *e.g.*, chicken, emu, ostrich, and fish, *e.g.*, trout, catfish and salmon. In some embodiments, the subject is a mammal, *e.g.*, a primate, *e.g.*, a human. The terms, "individual," "patient" and "subject" are used interchangeably herein.

[00109] Preferably, the subject is a mammal. The mammal can be a human, non-human primate, mouse, rat, dog, cat, horse, or cow, but is not limited to these examples. Mammals other than humans can be advantageously used as subjects that represent animal models of, *e.g.* lung cancer. A subject can be male or female.

[00110] A subject can be one who has been previously diagnosed with or identified as suffering from or having a condition in need of treatment (*e.g.* cancer) or one or more complications related to such a condition, and optionally, have already undergone treatment for the condition or the one or more complications related to the condition. Alternatively, a subject can also be one who has not been previously diagnosed as having the condition (*e.g.* cancer) or one or more complications related to the condition. For example, a subject can be one who exhibits one or more risk factors for the condition or one or more complications related to the condition or a subject who does not exhibit risk factors.

[00111] A "subject in need" of treatment for a particular condition can be a subject having that condition, diagnosed as having that condition, or at risk of developing that condition.

[00112] As used herein, a "disease associated with a genetic alteration" refers to any disease

which is caused by, at least in part, by an alteration in the genetic material of the subject as compared to a healthy wildtype subject, *e.g.* a deletion, an insertion, a SNP, a gene rearrangement. A disease can be caused by, at least in part, an alteration in the genetic material of the subject if the alteration increases the risk of the subject developing the disease, increases the subject's susceptibility to a disease (including infectious diseases, or diseases with an infectious component), causes the production of a disease-associated molecule, or causes cells to become diseased or abnormal (*e.g.* loss of cell cycle regulation in cancer cells). Diseases can be associated with multiple genetic alterations, *e.g.* cancers.

[00113] As used herein, the term "nucleic acid" refers to any molecule, preferably a polymeric molecule, incorporating units of ribonucleic acid, deoxyribonucleic acid or an analog thereof. The nucleic acid can be either single-stranded or double-stranded. A single-stranded nucleic acid can be one strand nucleic acid of a denatured double- stranded DNA. Alternatively, it can be a single-stranded nucleic acid not derived from any double-stranded DNA. In one aspect, the template nucleic acid is DNA. In another aspect, the template is RNA. Suitable nucleic acid molecules are DNA, including genomic DNA or cDNA. Other suitable nucleic acid molecules are RNA, including mRNA.

[00114] The term "isolated" or "partially purified" as used herein refers, in the case of a nucleic acid, to a nucleic acid separated from at least one other component (*e.g.*, nucleic acid or polypeptide) that is present with the nucleic acid as found in its natural source and/or that would be present with the nucleic acid when expressed by a cell. A chemically synthesized nucleic acid or one synthesized using *in vitro* transcription/translation is considered "isolated."

[00115] The term "gene" means a nucleic acid sequence which is transcribed (DNA) to RNA *in vitro* or *in vivo* when operably linked to appropriate regulatory sequences. The gene can include regulatory regions preceding and following the coding region, e.g. 5' untranslated (5'UTR) or "leader" sequences and 3' UTR or "trailer" sequences, as well as intervening sequences (introns) between individual coding segments (exons).

[00116] As used herein, the term "complementary" refers to the ability of nucleotides to form hydrogen-bonded base pairs. In some embodiment, complementary refers to hydrogen-bonded base pair formation preferences between the nucleotide bases G, A, T, C and U, such that when two given polynucleotides or polynucleotide sequences anneal to each other, A pairs with T and G pairs with C in DNA, and G pairs with C and A pairs with U in RNA. As used herein, "substantially complementary" refers to a nucleic acid molecule or portion thereof (*e.g.* a primer) having at least 90% complementarity over the entire length of the molecule or portion thereof with a second nucleotide sequence, *e.g.* 90% complementary, 95% complementary, 98% complementary, 99% complementary, or 100% complementary. As used herein, "substantially

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identical" refers to a nucleic acid molecule or portion thereof having at least 90% identity over the entire length of a the molecule or portion thereof with a second nucleotide sequence, *e.g.* 90% identity, 95% identity, 98% identity, 99% identity, or 100% identity.

[00117] As used herein, "specific" when used in the context of a primer specific for a target nucleic acid refers to a level of complementarity between the primer and the target such that there exists an annealing temperature at which the primer will anneal to and mediate amplification of the target nucleic acid and will not anneal to or mediate amplification of non-target sequences present in a sample.

[00118] As used herein, "amplified product", "amplification product", or "amplicon" refers to oligonucleotides resulting from an amplification reaction that are copies of a portion of a particular target nucleic acid template strand and/or its complementary sequence, which correspond in nucleotide sequence to the template nucleic acid sequence and/or its complementary sequence. An amplification product can further comprise sequence specific to the primers and which flanks sequence which is a portion of the target nucleic acid and/or its complement. An amplified product, as described herein will generally be double-stranded DNA, although reference can be made to individual strands thereof.

[00119] As used herein, a "portion" of a nucleic acid molecule refers to contiguous set of nucleotides comprised by that molecule. A portion can comprise all or only a subset of the nucleotides comprised by the molecule. A portion can be double-stranded or single-stranded.

[00120] As used herein, the terms "treat," "treatment," "treating," or "amelioration" refer to therapeutic treatments, wherein the object is to reverse, alleviate, ameliorate, inhibit, slow down or stop the progression or severity of a condition associated with a disease or disorder, *e.g.* lung cancer. The term "treating" includes reducing or alleviating at least one adverse effect or symptom of a condition, disease or disorder associated with a condition. Treatment is generally "effective" if one or more symptoms or clinical markers are reduced. Alternatively, treatment is "effective" if the progression of a disease is reduced or halted. That is, "treatment" includes not just the improvement of symptoms or markers, but also a cessation of, or at least slowing of, progress or worsening of symptoms compared to what would be expected in the absence of treatment. Beneficial or desired clinical results include, but are not limited to, alleviation of one or more symptom(s), diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, delay or slowing of disease progression, amelioration or palliation of the disease state, remission (whether partial or total), and/or decreased mortality, whether detectable or undetectable. The term "treatment" of a disease also includes providing relief from the symptoms or side-effects of the disease (including palliative treatment).

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[00121] The term "statistically significant" or "significantly" refers to statistical significance and generally means a two standard deviation (2SD) below normal, or lower, concentration of the marker.

[00122] Other than in the operating examples, or where otherwise indicated, all numbers expressing quantities of ingredients or reaction conditions used herein should be understood as modified in all instances by the term "about." The term "about" when used in connection with percentages can mean ±1%.

[00123] As used herein the term "comprising" or "comprises" is used in reference to compositions, methods, and respective component(s) thereof, that are essential to method or composition, yet open to the inclusion of unspecified elements, whether essential or not.

[00124] The term "consisting of" refers to compositions, methods, and respective components thereof as described herein, which are exclusive of any element not recited in that description of the embodiment.

[00125] As used herein the term "consisting essentially of" refers to those elements required for a given embodiment. The term permits the presence of elements that do not materially affect the basic and novel or functional characteristic(s) of that embodiment.

[00126] The singular terms "a," "an," and "the" include plural referents unless context clearly indicates otherwise. Similarly, the word "or" is intended to include "and" unless the context clearly indicates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of this disclosure, suitable methods and materials are described below. The abbreviation, "*e.g.*" is derived from the Latin exempli gratia, and is used herein to indicate a non-limiting example. Thus, the abbreviation "*e.g.*" is synonymous with the term "for example."

[00127] Definitions of common terms in cell biology and molecular biology can be found in "The Merck Manual of Diagnosis and Therapy", 19th Edition, published by Merck Research Laboratories, 2006 (ISBN 0-911910-19-0); Robert S. Porter et al. (eds.), The Encyclopedia of Molecular Biology, published by Blackwell Science Ltd., 1994 (ISBN 0-632-02182-9). Definitions of common terms in molecular biology can also be found in Benjamin Lewin, Genes X, published by Jones & Bartlett Publishing, 2009 (ISBN-10: 0763766321); Kendrew et al. (eds.), , Molecular Biology and Biotechnology: a Comprehensive Desk Reference, published by VCH Publishers, Inc., 1995 (ISBN 1-56081-569-8) and Current Protocols in Protein Sciences 2009, Wiley Intersciences, Coligan et al., eds.

[00128] Unless otherwise stated, the present invention was performed using standard procedures, as described, for example in Sambrook et al., Molecular Cloning: A Laboratory Manual (3 ed.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., USA (2001);

and Davis et al., Basic Methods in Molecular Biology, Elsevier Science Publishing, Inc., New York, USA (1995) which are all incorporated by reference herein in their entireties.

[00129] Other terms are defined herein within the description of the various aspects of the invention.

[00130] All patents and other publications; including literature references, issued patents, published patent applications, and co-pending patent applications; cited throughout this application are expressly incorporated herein by reference for the purpose of describing and disclosing, for example, methodologies described in such publications that might be used in connection with technology described herein. These publications are provided solely for their disclosure prior to the filing date of the present application. Nothing in this regard should be construed as an admission that the inventors are not entitled to antedate such disclosure by virtue of prior invention or for any other reason. All statements as to the date or representation as to the contents of these documents is based on the information available to the applicants and does not constitute any admission as to the correctness of the dates or contents of these documents.

[00131] The description of embodiments of the disclosure is not intended to be exhaustive or to limit the disclosure to the precise form disclosed. While specific embodiments of, and examples for, the disclosure are described herein for illustrative purposes, various equivalent modifications are possible within the scope of the disclosure, as those skilled in the relevant art will recognize. For example, while method steps or functions are presented in a given order, alternative embodiments may perform functions in a different order, or functions may be performed substantially concurrently. The teachings of the disclosure provided herein can be applied to other procedures or methods as appropriate. The various embodiments described herein can be combined to provide further embodiments. Aspects of the disclosure can be modified, if appropriate, to employ the compositions, functions and concepts of the above references and application to provide yet further embodiments of the disclosure. These and other changes can be made to the disclosure in light of the detailed description. All such modifications are intended to be included within the scope of the appended claims.

[00132] Specific elements of any of the foregoing embodiments can be combined or substituted for elements in other embodiments. Furthermore, while advantages associated with certain embodiments of the disclosure have been described in the context of these embodiments, other embodiments may also exhibit such advantages, and not all embodiments need necessarily exhibit such advantages to fall within the scope of the disclosure.

[00133] Technology described herein is further illustrated by the following examples which in no way should be construed as being further limiting.

EXAMPLES

Example 1

[00134] Described herein is a method (described for simplicity as "AMP2" for Anchored Multiplex PCR version 2; see Figure 1) that comprises an improvement of AMP (Anchored Multiplex PCR) (described, e.g. in US Patent Application Serial No 13/793,564; which is incorporated by reference herein in its entirety). The original AMP is a method to construct targeted sequencing libraries for next generation sequencing (NGS) in which a single type of double-stranded DNA adapter (containing one sequencing primer) is ligated to the double-stranded DNA (gDNA or cDNA) template. Two rounds of hemi-nested PCR are peformed with pools of gene specific primers (GSP1s and GSP2s). GSP2 contains the second sequencing primer sequence, thus allowing a fully-competent sequencing library to be completed. Since one side of each and any of multiple fragments has a specific gene specific sequence (the anchor) and the other side has a randomly ligated adaptor, it is termed anchored multiplex PCR.

[00135] Described herein is AMP2, which simplifies the approach described above and improves its ability to use poor quality archived nucleic acid which is critical to certain applications (e.g. clinical tumor genotyping). A new synthetic oligonucleotide design for incorporating the first sequencing primer into the library consists of a primer with a 5' sequencing primer sequence (e.g., an Illumina, Roche, Life Technologies, Ion Torrent or any other NGS method-compatable primer) and a 3' sequence containing at least 6 random nucleotides (can be up to 12 nucleotides). Step one involves incubation of this oligonucleotide primer with the template DNA (gDNA or cDNA is acceptable), annealing of the oligonucleotide primer randomly with the template, and extension of the primer using a DNA polymerase. Following removal of the unincorporated primers, the new extension products can be used in an amplification protocol similar to that of AMP, starting at the GSP1 PCR step. This new method allows one to avoid mechanical shearing, end-repair, A-tailing, ligation of adapters, and multiple clean-up steps. The AMP2 method also has the advantage of utilizing a random 6 to 12mer sequencing primer that will be sequenced and could serve as a unique molecular barcode, allowing bioinformatic algorithms to improve variant calling accuracy for both single nucleotide, indel, and copy number variants. Thus AMP2 permits a simplified targeted library construction method with improved performance for nucleic acid from archived material regardless if they are in double-stranded or single-stranded form, and permits higher-quality variant/mutation assessment.

[00136] The disclosed method allows for several novel improvements over the previously described "AMP" method:

1. Use of tailed random primer for the 1st step in AMP2 method avoids the need for mechanical shearing of samples nucleic acid needed in AMP1, since the random primed replication of

original template will result in sequencing primer-tailed shorter fragments. These fragments are in the required size range for effective downstream NGS library construction.

2. Since shearing is not longer required in AMP2 method, several subsequent steps can be omitted, simplifying and shortening the protocol. Post-shearing end-repair with Klenow enzyme, addition of deoxyadenosine, and ligation of double stranded adapters would not be needed.
3. As previously described, the AMP1 method requires double stranded DNA (gDNA or cDNA) templates for ligation with the double-stranded sequencing adapter. This requirement can limit the effectiveness of the assay with archived samples. Archived samples often have significant degradation of nucleic acids compared to fresh or frozen samples, both typified by fragmentation of the nucleic acid and the presence of a significant fraction of single-stranded nucleic acid. The large amount of single stranded template would prevent effective ligation of double stranded adapters in AMP1. Thus, AMP2 would allow higher library construction success with less starting input material relative to AMP1, which would increase the number of archived samples to be processed and analyzed.

[00137] The use of random priming in the first step, creates a unique molecular identifier for each extension reaction, allowing identification (or single molecule barcoding) of each unique template molecule. This offers major advantages, including improved sequencing error correction via bioinformatic algorithms which exploit the molecular barcodes to consolidate truly duplicated sequencing fragments/reads into a singular accurate consensus read (Figure 2).

[00138] The methods described herein permit assays (including diagnostics and companion diagnostics) for the detection of DNA or RNA sequence variants or abundance using next generation sequencing. This can include gene-specific kits, or general-purpose library construction kits suitable for use with the user's targeted primers of choice.

[00139] The methods described herein permit the detection of mutations in nucleic acids in targeted sequencing for both germline and somatic tumor mutation applications in humans. This method can also be used for sequencing of non-human nucleic acid.

[00140] SEQ ID NO: 1 ALK mRNA NCBI Ref Seq: NM_004304

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What is claimed herein is:

1. A method of determining the nucleotide sequence contiguous to a known target nucleotide sequence, the method comprising;

   (a) hybridizing a target nucleic acid molecule comprising the known target nucleotide sequence with a population of tailed random primers;

   (b) extension of a hybridized tailed random primer using the portion of the target nucleic acid molecule downstream of the site of hybridization as a template;

   (c) amplifying a portion of the target nucleic acid molecule and the tailed random primer sequence with a first tail primer and a first target-specific primer;

   (d) amplifying a portion of the amplicon resulting from step (c) with a second tail primer and a second target-specific primer;

   (e) sequencing the amplified portion from step (d) using a first and second sequencing primer;

   wherein the population of tailed random primers comprises single-stranded oligonucleotide molecules having a 5' nucleic acid sequence identical or complementary to a first sequencing primer and a 3' nucleic acid sequence comprising from about 6 to about 12 random nucleotides;

   wherein the first target-specific primer comprises a nucleic acid sequence that can specifically anneal to the known target nucleotide sequence of the target nucleic acid at the annealing temperature;

   wherein the second target-specific primer comprises a 3' portion comprising a nucleic acid sequence that can specifically anneal to a portion of the known target nucleotide sequence comprised by the amplicon resulting from step (c), and a 5' portion comprising a nucleic acid sequence that is identical to a second sequencing primer and the second target-specific primer is nested with respect to the first target-specific primer;

   wherein the first tail primer comprises a nucleic acid sequence identical or complementary to all or a portion of the 5' portion of the tailed random primer; and

   wherein the second tail primer comprises a nucleic acid sequence identical or complementary to a portion of the first sequencing primer and is nested with respect to the first tail primer.

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QIAGEN Sciences, LLC v. Tecan Genomics - IPR2025-00029

2. The method of claim 1, wherein the 5' nucleic acid sequence of the tailed random primers is identical to a first sequencing primer.

3. The method of any of claims 1-2, wherein the first tail primer comprises a nucleic acid sequence identical to the 5' portion of the tailed random primer.

4. The method of any of claims 1-3, wherein the second tail primer comprises a nucleic acid sequence identical to a portion of the first sequencing primer.

5. The method of any of claims 1-4, wherein the each tailed random primer further comprises a spacer nucleic acid sequence between the 5' nucleic acid sequence identical or complementary to a first sequencing primer and the 3' nucleic acid sequence comprising about 6 to about 12 random nucleotides.

6. The method of any of claims 1-5, wherein the unhybridized primers are removed from the reaction after an extension step.

7. The method of any of claims 1-6, wherein the second tail primer is nested with respect to the first tail primer by at least 3 nucleotides.

8. The method of any of claims 1-7, wherein the first target-specific primer further comprises a 5' tag sequence portion comprising a nucleic acid sequence of high GC content which is not substantially complementary to or substantially identical to any other portion of any of the primers.

9. The method of any of claims 1-8, wherein the second tail primer is identical to the full-length first sequencing primer.

10. The method of any of claims 1-9, wherein the portions of the target-specific primers that specifically anneal to the known target will anneal specifically at a temperature of about 65°C in a PCR buffer.

11. The method of any of claims 1-10, wherein the sample comprises genomic DNA.

12. The method of any of claims 1-11, wherein the sample comprises RNA and the method further comprises a first step of subjecting the sample to a reverse transcriptase regimen.

13. The method of any of claims 1-13, wherein the nucleic acids present in the sample have not been subjected to shearing or digestion.

14. The method of any of claims 1-14, wherein the sample comprises single-stranded gDNA or cDNA.

15. The method of any of claims 12-14, wherein the reverse transcriptase regimen comprises the use of random hexamers.

16. The method of any of claims 1-15, wherein a gene rearrangement comprises the known target sequence.

17. The method of claim 16, wherein the gene rearrangement is present in a nucleic acid selected from the group consisting of: genomic DNA; RNA; and cDNA.

18. The method of any of claims 16-17, wherein the gene rearrangement comprises an oncogene.

19. The method of claim 18, wherein the gene rearrangement comprises a fusion oncogene.

20. The method of any of claims 1-19, wherein the nucleic acid product is sequenced by a next-generation sequencing method.

21. The method of claim 20, wherein the next-generation sequencing method comprises a method selected from the group consisting of:

    Ion Torrent, Illumina, SOLiD, 454; Massively Parallel Signature Sequencing solid-phase, reversible dye-terminator sequencing; and DNA nanoball sequencing.

22. The method of any of claims 1-21, wherein the first and second sequencing primers are compatible with the selected next-generation sequencing method.

23. The method of any of claims 1-22, wherein the method comprises contacting the sample, or separate portions of the sample, with a plurality of sets of first and second target-specific primers.

24. The method of any of claims 1-23, wherein the method comprises contacting a single reaction mixture comprising the sample with a plurality of sets of first and second target-specific primers.

25. The method of any of claims 1-24, wherein the plurality of sets of first and second target-specific primers specifically anneal to known target nucleotide sequences comprised by separate genes.

26. The method of any of claims 24-25, wherein at least two sets of first and second target-specific primers specifically anneal to different portions of a known target nucleotide sequence.

27. The method of any of claims 24-26, wherein at least two sets of first and second target-specific primers specifically anneal to different portions of a single gene comprising a known target nucleotide sequence.

28. The method of any of claims 24-27, wherein at least two sets of first and second target-specific primers specifically anneal to different exons of a gene comprising a known nucleotide target sequence.

29. The method of any of claims 24-28, wherein the plurality of first target-specific primers comprise identical 5' tag sequence portions.

30. The method of any of claims 1-29, wherein each amplification step comprises a set of cycles of a PCR amplification regimen from 5 cycles to 20 cycles in length.

31. The method of any of claims 1-30, wherein the target-specific primers and the tail primers are designed such that they will specifically anneal to their complementary sequences at an annealing temperature of from about 61 to 72 °C.

32. The method of any of claims 1-31, wherein the target-specific primers and the tail primers are designed such that they will specifically anneal to their complementary sequences at an annealing temperature of about 65 °C.

33. The method of any of claims 1-32, wherein the target nucleic acid molecule is from a sample, optionally which is a biological sample obtained from a subject.

34. The method of any of claims 1-33, wherein the sample is obtained from a subject in need of treatment for a disease associated with a genetic alteration.

35. The method of claim 34, wherein the disease is cancer.

36. The method of any of claims 1-35, wherein the sample comprises a population of tumor cells.

37. The method of any of claims 1-36, wherein the sample is a tumor biopsy.

38. The method of any of claims 35-37, wherein the cancer is lung cancer.

39. The method of any of claims 1-38, wherein a disease-associated gene comprises the known target sequence.

40. The method of any of claims 1-39, wherein the target nucleic acid is a ribonucleic acid.

41. The method of claim 1-39, wherein the target nucleic acid is a deoxyribonucleic acid.

42. The method of claim 40, wherein the target nucleic acid is a messenger RNA encoded from a chromosomal segment that comprises a genetic rearrangement.

43. The method of claim 41, wherein the target nucleic acid is a chromosomal segment that comprises a portion of a genetic rearrangement.

44. A method of preparing nucleic acids for analysis, the method comprising:

contacting a nucleic acid template comprising with a plurality of different primers that share a common sequence that is 5' to different hybridization sequences, under conditions to promote template-specific hybridization and extension of at least one of the plurality of different primers;

contacting the extension product of the first step with a first tail primer and a first target-specific primer under conditions to promote template-specific hybridization and extension from the first tail primer and first target-specific primer;

contacting the extension product of the second step with a second tail primer and a second target-specific primer under conditions to promote template-specific hybridization and extension from the second tail primer and second target-specific primer.

wherein the first target-specific primer comprises a nucleic acid sequence that can specifically anneal to a known target nucleotide sequence of the target nucleic acid at the annealing temperature;

wherein the second target-specific primer comprises a 3' portion comprising a nucleic acid sequence that can specifically anneal to a portion of the known target nucleotide sequence comprised by the amplicon resulting from the second step, and a 5' portion comprising a nucleic acid sequence that is identical to a second sequencing primer and the second target-specific primer is nested with respect to the first target-specific primer;

wherein the first tail primer comprises a nucleic acid sequence identical or complementary to the common sequence of the primers of the first step; and

wherein the second tail primer comprises a nucleic acid sequence identical or complementary to a portion of the first sequencing primer and is nested with respect to the first tail primer.

45. The method of claim 44, wherein the target nucleic acid is a ribonucleic acid.

46. The method of claim 44, wherein the target nucleic acid is a deoxyribonucleic acid.

47. The method of claim 45, wherein the target nucleic acid is a messenger RNA encoded from a chromosomal segment that comprises a genetic rearrangement.

48. The method of claim 46, wherein the target nucleic acid is a chromosomal segment that comprises a portion of a genetic rearrangement.

49. The method of claim 48, wherein the genetic rearrangement is an inversion, deletion, or translocation.

50. The method of any one of claims 44-49, further comprising amplifying one or more of the extension products

51. The method of any of claims 44-50, wherein the each of the primers of the first step further comprises a spacer nucleic acid sequence between the common sequence and the hybridization sequence, the spacer sequence comprising about 6 to about 12 random nucleotides.

52. The method of any of claims 44-51, wherein the unhybridized primers are removed from the reaction after extension.

53. The method of any of claims 44-52, wherein the second tail primer is nested with respect to the first tail primer by at least 3 nucleotides.

54. The method of any of claims 44-53, wherein the first target-specific primer further comprises a 5' tag sequence portion comprising a nucleic acid sequence of high GC content which is not substantially complementary to or substantially identical to any other portion of any of the primers.

55. The method of any of claims 44-54, wherein the portions of the target-specific primers that specifically anneal to the known target will anneal specifically at a temperature of about 65°C in a PCR buffer.

ABSTRACT

Aspects of the technology disclosed herein relate to methods for preparing and analyzing nucleic acids. In some embodiments, methods for preparing nucleic acids for sequence analysis (*e.g.*, using next-generation sequencing) are provided herein.

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Methods For Determining A Nucleotide Sequence
First Named Inventor/Applicant Name:	Anthony John Iafrate
Filer:	David S. Resnick
Attorney Docket Number:	030258-079360-P

Filed as Small Entity

Provisional Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Provisional Application Filing Fee	2005	1	130	130
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**130**

Electronic Acknowledgement Receipt

EFS ID:	18032158
Application Number:	61931943
International Application Number:	
Confirmation Number:	1056
Title of Invention:	Methods For Determining A Nucleotide Sequence
First Named Inventor/Applicant Name:	Anthony John Iafrate
Customer Number:	50828
Filer:	David S. Resnick
Filer Authorized By:	
Attorney Docket Number:	030258-079360-P
Receipt Date:	27-JAN-2014
Filing Date:	
Time Stamp:	16:16:08
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$130
RAM confirmation Number	3342
Deposit Account	500850
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Miscellaneous Incoming Letter	20140127_EFSTransmittalProvisionalApplication_030258_079360_P.pdf	90902 ca9cfc4d49dfdd720ab34de44ca39d8e4051afcb	no	1
Warnings:					
Information:					
2	Provisional Cover Sheet (SB16)	20140127_ProvisionalCoversheet_030258_079360_P.pdf	1477419 29a621f780bf67da131a5797e599e1e81f12f1ed	no	3
Warnings:					
Information:					
3	Drawings-other than black and white line drawings	20140127_ProvisionalApplicationColorFigures_030258_079360_P.pdf	1331129 317cfd861e82f5954bff020775b991b9826d66c6	no	4
Warnings:					
Information:					
4	Miscellaneous Incoming Letter	20140127_PetitionColorDrawings_030258_079360_P.pdf	89310 aae8317d9e71ca5329899063ea82efbab6a104e	no	1
Warnings:					
Information:					
5		20140127_ProvisionalApplication_030258_079360_P.pdf	296944 dc9ee07942863f67cfea3b246c221a35b5b867bf	yes	56

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	49
Claims	50	55
Abstract	56	56

Warnings:					
Information:					
6	Fee Worksheet (SB06)	fee-info.pdf	29556 ba600f461fdea80f38cc2ab1a7c1da277e7a2929	no	2
Warnings:					
Information:					

Total Files Size (in bytes):	3315260

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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.

EXHIBIT 16

8023619

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

November 08, 2019

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF THE FILE WRAPPER AND CONTENTS OF:

APPLICATION NUMBER: *14/605,363*
FILING DATE: *January 26, 2015*
PATENT NUMBER: *10450597*
ISSUE DATE: *October 22, 2019*

Certified by

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

ADX - 000485453

PTO/AIA/15 (07-12)
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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.

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	030258-079365-US
First Inventor	Anthony John Iafrate
Title	METHODS OF PREPARING NUCLEIC ACIDS FOR SEQUENCING
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

1. ☐ **Fee Transmittal Form.** (PTO/SB/17 or equivalent)
2. ☒ **Applicant claims small entity status.** See 37 CFR 1.27.
3. ☒ **Specification.** [*Total Pages* 81] Both the claims and abstract must start on a new page *(For information on the preferred arrangement, see MPEP § 608.01(a))*
4. ☒ **Drawing(s).** (*35 U.S.C. 113*) [*Total Sheets* 5]
5. **Inventor's Oath or Declaration.** [*Total Sheets*] *(including substitute statements under 37 CFR 1.64 and assignments serving as an oath or declaration under 37 CFR 1.63(e))*
   a. ☐ Newly executed (original or copy)
   b. ☐ A copy from a prior application (37 CFR 1.63(d))
6. ☒ **Application Data Sheet.** **See Note below.* See 37 CFR 1.76 (PTO/AIA/14 or equivalent)
7. ☐ **CD-ROM or CD-R.** in duplicate, large table or Computer Program *(Appendix)*
   ☐ Landscape Table on CD
8. **Nucleotide and/or Amino Acid Sequence Submission.** *(if applicable, items a. – c. are required)*
   a. ☐ Computer Readable Form (CRF)
   b. ☐ Specification Sequence Listing on:
      i. ☐ CD-ROM or CD-R (2 copies); or
      ii. ☐ Paper
   c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

9. ☐ **Assignment Papers.** (cover sheet & document(s))
   Name of Assignee
10. ☐ **37 CFR 3.73(c) Statement.** ☐ **Power of Attorney.** *(when there is an assignee)*
11. ☐ **English Translation Document.** *(if applicable)*
12. ☐ **Information Disclosure Statement.** (PTO/SB/08 or PTO-1449)
    ☐ Copies of citations attached
13. ☐ **Preliminary Amendment.**
14. ☐ **Return Receipt Postcard.** *(MPEP § 503) (Should be specifically itemized)*
15. ☐ **Certified Copy of Priority Document(s).** *(if foreign priority is claimed)*
16. ☐ **Nonpublication Request.** Under 35 U.S.C. 122(b)(2)(B)(i). Applicant must attach form PTO/SB/35 or equivalent.
17. ☐ **Other:**

***Note:** (1) Benefit claims under 37 CFR 1.78 and foreign priority claims under 1.55 **must** be included in an Application Data Sheet (ADS).
(2) For applications filed under 35 U.S.C. 111, the application must contain an ADS specifying the applicant if the applicant is an assignee, person to whom the inventor is under an obligation to assign, or person who otherwise shows sufficient proprietary interest in the matter. See 37 CFR 1.46(b).

18. CORRESPONDENCE ADDRESS

☒ The address associated with Customer Number: 50828 **OR** ☐ Correspondence address below

Name					
Address					
City		State		Zip Code	
Country		Telephone		Email	

Signature	/David S. Resnick, Reg. No. 34,235/	Date	January 26, 2015
Name (Print/Type)	David S. RESNICK	Registration No. (Attorney/Agent)	34235

This collection of information is required by 37 CFR 1.53(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.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/605,363	01/26/2015	Anthony John Iafrate	030258-079365-US	6670

50828 7590 01/31/2018

DAVID S. RESNICK
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BOSTON, MASSACHUSETTS 02110-2131

EXAMINER	
CHUNDURU, SURYAPRABHA	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
01/31/2018	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):

bostonpatent@nixonpeabody.com
ipairlink@nixonpeabody.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 14/605,363	Applicant(s) Iafrate et al.	
	Examiner SURYAPRABHA CHUNDURU	Art Unit 1637	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 10/30/2017

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-20 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, 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.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 26 January 2015 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date 9/11/2017; 1/16/2018.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

1. The Applicants' response to the office action filed on October 30, 2017 has been considered and acknowledged.

Status of the application

2. Claims 1-20 are pending under examination. The Applicants' arguments and the amendment have been fully considered and deemed persuasive in- part for the reasons that follow. The action is made FINAL necessitated by the IDS with fee.

Response to arguments:

3. The rejection of claims under 35 USC 112, second paragraph, has been withdrawn in view of the amendment.

4. The rejection of claims 1-20 under 35 USC 102(a)(1) as being anticipated by Anderson et al. has been withdrawn in view of the Applicant's arguments and the amendment.

5. With reference to the rejection of claims 1-20 under obviousness type of provisional double patenting, the Applicant's arguments were fully considered and the rejection has been maintained because the instant claims are within the scope of the claims in the copending application and no terminal disclaimer has been filed.

New Rejections necessitated by the IDS with fee

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.
(a)(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

A. Claims 1-18 and 20 are rejected under 35 U.S.C. 102(a)(2) as being anticipated by Iafrate et al. (US 9,487,828).

Iafrate et al. teach a method of claim 1, 4-6, 18, preparing nucleic acids for analysis and determining the nucleotide sequence comprising:

a) contacting a first nucleic acid template comprising a first strand of a target nucleic acid with a complementary target-specific primer that comprises a target-specific hybridization sequence, under conditions to promote template-specific hybridization and extension of the target-specific primer and produce extension product (see entire document, at least col. 17, line 42-49);

b) contacting a second nucleic acid template (first primer extension product from step a)) comprising a second strand that is complementary to the first strand of the

target nucleic acid with a plurality (two or more) of different primers that share a common sequence (tail-adaptor primers comprising 5' random tail and 3' target complementary sequence) that is 5 ' to different hybridization sequences, under conditions to promote template-specific hybridization and extension of at least one of the plurality of different primers and produce extension product (see entire document, at least col. 17, line 50-59);

c) amplifying a portion of the target nucleic acid and the tailed random primer sequence (primer extension product) with a first tail primer and a first-specific primer (see entire document, at least col. 17, line 50-59);

d) amplifying a portion of the amplicon resulting from the step c) with a second tail primer and a second target-specific primer (see entire document, at least col. 17, line 60-67, col. 18, line 1-3);

e) sequencing the amplified portion from step d) using a first and a second sequencing primer; wherein the population of tailed random primers comprise single-stranded oligonucleotides having 5' nucleic acid sequence identical to the first sequencing primer, and the 3' nucleic acid sequence comprising about 6-12 random nucleotides; wherein the first target-specific primer a nucleic acid sequence that can specifically anneal to the known target sequence; wherein the second target-specific primer comprises a 3' portion comprising a nucleic acid sequence that can specifically anneal to a portion of the known target sequence of the amplicon and a 5' portion identical to a second sequencing primer and the second-target primer is nested with respect to the first target-specific primer; wherein the first sequencing primer comprises

a sequence identical to the tailed random primer and, the second tail primer comprises a sequence identical to the first sequencing primer and is nested with respect to the first tail primer (see entire document, at least col. 18, line 4-67, col. 19, line 1-35, col. 16, line 47-67, col. 17, line 1-30).

With reference to claims 2-3, 7-9, lafrate et al. teach that the sample is a genomic DNA, single stranded gDNA, or mRNA, and the target comprises a gene rearrangement comprising chromosomal segment, wherein the rearrangement is an inversion, deletion or translocation (see entire document, at least col. 19, line 31-67, col. 20, line 1-67).

With reference to the claims 10-11, lafrate et al. teach that the method further comprises amplifying extension products and immobilizing the products with an immobilized oligonucleotide under conditions of hybridization (see at least col. 19, line 47-57).

With reference to claims 12-17, 20, lafrate et al. teach that the target comprises a target portion having a known sequence and a flanking portion having an unknown sequence, wherein different hybridization sequences are complementary to the flanking portion and target specific hybridization sequence is complementary to the target portion and the target specific primer and the common sequence further comprises a barcode, index sequence or adaptor sequence, wherein the adaptor sequence is a cleavable adaptor for immobilizing oligonucleotides in a flow cell and the method comprises treating the products with RNase after extension of the initial target-specific

primer (see entire document, at least col. 19, line 36-67, col. 20, line 1-36, col.22, line 19-65, Fig. 1, 8 (RNase)). For all the above the claims are anticipated.

B. Claims 1-17 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Kurn et al. (US 20090203085).

Kurn et al. teach a method of claim 1, 4-6, preparing nucleic acids for analysis comprising:

a) contacting a first nucleic acid template comprising a first strand of a target nucleic acid with a complementary target-specific primer that comprises a target-specific hybridization sequence, under conditions to promote template-specific hybridization and extension of the target-specific primer and produce extension product (see entire document, at least para 0074-0075, 0081, para 0136);

b) contacting a nucleic acid template primer (first primer extension product) comprising a second strand that is complementary to the first strand of the target nucleic acid with a plurality of different primers that share a common sequence (5' random tail primers comprising 3' target complementary sequence) that is 5 ' to different hybridization sequences, under conditions to promote template-specific hybridization and extension of at least one of the plurality of different primers and produce extension product (see entire document, at least para 0083-0087, 0136, 0175-0176).

With reference to claims 2-3, 7-9, Kurn et al. teach that the sample is a genomic DNA, single stranded gDNA, or mRNA, and the target comprises a gene rearrangement comprising chromosomal segment, wherein the rearrangement is an

inversion, deletion or translocation (see entire document, at least para 0073-0075, 0081, 0083-0087, 0195, 0156, 0201, 0293-319).

With reference to the claims 10-11, Kurn et al. teach that the method further comprises amplifying extension products and immobilizing the products with an immobilized oligonucleotide under conditions of hybridization (see at least para 0139).

With reference to claims 12-17, Kurn et al. teach that the target comprises a target portion having a known sequence and a flanking portion having an unknown sequence, wherein different hybridization sequences are complementary to the flanking portion and target specific hybridization sequence is complementary to the target portion and the target specific primer and the common sequence further comprises a barcode, index sequence or adaptor sequence , wherein the adaptor sequence is a cleavable adaptor for immobilizing oligonucleotides in a flow cell (see entire document, at least para 0073-0075, 081, 0139). For all the above the claims are anticipated.

C. Claims 19 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by Callaway et al. (Virology, Vol. 330, p. 186-195, 2004).

Callaway et al. teach a method of claim 19, of determining the nucleotide sequence contiguous to a known target nucleotide sequence comprising:

a) and b) contacting a target nucleic acid molecule comprising a known target nucleic acid (viron RNA from TRoV infected turnip and Arabidopsis plants) with a population of tailed random primers under hybridization conditions and performing a template-dependent extension reaction of tailed random primers (see page 192-193,

paragraph under materials and methods section indicating 3' and 5' tailed random primers to synthesize first strand cDNA);

c) to e) contacting the product of step b) with an initial target-specific primer and performing a template-dependent extension, amplifying a portion of the target nucleic acid and the tailed random primer sequence with a first tail primer and a first target-specific primer (see page 192-192, paragraph 1 under materials and methods section indicating PCR amplification of first strand cDNA using TRoV-specifc primer and a 5' tailed random primer);

f) amplifying a portion of the amplicon resulting from step c) with a second tail primer and a second target specific primer (see page 192-192, paragraph 1 under materials and methods section indicating nested amplification using the amplicon of step c) with a target-specific primer and a tail random primer);

g) sequencing the amplified portion from the step d) using a first and second sequencing primer, and sequenced by next-generation sequencing (see page 193, paragraph 1 under materials and methods section indicating sequencing the nested amplicons).

Wherein the 5' nucleic acid sequence of the tailed random primers is identical to a first sequencing primer, the first tail primer comprises a nucleic acid sequence identical to the 5 ' portion of the tailed random primer, the second tail primer comprises a nucleic acid sequence identical to a portion of the first sequencing primer, each tailed random primer further comprises a spacer comprising 6-12 random nucleotides between 5 ' and

3 ' nucleic acid sequence of the first sequencing primer, the second tail primer is nested with respect to the first tail primer by at least 3 nucleotides or identical to the first sequencing primer, the first target-specific primer comprises a 5' tag (see page 192-192-193, paragraphs 1-4 under materials and methods section, Fig. 6 on page 191).

Restatement of rejections maintained

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(1)(1) - 706.02(1)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-Lisp.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 14/605,482. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims 1-20 are generic to all that is recited in claims 1-20 of the co-pending application. That is, the claims 1-20 fall entirely within the scope of claims 1-20 of the co-pending application, or in other words, claims 1-20 are obvious over the claims 1-20 of the co-pending application. Specifically the method of

preparing nucleic acids and determining the nucleotide sequence contiguous to a known target sequence is within the scope of the claims 1-20 of the co-pending application. The only difference is that, the claims in the co-pending application uses both a target specific primer and a random tail primer. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

No claim is allowable.

Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on 9/11/2017 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609.04(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SURYAPRABHA CHUNDURU whose telephone number is (571)272-0783. The examiner can normally be reached on 8.00am-4.30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. 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.

/SURYAPRABHA CHUNDURU/
Primary Examiner, Art Unit 1637

Attorney Docket No. 030258-079365-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Iafrate, Anthony John *et al.*	Confirmation No.:	6670
Application No.:	14/605,363	Art Unit:	1637
Filing Date:	January 26, 2015	Examiner:	Chunduru, Suryaprabha
For:	METHODS OF PREPARING NUCLEIC ACIDS FOR SEQUENCING		

VIA EFS-WEB RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

GENERAL TRANSMITTAL & CERTIFICATE OF EFS SUBMISSION

Pursuant to 37 C.F.R. § 1.8(a)(1)(i)(C) I hereby certify that the following documents are being submitted to the Patent and Trademark Office via the Office Electronic Filing System in accordance with § 1.6(a)(4) on **July 31, 2018**:

1. **General Transmittal & Certificate of EFS Submission (1 pg.);**
2. **Response to Final Office Action (7 pp.);**
3. **Request for Continued Examination (3 pp.);**
4. **Petition for Extension of Time (2 pp.); and**
5. **Electronic Fee Transmittal (2 pp.).**

AUTHORIZATION TO CHARGE/CREDIT DEPOSIT ACCOUNT

The Director of the USPTO is hereby authorized to charge any fee deficiencies associated with the instant filing **except excess claims fees** and credit any overpayments to NIXON PEABODY LLP Deposit Account No. **50-0850**, from which the undersigned is authorized to withdraw.

Customer No.: 50828

Date: July 31, 2018

Respectfully submitted,

/Nicole D. Kling/

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4824-5898-6094.1

Attorney Docket No. 030258-079365-US PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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VIA EFS-WEB RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE TO NON-FINAL OFFICE ACTION

This Amendment is being filed in response to the Final Office Action dated January 31, 2018. A Petition for a 3-Month Extension of Time and a Request for Continued Examination are submitted concurrently herewith. Please consider the following amendments and remarks in connection with the above-identified application:

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

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

Listing of Claims:

1. (Currently Amended) A method of preparing nucleic acids for analysis, the method comprising:

(a) contacting a first nucleic acid template comprising a first strand of a target nucleic acid with a complementary target-specific primer that comprises a target-specific hybridization sequence, under conditions to promote template-specific hybridization and extension of the target-specific primer; ~~and~~

(b) contacting a second nucleic acid template comprising a second strand that is complementary to the first strand of the target nucleic acid with a plurality of different primers that share a common sequence that is 5' to different hybridization sequences, under conditions to promote template-specific hybridization and extension of at least one of the plurality of different primers, wherein each primer of the plurality of different primers does not anneal to the same sequence of the target nucleic acid as any other primer of the plurality of different primers,

wherein, following (a) and (b), an extension product is generated to contain both a sequence that is characteristic of the target-specific primer and a sequence that is characteristic of the at least one of the plurality of different primers; and

(c) subjecting the extension product to an amplification reaction comprising successive rounds of polymerase extension of i) a tail primer that comprises a 3' sequence that specifically anneals to the complement of the common sequence and that comprises a 5' tail sequence, and ii) a primer that specifically anneals to the complement of the target-specific hybridization sequence.

2. (Original) The method of claim 1, wherein the target nucleic acid is a ribonucleic acid.

3. (Original) The method of claim 1, wherein the target nucleic acid is a deoxyribonucleic acid.

4. (Original) The method of claim 1, wherein steps (a) and (b) are performed sequentially.

5. (Previously Presented) The method of claim 1, wherein the first nucleic acid template comprises an extension product resulting from the hybridization and extension of the at least one of the plurality of different primers in step (b).

6. (Previously Presented) The method of claim 1, wherein the second nucleic acid template comprises an extension product resulting from the hybridization and extension of the target-specific primer in step (a).

7. (Original) The method of claim 2, wherein the target nucleic acid is a messenger RNA encoded from a chromosomal segment that comprises a genetic rearrangement.

8. (Original) The method of claim 3, wherein the target nucleic acid is a chromosomal segment that comprises a portion of a genetic rearrangement.

9. (Original) The method of claim 8, wherein the genetic rearrangement is an inversion, deletion, or translocation.

10. (Canceled)

11. (Currently Amended) The method of claim 1[[10]], further comprising contacting the extension product or amplified extension product with an immobilized oligonucleotide under conditions in which hybridization occurs between the extension product and immobilized oligonucleotide.

12. (Original) The method of claim 1 wherein the target nucleic acid comprises a target portion having a known sequence and a flanking portion having an unknown sequence.

13. (Original) The method of claim 12, wherein different hybridization sequences are complementary to the flanking portion.

14. (Original) The method of claim 12, wherein the target-specific hybridization sequence is complementary to the target portion.

15. (Original) The method of claim 1, wherein the target-specific primer further comprises, 5' to the target-specific hybridization sequence, at least one of an index sequence, a barcode sequence and an adaptor sequence.

16. (Original) The method of claim 1, wherein the common sequence comprises at least one of an index sequence, barcode sequence and an adaptor sequence.

17. (Original) The method of claim 15, wherein the adaptor sequence is a cleavable adaptor sequence for immobilizing oligonucleotides in a flow cell.

18-20. (Canceled)

21. (New) The method of claim 1, wherein the tail primer comprises a nucleic acid sequence identical to the common sequence.

22. (New) The method of claim 1, wherein the 5' tail sequence comprises at least one of an index sequence, a barcode sequence, an adaptor sequence, and a sequencing primer hybridization sequence.

23. (New) The method of claim 1, wherein the primer that specifically anneals to the complement of the target-specific hybridization sequence comprises a sequence identical to the target-specific primer.

24. (New) The method of claim 1, wherein the primer that specifically anneals to the complement of the target-specific hybridization sequence comprises at least one modified internucleoside linkage.

25. (New) The method of claim 1, wherein the target-specific primer comprises at least one modified internucleoside linkage.

26. (New) The method of claim 1 further comprising purifying the extension product prior to (c).

27. (New) The method of claim 1 further comprising purifying the amplified product of (c).

28. (New) The method of claim 1, wherein the plurality of different primers can specifically anneal to sequences comprised by separate genes.

29. (New) The method of claim 1, wherein the plurality of different primers can specifically anneal to different portions of the target nucleic acid comprised by a single gene.

30. (New) The method of claim 1, wherein the plurality of different primers can specifically anneal to different exons of a gene comprising the target nucleic acid.

31. (New) The method of claim 1, wherein the target nucleic acid is derived from a biological sample.

32. (New) The method of claim 31, wherein the target nucleic acid is a cDNA produced from RNA in the biological sample.

33. (New) The method of claim 1, wherein the target nucleic acid is derived from a sample comprising nucleic acids that have been ligated to an oligonucleotide comprising a barcode sequence.

REMARKS

Applicant respectfully requests reconsideration. Claims 1-20 were previously pending in this application. By this amendment, Applicant is canceling claims 10 and 18-20 without prejudice or disclaimer. Claims 1 and 11 have been amended. New claims 21-33 have been added. As a result, claims 1-9, 11-17, and 21-33 are pending for examination with claim 1 being an independent claim. No new matter has been added.

Entry and consideration of the proposed amendments is respectfully requested. The Applicants have amended the claims to expedite prosecution of preferred embodiments. The Applicants reserve the right to prosecute any cancelled subject matter in continuation, divisional or continuation-in-part applications, claiming priority to this application.

Rejections Under 35 U.S.C. §102

Claims 1-18 and 20 stand rejected under 35 U.S.C. §102 as allegedly being anticipated by Iafrate et al. (U.S. Patent No. 9,487,828; hereinafter, "Iafrate").

Applicant respectfully disagrees with the rejection. Nonetheless, in the interest of expediting prosecution and without acquiescing to the assertions of the Office, claim 1 has been amended to recite, *inter alia*:

> . . . subjecting the extension product to an amplification reaction comprising successive rounds of polymerase extension of i) a tail primer that comprises a 3' sequence that specifically anneals to the complement of the common sequence and that comprises a 5' tail sequence, and ii) a primer that specifically anneals to the complement of the target-specific hybridization sequence.

Applicant submits that Iafrate does not teach all elements of claim 1. Thus, claim 1, and claims 2-17 depending therefrom, are not anticipated by Iafrate. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-17.

In the interest of expediting prosecution and without conceding correctness of the rejection, claims 18 and 20 have been canceled, thereby rendering the rejection of these claims moot.

Claims 1-17 stand rejected under 35 U.S.C. §102 as allegedly being anticipated by Kurn et al. (U.S. Publication No. 2009/0203085; hereinafter, "Kurn").

Applicant respectfully disagrees with the rejection. Nonetheless, in the interest of expediting prosecution and without conceding correctness of the rejection, claim 1 has been amended to recite, *inter alia*, an amplification reaction.

In contrast to the instant claims, which recite amplification using two primers, methods disclosed in Kurn relate to single primer isothermal amplification ("SPIA"). Amplification via this process occurs in an isothermal reaction that relies on the use of a single primer to linearly amplify a nucleic acid. Kurn therefore disclosed amplifying with one primer, whereas the instant claims recite amplification with two primers. Thus, Kurn fails to teach all elements recited in the instant claims. To the extent that Kurn generically disclosed an optional PCR amplification, Kurn does not teach or suggest amplification using a tail primer that specifically anneals to the complement of a common sequence, as recited in the instant claims.

Accordingly, for at least the above reasons, the claims as amended are not anticipated by Kurn. Applicant respectfully requests that this rejection be reconsidered and withdrawn.

Claim 19 stands rejected under 35 U.S.C. §102 as allegedly being anticipated by Callaway et al. (Virology, vol. 330, p. 186-195, 2004; hereinafter, "Callaway").

Applicant respectfully disagrees with the rejection. Nonetheless, in the interest of expediting prosecution and without conceding correctness of the rejection, claim 19 has been canceled as of this amendment, thereby rendering this rejection moot.

Double Patenting Rejection

Claims 1-20 stand rejected as allegedly being unpatentable over claims 1-20 of copending Application No. 14/605,482. Applicant respectfully requests that this rejection be held in abeyance pending reconsideration in view of the instant response.

In view of the above, Applicant submits that all issues raised in the Office Action are addressed herein. Entry of the proposed amendments and reconsideration of the claims is respectfully requested.

Applicant does not acquiesce in the Examiner's characterizations of the art. For brevity and to advance prosecution, however, applicants may have not addressed all characterizations of the art and reserve the right to do so in further prosecution of this or a subsequent application. The absence of an explicit response by the applicants to any of the Examiner's positions does not constitute a concession of

the Examiner's positions. The fact that applicants' comments have focused on particular arguments does not constitute a concession that there are no other arguments for patentability of the claims. All of the dependent claims are patentable for at least the reasons given with respect to the claims on which they depend.

AUTHORIZATION TO CHARGE/CREDIT DEPOSIT ACCOUNT

The Director of the USPTO is hereby authorized to charge any fee deficiencies associated with the instant filing **except excess claims fees** and credit any overpayments to NIXON PEABODY LLP Deposit Account No. **50-0850**, from which the undersigned is authorized to withdraw.

Customer No.: 50828

Date: July 31, 2018

Respectfully submitted,

/Nicole D. Kling/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/605,363	01/26/2015	Anthony John Iafrate	030258-079365-US	6670

50828 7590 09/07/2018

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EXAMINER	
CHUNDURU, SURYAPRABHA	

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
09/07/2018	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):

bostonpatent@nixonpeabody.com
ipairlink@nixonpeabody.com

PTOL-90A (Rev. 04/07)

Office Action Summary	Application No. 14/605,363	Applicant(s) Iafrate et al.	
	Examiner SURYAPRABHA CHUNDURU	Art Unit 1637	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/31/2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ 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.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1-9,11-17 and 21-33 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1-9,11-17 and 21-33 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, 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.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on 1/26/2015 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ 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)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 31, 2018 has been entered.

Status of the Application

2. Claims 1-9 and 11-17 are pending under examination. New claims 21-33 are added. Claims 10 and 18-20 were canceled. The Applicant's arguments and the amendment were fully considered and found persuasive in-part for the reasons that follow.

Response to Arguments:

3. The rejection of claims 1-18 and 20 under 35 USC 102(a)(1) as anticipated by Lafrate et al., has been withdrawn in view of the amendment.

4. The rejection of claims 1-17 under 35 USC 102(a)(1) as being anticipated by Kurn et al. has been withdrawn in view of the amendment.

5. The rejection of claim 19 under 35 USC 102(a)(1) as being anticipated by Callaway et al. has been withdrawn in view of the amendment.

6. With reference to the rejection of claims 1-20 under obvious type of double patenting over the claims in the co-pending application 14/605,482, the Applicant's arguments

were fully considered and the rejection has been maintained because the instant claims are within the scope of the claims in the co-pending application and no terminal disclaimer is filed.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir.

1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory

double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(1)(1) - 706.02(1)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-Lisp.

Claims 1-9, 11-17 and 21-33 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 -20 of copending Application No. 14/605,482. Although the claims at issue are not identical, they are not patentably distinct from each other because the claims 1-9, 11-17 and 21-33 are generic to all that is recited in claims 1-20 of the co-pending application. That is, the claims 1-9, 11-17 and 21-33 fall entirely within the scope of claims 1-20 of the co-

pending application, or in other words, claims 1-9, 11-17 and 21-33 are obvious over the claims 1-20 of the co-pending application. Specifically the method of preparing nucleic acids and determining the nucleotide sequence contiguous to a known target sequence is within the scope of the claims 1-20 of the co-pending application. The only difference is that, the claims in the co-pending application uses both a target specific primer and a random tail primer, which is considered obvious variation. This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Claims 1-9, 11-17 and 21-33 are free of art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SURYAPRABHA CHUNDURU whose telephone number is (571)272-0783. The examiner can normally be reached on 8.00am-4.30pm.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. 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.

/SURYAPRABHA CHUNDURU/
Primary Examiner, Art Unit 1637

EXHIBIT 17

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ARCHERDX, INC. and THE GENERAL HOSPITAL CORPORATION d/b/a MASSACHUSETTS GENERAL HOSPITAL, Plaintiffs, v. QIAGEN SCIENCES, LLC, QIAGEN LLC f/k/a QIAGEN, INC., QIAGEN BEVERLY, INC., QIAGEN GAITHERSBURG, INC., QIAGEN GMBH, QIAGEN N.V., and JONATHAN ARNOLD, Defendants.	Civil Action No. 18-cv-01019-MN-CJB **HIGHLY CONFIDENTIAL – ATTORNEYS' EYES ONLY**

NONINFRINGEMENT AND NO TRADE SECRET MISAPPROPRIATION EXPERT REPORT OF DR. MICHAEL METZKER RESPONDING TO THE EXPERT REPORT OF NIALL LENNON

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4. The Accused Products Do Not Have a Primer That Is Equivalent to a Second Target Specific Primer[122]

233. I disagree with Dr. Lennon that the QIAGEN accused products infringe the limitation of a "second target specific primer" under the doctrine of equivalents.[123]

234. The QIAGEN accused products do not have any primer that is "equivalent" to the "second target specific primer" required by the asserted claims of the '810 Patent. Fundamentally, a "universal" primer is different from a "target-specific primer," both according to the intrinsic evidence and according to the understanding of one of ordinary skill in the art at the relevant time.

235. In my opinion, the QIAGEN SIP does not perform substantially the same function in substantially the same way to obtain substantially the same result as the claimed second target-specific primer. In fact, as I discuss in detail below, the QIAGEN SIP performs a completely different function in a completely different way to obtain a completely different result.

236. Dr. Lennon's application of the doctrine of equivalents strips all meaning from the term "second target specific primer" and essentially writes that term out of the claim. It is my understanding that it is impermissible to vitiate the meaning of a claim term through application of the doctrine of equivalents.

a) Substantially Different Functions

[122] I note that Dr. Lennon does not appear to have addressed the doctrine of equivalents for any other limitation of any asserted claim of either the '810 Patent or the '597 Patent. Therefore, given that neither he nor Plaintiffs have presented any other specific doctrine of equivalents argument, I have addressed the doctrine of equivalents in detail only with respect to this limitation of the '810 Patent, although I have responded to the other vague assertions of doctrine of equivalents to the extent possible in Plaintiffs' infringement contentions. *See* Plaintiffs' Disclosure of Amended Infringement Contentions for the '810 and '597 Patents at 3, 4, 6, 7, Ex. A at 89, Ex. B at 34, 40, 45. Should Dr. Lennon or Plaintiffs at any time offer a more specific doctrine of equivalents argument with respect to any other limitation of any other asserted claim of the '810 Patent or the '597 Patent, I reserve the right to respond at that time.

[123] *See* Lennon Opening Report ¶¶ 267-294.

237. Dr. Lennon identifies three functions for the "second target-specific primer":[124]

(1) amplifying the amplification product of step (ii);

(2) producing an amplification product that is capable of being sequenced; and

(3) reducing undesirable amplification products by being paired with the second adaptor primer.

238. These functions are not the appropriate "functions" to consider for application of the doctrine of equivalents because they are general to any primer that would be used, do not require the second target-specific primer to anneal to the known target nucleotide sequence, and therefore eliminate the phrase "second target-specific" from the term. These functions would permit the second target specific primer to anneal to universal sequence, rather than to the known target nucleotide sequence, as required by the Court's claim construction.

239. The first function is already expressly stated in element (iii) of the claim: "***amplifying an amplification product*** of (ii) using a second target-specific primer that specifically anneals to the amplification product of (ii)." Therefore, that would be a function of any primer, whether or not "target-specific."

240. Dr. Lennon's argues that the second function is appropriate for his doctrine of equivalents analysis because the Court's construction of the term "second target-specific primer" refers to "a second sequencing primer."[125] As I discussed above, the Court's construction of the term "second target-specific primer" includes the requirement that the second target-specific primer comprise "a 5' portion comprising a nucleic acid sequence that is identical to a second

[124] *See* Lennon Opening Report ¶ 269.

[125] *See* Lennon Opening Report ¶ 271.

sequencing primer." Again, Dr. Lennon seeks to broaden the function of the "second target-specific primer" through reference to general functions that would be true of any primer that bound specifically to the amplification product and had a tail comprising sequence identical to a second sequencing primer. There is nothing specific to a "second target-specific primer" in Dr. Lennon's second function.

241. Dr. Lennon's third function, similarly, simply states that the second target-specific primer is paired with the second adaptor primer in the PCR reaction. This function is expressly stated in the claim, which recites that the amplification product of step (ii) is amplified using a second target-specific primer that "specifically anneals" to the amplification product of (ii) and a second adaptor primer. Again, Dr. Lennon's third function would be carried out by any primer that "specifically annealed" to the amplification product of step (ii). Dr. Lennon's third function writes out the requirement from the claim of a ***second target-specific*** primer.

242. Moreover, Dr. Lennon appears to attribute any added specificity from step (iii) of the reaction to the use of a "nested" second adaptor primer, and relegates the function of the second target-specific primer to merely serving as the opposing primer for the second adaptor primer.[126] Dr. Lennon states: "The claimed amplifying cannot occur without the presence of both primers; paired with a nested adaptor primer, the second target-specific primer makes possible the benefits associated with a nested adaptor primer, i.e., reducing undesirable amplification products caused by a first adaptor primer that is identical to a 5' portion of the first sequencing primer."[127]

243. This interpretation of the claim is contrary to the plain language of the claim, the

[126] *See* Lennon Opening Report ¶ 272.

[127] *See* Lennon Opening Report ¶ 272.

intrinsic evidence, and the interpretation of one of ordinary skill in the art. The primary function of the claimed second target-specific primer is to bind to ***the known target nucleotide sequence*** to enrich for particular targets having that sequence and to eliminate unwanted products from the first round of PCR. The accused QIAGEN SIP does not carry out that function. The function of the accused QIAGEN SIP is to bind to universal or common sequence added by the tail of the GSP from the first round of PCR in the accused QIAGEN products to amplify ***all*** products from the first round of PCR, not to eliminate any unwanted products from the first PCR round.

244. These functions – binding to the known target nucleotide sequence to enrich a particular target and eliminate unwanted products from the first round of PCR, thus increasing specificity, versus binding to universal or common sequence added via the tail of the accused GSP primer from the first round to amplify ***all*** products from the first round and not elminate unwanted products from the first round – are substantially different.

245. The purpose of carrying out a second PCR with a "second target-specific primer," as I have discussed in detail above, is to obtain the benefits of specificity associated with using a second primer that will not bind to unwanted, off-target sequences in the sample that are present in non-specific amplification products from the first round of PCR. Whether or not the nested second adaptor primer confers additional specificity does not detract from this central function of the second target-specific primer.

246. Instead, the appropriate function that should be considered for application of the doctrine of equivalents to the term "second target-specific primer" is the function of increasing specificity of the overall method by carrying out a second PCR reaction with a second primer that distinguishes between amplification products from the first round of PCR containing the desired target sequences from the sample and amplification products from the first round of PCR

that contain undesirable non-specific, non-target sequences.

247. Having incorrectly defined the functions of the "second target-specific primer," Dr. Lennon then incorrectly concludes that QIAGEN's SIP carries out substantially the same function as the claimed second target-specific primer. Dr. Lennon's analysis fails because ***any*** primer that bound specifically to the amplicon produced in step (ii) of the method and met the requirement of having a tail with sequence identical to a second sequencing primer would satisfy these functions. Again, Dr. Lennon eliminates the phrase "second target-specific" primer from the claim.

248. Dr. Lennon's equivalents analysis, like his literal infringement analysis, eliminates the logic and structure of the claim that requires two steps, each with a target-specific primer that binds to the same target, where the second step is intended to increase specificity of the overall method. He broadens the second step to include universal PCR, with QIAGEN's SIP primer, and therefore disconnects element (iii) from the structure and logic of the claim.

249. Dr. Lennon concludes incorrectly that the SIP satisfies the "function" of the "second target-specific primer" because the SIP amplifies the PCR product of the prior step, has a tail with a "second sequencing primer sequence," and enables a PCR reaction with the second adaptor primer.[128]

250. I disagree with Dr. Lennon. The SIP does not satisfiy the appropriately defined "function" of the "second-target specific primer" because it does not increase the specificity of the overall method by enabling a second PCR reaction with a second primer that distinguishes between amplification products from the first round of PCR containing the desired target sequences from the sample and amplification products from the first round of PCR that contain

[128] *See* Lennon Opening Report ¶¶ 273-276.

undesirable non-specific, non-target sequences. Instead, QIAGEN's SIP is directed to increasing sensitivity, not specificity, through a universal PCR reaction, as I discussed above. As I have explained, the function of the accused QIAGEN SIP is to bind to all amplification products from the first round. The function of the claimed second target-specific primer is to amplify products containing the the known target nucleotide sequence and eliminate unwanted products from the first PCR round. Thesse functions are substantially different.

251. Dr. Lennon also states in a conclusory fashion that "Claim 16 is directed to a hemi-nested second amplification reaction, i.e., nested on one side of the molecule (second adaptor primer) and non-nested on the other (second target-specific primer)."[129]

252. I disagree. The phrase "hemi-nested" does not appear anywhere in the asserted claims. In fact, the phrase "hemi-nested" appears only twice in the entire '810 Patent, in the following passage:

> The use of ***nested adaptor primers*** eliminates the possibility of producing final amplicons that are amplifiable (e.g. during bridge PCR or emulsion PCR) but cannot be sequence, a situation that can arise during ***hemi-nested methods***. In other situations, ***hemi-nested approaches*** using a primer identical to a sequencing primer can result in the carry-over of undesired amplification products from the first PCR step to the second PCR step and would ultimately yield artificial sequencing reads. The use of ***two adaptor primers***, as described herein can reduce, and in some embodiments eliminate, these problems.[130]

This paasage demonstrates that the specification uses the term "hemi-nested" in precisely the opposite sense from that in which Dr. Lennon uses the term. The specification refers to "hemi-nested" methods in which the ***target-specific primers are nested but the adaptor primers are not***, and discusses problems arising from this method relating to the generation of non-specific amplification products. This passage recommends the use of nested adaptor primers for a fully

[129] *See* Lennon Opening Report ¶ 276.

[130] *See* '810 Patent 17:35:45 (emphases added).

nested, rather than hemi-nested approach.

253. Dr. Lennon, on the other hand, attempts to read the method of Claim 16 as a "hemi-nested" method in which only the adaptor primers are nested but the target-specific primers are not. Such a method is nowhere contemplated in the specification and I note that Dr. Lennon cites no specification support for his "hemi-nested" argument.[131]

b) Substantially Different Way

254. Dr. Lennon incorrectly concludes that the SIP primer and the "second target-specific primer" carry out his incorrectly defined "function" in "substantially the same way."[132] Dr. Lennon argues incorrectly that QIAGEN's interpretation of the term "second target-specific primer" under the Court's construction encompasses a second target-specific primer that binds to exactly the same sequence as the first target-specific primer.[133] Dr. Lennon then argues that QIAGEN's SIP and this hypothetical second target-specific primer (which Dr. Lennon refers to as "TS2") both amplify the PCR product from the first PCR reaction, both include a sequence identical to a second sequencing primer as a common tail, and both pair with a nested second adaptor primer to "reduce undesirable amplification products."[134]

255. This argument is incorrect in multiple respects. As a preliminary matter, the Court's construction of the term "second target-specific primer" ***requires*** the second target-specific primer to be nested with respect to the first target-specific primer and precludes a primer that binds to exactly the same sequence as the first target-specific primer.

256. Although the Court declined to read the express term, "nested," into Claim 16, the

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[131] *See* Lennon Opening Report ¶ 276.

[132] *See* Lennon Opening Report ¶¶ 278-84.

[133] *See* Lennon Opening Report ¶¶ 279-281.

[134] *See* Lennon Opening Report ¶ 282.

Court construed the term "second target-specific primer" to require that the second target-specific primer "can specifically anneal to ***a portion of the known target nucleotide sequence*** comprised by the amplicon resulting from step (b)." This construction requires the second target-specific primer to anneal to ***the known target nucleotide sequence***, not merely to anneal to the sequence of the first target-specific primer introduced during the first round of PCR amplification.

257. Dr. Lennon's hypothetical primer is a primer that anneals to the first target-specific primer but not ***to the known target nucleotide sequence*** and therefore does not satisfy the Court's construction. Specifically, such a primer could anneal to off target sequences amplified by the first target-specific primer. Notably, such a primer is also not "target-specific" given that it anneals to off target sequences present from the first round of PCR.

258. Therefore, the claimed second target-specific primer must anneal to a different portion of the known target nucleotide sequence than the first target-specific primer and therefore must be nested with respect to, *i.e.*, anneal to a sequence downstream of, the first target-specific primer.

259. Dr. Lennon's hypothetical primer is therefore inconsistent with the Court's claim construction and cannot be encompassed as an equivalent without impermissibly vitiating the limitation of a "second target-specific primer."

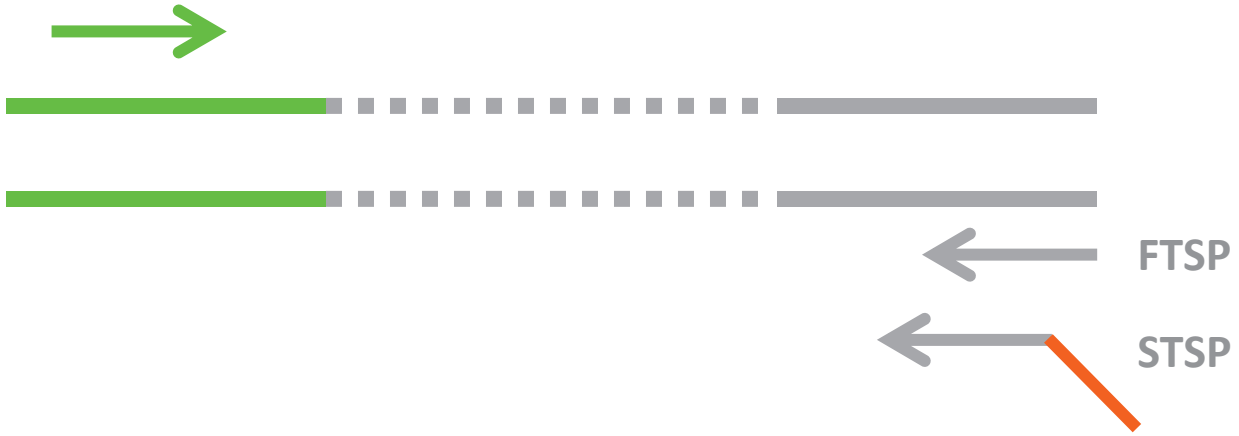
260. I note that the fact that the Court did not specifically insert the term "nested" into the claim is not inconsistent with my opinion. For example, Dr. Lennon interprets the "second adaptor primer" as being "nested" with respect to the first adaptor primer, despite the fact that the term "nested" does not appear in Claim 16.[135] Instead, the term "nested" with respect to the

[135] *See* Lennon Opening Report ¶ 276.

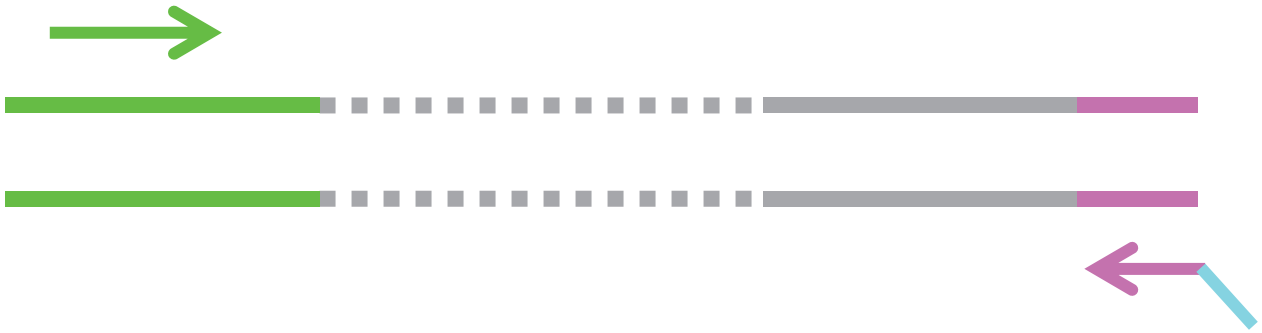
second adaptor primer is introduced through the Court's construction of the term "second adaptor primer." There is no reason that a requirement for the second target-specific primer to be nested with respect to the first target-specific primer is not similarly introduced through the Court's definition of "second target-specific primer."

261. The plain meaning of the terms "first target-specific primer" and "second target-specific primer," consistent with every example and figure in the specification, is that they are two ***different*** target-specific primers that bind to different parts of "the known target nucleotide sequence." Given the method steps that I digrammed above, for the second target-specific primer to be different from the first target-specific primer, it must anneal to a different portion of the known target nucleotide sequence. To do so, it must anneal downstream of the first target-specific primer, such that it is nested with respect to the first target-specific primer. And, as I discussed at length above, all the examples in the specification of the '810 Patent involve a second round of PCR using a nested second target-specific primer because the inventors were never able to develop a working method that did not have a second round of nested PCR.

262. The claimed second target-specific primer therefore carries out its function in a substantially different "way" from QIAGEN's SIP, which anneals to universal sequence. The claimed second target-specific primer anneals to a ***downstream*** portion ***of the known target nucleotide sequence*** (solid gray line):



263. QIAGEN's SIP, in contrast, anneals ***upstream*** of the known target nucleotide sequence (solid gray line), to ***universal*** sequence (shown in pink below) added from the common tail of QIAGEN's GSP from the prior PCR reaction.



264. Therefore, the claimed second target-specific primer carries out its function in a substantially different way from the accused QIAGEN SIP.

265. Even Dr. Lennon's hypothetical primer that anneals to the same sequence as the first target-specific primer is substantially different from a universal primer and carries out its function in a substantially different way from a universal primer:

266. As the figures show, a second target-specific primer that anneals to the same sequence (solid gray line) as the first target-specific primer and does not anneal universally to all sequences present from the first PCR reaction. In contrast, QIAGEN's SIP anneals to the universal (pink) sequence added from the common tail of QIAGEN's GSP primer used in the first PCR reaction.

267. Moreover, as I discussed above, a ***universal*** primer such as the SIP primer is designed to anneal to ***universal*** sequence present on every sequence in the sample that was amplified in the prior round by a primer bearing the common tail, irrespective of the sequence of the first target-specific primer, or of any particular known target nucleotide sequence. The SIP, in other words, is completely indifferent as to the sequence of the known target nucleotide sequence and will amplify any amplification product from the first round irrespective of whether any particular known target nucleotide sequence is present or is absent.

268. In contrast, Dr. Lennon's hypothetical second primer that anneals to exactly the same sequence as the first target-specific primer, does not anneal to universal sequence. Dr. Lennon's hypothetical primer does not bind to universal sequence present on all different targets from the first round of PCR.

269. Therefore the accused SIP, a universal primer, carries out its function in a

substantially different way from Dr. Lennon's hypothetical primer.

270. Dr. Lennon argues that the "universal sequence added by the common tail of QIAGEN's GSP "has become part of the known target nucleotide sequence."[136] This statement is incorrect. As I have discussed, the known target nucleotide sequence does not change throughout the claim, and the second target-specific primer binds to the known target nucleotide sequence that has antecedent basis in step (i) of the claimed method. Dr. Lennon's argument that the common sequence added via the tails of QIAGEN's GSP primers becomes part of the "known target nucleotide sequence" directly contradicts the plain language of the claims and specification, as I discussed above, in addition to contradicting the Court's claim construction.

271. Dr. Lennon also argues that QIAGEN's SIP and the claimed second target-specific primer carry out substantially the same function in substantially the same way in that both "hybridize such that a primer extension substrate for a template-dependent polymerase is formed," quoting the definition of "anneal" in the '810 Patent.[137] Dr. Lennon's reliance on the generic definition of the term "anneal" in the '810 Patent does not demonstrate that QIAGEN's SIP and the claimed second target-specific primer carry out their functions in substantially the same way. The claim requires a second target-specific primer "that specifically anneals to the amplification product of (ii)."[138] This requirement that the second target-specific primer "anneal" to the product of the first PCR reaction says nothing about the specific sequence to which the primer must anneal – that requirement is contained in the term "second target-specific primer." The SIP anneals to a substantially different, universal, sequence from the portion of the known target nucleotide sequence to which the claimed second target-specific primer anneals.

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[136] *See* Lennon Opening Report ¶ 283.

[137] *See* Lennon Opening Report ¶ 284; '810 Patent, 13:53-58.

[138] *See* '810 Patent Claim 16, 78:10-11.

c) Substantially Different Results

272. I disagree with Dr. Lennon that QIAGEN's SIP achieves substantially the same "results" as the claimed second target-specific primer.[139] Dr. Lennon again focuses on his hypothetical second primer that binds to the same sequence as the first primer. Again, I disagree that such a primer is consistent with the Court's claim construction and cannot be encompassed by the Court's claim construction as an equivalent without vitiating the limitation of a "second target-specific primer."

273. According to Dr. Lennon, the second target-specific primer is insubstantially different from QIAGEN's SIP because both primers, the SIP and the hypothetical primer, would "produce an amplification product that is larger than the amplification product of the first round."[140] According to Dr. Lennon, both products would be larger than the amplification product from the first PCR reaction because both the SIP and Dr. Lennon's hypothetical primer that anneals to the same sequence as the first target-specific primer have a common tail that adds on to the length of the amplicon from the first PCR reaction.[141]

274. This argument completely misses the point and proves nothing about whether QIAGEN's SIP achieves substantially the same result as the claimed second target-specific primer.

275. The "result" that the claimed second target-specific primer achieves in preparing a library for sequencing is substantially different from the "result" QIAGEN's universal SIP achieves in preparing a library for sequencing. The "result" achieved by the claimed second target-specific primer is to increase the specificity of the library with respect to certain targets by

[139] *See* Lennon Opening Report ¶¶ 285-289.

[140] *See* Lennon Opening Report ¶ 287.

[141] *See id.*

selectively amplifying certain sequences from the first round of PCR and eliminating unwanted products. The "result" achieved by the accused universal SIP is to amplify all sequences from the first round of PCR.

276. First, in terms of the size of the resulting amplicon from the second round of PCR, given that the claimed second target-specific primer is nested with respect to the first target-specific primer, the ***portion of the known target nucleotide sequence*** amplified may be smaller than the known target nucleotide sequence present in the amplicon from the first round of PCR. On the other hand, QIAGEN's accused SIP produces an amplicon in which the size of the known target nucleotide sequence is always the same as the size of the known target nucleotide sequence in the amplicon from the first round of PCR. Therefore this "result" of using the accused QIAGEN SIP is substantially different from the result of using the claimed second target-specific primer.

277. Second, as I explained in detail above, the claimed second target-specific primer significantly increases the specificity of the system, eliminating unwanted amplification products from the first PCR reaction. In contrast, the universal SIP primer achieves the opposite function – to amplify every amplification product from the first round of PCR by binding to universal sequence added via the common tail of every different GSP that was used in the first round of PCR. As I discussed above, the claimed second target-specific primer is intended to achieve the result of increased ***specificity*** while QIAGEN's SIP is intended to achieve the result of increased ***sensitivity***. The two results are substantially different.

278. Even if Dr. Lennon were correct, which he is not, that the Court's construction encompasses a second target-specific primer that binds to exactly the same sequence as the first target-specific primer, QIAGEN's SIP nonetheless achieves a substantially different result.

279. First, in terms of the size of the resulting amplicons, the "result" is still substantially different, as shown in Dr. Lennon's drawing.[142] Even with Dr. Lennon's hypothetical second primer, the resulting amplicon sizes are different, as the figure shows.[143] The amplicon created from the hypothetical second primer is increased by the length of the tail on the second primer, while the amplicon created by the accused QIAGEN SIP is increased by the length of the entire SIP primer.

280. Second, the "result" achieved by Dr. Lennon's hypothetical second primer[144] is to amplify all sequences from the first round that have the sequence of the first target specific primer, not to amplify all sequences from the first round of PCR. The "result" achieved by the accused QIAGEN SIP primer is to amplify all sequences from the first round. These two results are substantially different.

281. Therefore, in my opinion, QIAGEN's accused products do not infringe under the doctrine of equivalents because QIAGEN's accused SIP primer carries out a substantially different function in a substantially different way to achieve a substantially different result than the claimed second target-specific primer.

5. The Accused "Second Target Specific Primer" Does Not Have a Nucleic Acid Sequence Identical to a Second Sequencing Primer

Claim(s)	'810 Patent Claim Term	Construction
claims 1 and 16	second target-specific primer	a single-stranded oligonucleotide comprising a 3' portion comprising a nucleic acid sequence that can specifically anneal to a portion of the known target nucleotide sequence comprised by the amplicon resulting from step (b), and a 5' portion

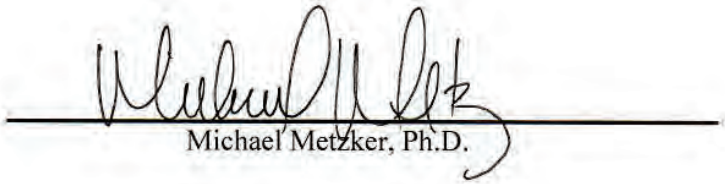
[142] Lennon Opening Report ¶ 287.

[143] *See id.*

[144] *See id.*

I declare under penalty of perjury that the foregoing is true and correct.

Executed on November 20, 2020.



Michael Metzker, Ph.D.

EXHIBIT 18

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ARCHERDX, INC. and THE GENERAL HOSPITAL CORPORATION d/b/a MASSACHUSETTS GENERAL HOSPITAL, Plaintiffs, v. QIAGEN SCIENCES, LLC, QIAGEN LLC f/k/a QIAGEN, INC., QIAGEN BEVERLY, LLC f/k/a QIAGEN BEVERLY, INC. QIAGEN GAITHERSBURG, LLC f/k/a QIAGEN GAITHERSBURG, INC., QIAGEN GMBH, QIAGEN N.V. and JONATHAN ARNOLD. Defendants.	)	Civil Action No. 18-cv-01019-MN

DEFENDANTS' SECOND AMENDED INVALIDITY CONTENTIONS

Pursuant to the Court's Scheduling Order (D.I. 138), Defendants QIAGEN Sciences, LLC, QIAGEN LLC (f/k/a QIAGEN, Inc.), QIAGEN Beverly, LLC (f/k/a QIAGEN Beverly, Inc.), QIAGEN Gaithersburg, LLC (f/k/a QIAGEN Gaithersburg, Inc.), QIAGEN GmbH, QIAGEN N.V. (collectively, "QIAGEN"), and Jonathan Arnold ("Arnold," and as used collectively with QIAGEN, "Defendants") submit their invalidity contentions and document productions for U.S. Patent Number 10,450,597 (the "'597 patent" or "Asserted Patent"). ArcherDX, Inc. and the General Hospital Corporation d/b/a/ Massachusetts General Hospital are collectively referred to herein as "Plaintiffs."

RESERVATION OF RIGHTS

These invalidity contentions do not directly address issues such as non-infringement. QIAGEN reserves all rights with respect to such issues, including but not limited to its position that claims of the '597 patent are to be construed in a particular manner and are not infringed.

These invalidity contentions are based on QIAGEN's current knowledge, understanding, and belief as to the facts and information available as of the date of these contentions. QIAGEN has not yet completed its investigation, discovery, or analysis of information related to this action, and additional discovery may require QIAGEN to supplement or amend its invalidity contentions. While QIAGEN has made a good-faith effort to provide a comprehensive list of prior art relevant to this case, QIAGEN reserves the right to modify or supplement its prior art list and invalidity contentions at a later time with or based upon pertinent information that may be subsequently discovered from Plaintiffs or third-parties. Moreover, discovery is ongoing and QIAGEN reserves the right to pursue all other defenses that may be available to it, including but not limited to defenses that the '597 patent is unenforceable based on laches, estoppel, waiver acquiescence, inequitable conduct, patent misuse, patent exhaustion, express or implied license, or any other grounds.

QIAGEN's invalidity contentions are directed to the claims asserted by Plaintiffs that are identified in Plaintiffs' December 6, 2019 Initial Infringement Contentions and the July 16, 2020 Plaintiffs' Disclosure of Amended Infringement Contentions. QIAGEN reserves the right to modify, amend, supplement or otherwise alter its invalidity contentions in the event that Plaintiffs' amended infringement contentions to be served on the same date as these amended invalidity contentions include any claim construction position that is different than or in addition to the Court's constructions (D.I. 254) or those set forth in Plaintiffs' Initial Infringement Contentions (to the extent a term was not construed by the Court), or for any other reason constituting good cause to modify, amend, supplement or otherwise alter these invalidity contentions. Defendants reserve the right to revise their ultimate contentions concerning the invalidity of the asserted claims, which may change depending on any amended infringement

contentions that Plaintiffs provide, or any positions that Plaintiffs or any expert witness may take concerning infringement, non-infringement, validity, or invalidity issues.

QIAGEN further contends that, to maintain claims of infringement, Plaintiffs are necessarily pursuing overly broad constructions of the asserted claims of the '597 patent in an effort to piece together an infringement claim where none exists and to accuse products that do not practice the claims as properly construed. In some instances, QIAGEN is applying the prior art references as Plaintiffs would necessarily have to be reading the claims in the '597 patent against the QIAGEN products. This does not mean, however, that QIAGEN accepts or adopts Plaintiffs' reading of the scope of those patents and the claims as correct. It simply means that QIAGEN is applying the disclosures consistent with the breadth that Plaintiffs are necessarily asserting them for purposes of infringement. At the same time, Plaintiffs' previous Infringement Contentions are in many places too general and vague to discern exactly how Plaintiffs contend each accused product practices each element of the asserted claims. These invalidity contentions are not intended to be, and are not, an admission that the asserted claims are infringed by any of QIAGEN's products or technology, that any particular feature or aspect of any of the accused products practices any elements of the asserted claims, or that any of Plaintiffs' apparent constructions are supportable or proper. To the extent that any of the prior art discloses the same functionality or feature of any of the accused products, QIAGEN reserves the right to argue that said feature or functionality does not practice any element of any of the asserted claims, and to argue, in the alternative, that if said feature or functionality is found to practice any element of any of the asserted claims of the '597 patent, then the prior art reference demonstrates that that element is not novel to the invention and that the claim is not patentable.

In this action, Plaintiffs asserts that QIAGEN infringes certain claims of the '597 patent. Although Plaintiffs assert that these claims are either literally infringed or infringed under the doctrine of equivalents, Plaintiffs have failed to provide any adequate analysis or explanation regarding alleged infringement of the asserted claims of the '597 patent under the doctrine of equivalents. QIAGEN reserves its rights to modify, amend, supplement or otherwise alter its invalidity contentions in the event Plaintiffs are permitted to modify, amend, supplement, or clarify their infringement contentions with respect to infringement under the doctrine of equivalents.

Prior art not included in these invalidity contentions, whether known or not known to QIAGEN, may become relevant. In particular, QIAGEN is currently unaware of the extent to which Plaintiffs will contend that limitations of the asserted claims are not disclosed in the prior art identified herein. To the extent that such an issue arises, QIAGEN reserves the right to identify additional teachings in the same references or in other references that anticipate or would have made the addition of the allegedly missing limitation obvious. Moreover, QIAGEN may subpoena third parties believed to have information relevant to these invalidity contentions or the '597 patent. QIAGEN expressly reserves the right to amend, supplement, or modify these invalidity contentions as additional information is obtained from third parties, or from Plaintiffs themselves.

QIAGEN further reserves the right to rely on uncited portions of the prior art references and in other publications and testimony as aids in understanding and interpreting the cited portions, as providing context thereto, and as additional evidence that a claim limitation is known or disclosed. QIAGEN further reserves the right to rely on uncited portions of the prior art

references, other publications, and testimony to establish bases for combinations of certain cited references that render the asserted claims obvious.

The references discussed in the claim charts identified herein or elsewhere may disclose the elements of the asserted claims explicitly and/or inherently, and/or they may be relied upon to show the state of the art in the relevant time frame. QIAGEN further reserves the right to rely on additional publications, materials, and testimony that are not yet currently identified for purposes other than as prior art, including but not limited to background, state of the art in the relevant time frame, level of ordinary skill in the art, and motivation to combine. The suggested obviousness combinations are provided in the alternative to QIAGEN's anticipation contentions and are not to be construed to suggest that any reference included in the combinations is not by itself anticipatory.

QIAGEN is providing invalidity contentions only for the claims asserted by Plaintiffs, but hereby reserves the right to seek invalidation of all claims of the '597 patent.

QIAGEN reserves the right to modify, amend, or supplement these invalidity contentions as additional information becomes available, and as its discovery and investigation proceed.

OVERVIEW

Attached hereto as Exhibits A through F are representative claim charts that demonstrate how the asserted claims of the '597 patent are invalid in view of certain prior art. The references cited in the attached Exhibits may disclose the limitations of the asserted claims of the '597 patent either expressly and/or inherently. Moreover, the suggested obviousness combinations are in the alternative to QIAGEN's anticipation contentions. The obviousness combinations set forth in these contentions should not be construed to suggest that any reference included in any combination is not anticipatory in its own right.

As detailed further in the attached invalidity charts at Exhibits A-F, the claimed invention is nothing more than an adaptation for next generation sequencing ("NGS") of a much earlier, well-known method used to determine unknown sequence adjacent to a known target sequence, a method sometimes referred to as "chromosome walking" or "genome walking." *See, e.g.*, QIA-00689179 ("Martin-Harris") (describing the method in 2010); QIA-00689150 ("Fraiture"); QIA-00689264 ("Morley"). The claimed method of the '597 patent involves using one primer (a "target-specific" primer) that binds to a known target sequence and amplifying the DNA using the polymerase chain reaction ("PCR"). A second round of PCR is performed using a plurality of different primers that share a common sequence 5' to different hybridization sequences, Additional rounds of PCR are then performed using one primer that comprises a 3' sequence that anneals to the complement of the common sequence and a 5' tail sequence and a primer that anneals to the complement of the target-specific hybridization sequence.

The use of a plurality of different primers that share a common sequence 5' to different hybridization sequences, with each primer having different hybridization sequences and different 3' ends that do not anneal to the same sequence was well-known in the art and referred to as "degenerate primers" or "degenerate random primers." These primers were commonly used for sequencing unknown regions flanking a known target sequence, such as in gene walking. *See, e.g.*, QIA-00689182 ("McCarty"), QIA-00689264 ("Morley"), QIA-00689102 ("APAgene Manual"), QIA-00689150 ("Fraiture"). These degenerate primers were almost always paired with target-specific primers. *See, e.g.*, QIA00689182("McCarty"), QIA-00689264 ("Morley"), QIA-00689102 ("APAgene Manual"), QIA-00689150 ("Fraiture").

NGS platforms require the addition of platform-specific sequences to the nucleic acid sample that is going to be sequenced on the platform. It was well known in the art that there

were a variety of methods available to attach platform-specific sequences to a nucleic acid sample. One such approach, well known in the art, was to attach these platform-specific sequences by carrying out PCR reactions with primers that included the platform-specific sequences. *See, e.g.*, QIA-00689182 ("McCarty").

The '597 patent claims a number of these standard, well-known methodologies as limitations in the dependent claims. These methodologies include the addition of Illumina adaptor sequences or index sequences. *See* QIA-00689087 ("Illumina Genomic Sequencing Data Sheet"); QIA-00689182 ("McCarty").

Multiple prior research groups had already adapted the well-known chromosome walking method to various NGS platforms, including the Illumina NGS platform and the 454 NGS platform, using adaptors, PCR primers, and combinations of adaptors and PCR primers. Plaintiffs may not remove this well-known method from the public domain simply by adapting it for NGS using additional well-known methods.

SECTION 112 VIOLATIONS

Plaintiffs' overbroad reading of the '597 patent claims, as set out in their infringement contentions, further renders the claims invalid under 35 U.S.C. § 112. The claims are invalid as lacking written description in several respects. First, there is no written description for a nucleic acid template, or the target specific section of it, being a universal adaptor sequence that was ligated to DNA fragments. There is no written description for the target specific primer being a universal primer that anneals to all universal oligonucleotide adaptors that have been ligated to fragments. There is no written description for calling a single stranded portion of a nucleic acid that acts as a target, a double stranded target nucleic acid. Additionally, each of these constructions are inconsistent with the Court's Memorandum Order Regarding Claim Construction ('597 Patent) (D.I. 254). *See* D.I. 254 at 1-2.

The '597 patent claims are also indefinite under 35 U.S. C. § 112. The claims are indefinite if step b of claim 1 is to be performed before step a, as Plaintiffs are asserting. There would be no antecedent basis for: "the first strand of the double stranded target nucleic acid". There would be no antecedent basis for "the first strand of the double-stranded target nucleic acid." There is also no clear antecedent basis in step b for: "the same sequence of the double stranded target nucleic acid." A first nucleic acid sequence is identified in step a, and a second nucleic acid sequence is identified in step b, but "the same sequence" does not identify which of those sequences it is referring to. To the extent that Plaintiffs are interpreting Claim 4 to permit or require that step (b) be carried out before step (a), the claim is also indefinite for these reasons. Furthermore, Claim 4 is indefinite in that it does not apprise a person of ordinary skill in the art at the relevant date of the meaning of the term "performed sequentially" with reasonable certainty. A person of ordinary skill in the art would not understand that "sequentially" could encompass performing step (b) before step (a).

By: */s/ Stephanie E. O'Byrne*

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Dated: October 2, 2020

INVALIDITY OF U.S. PATENT NO. 10,450,597

EXHIBIT A

U.S. Patent No. 10,450,597 ("the '597 Patent") has an effective filing date after March 16, 2013 and therefore is subject to the provisions of the Leahy-Smith America Invents Act. The earliest possible effective filing date listed on the face of the '597 Patent is the provisional filing date of January 27, 2014. The utility application was filed on January 26, 2015. The references listed below qualify as prior art at least under AIA 35 U.S.C. § 102(a).

The below prior art references, individually or in combination with each other and/or other references render each claim element/claim anticipated and/or obvious, as detailed below by exemplary citation. A person of ordinary skill in the art would be motivated to combine these references together because they are within the same or similar field of endeavor, in particular, methods of preparing nucleic acids for sequencing.

The Applied Biosystems DNA Sequencing by Capillary Electrophoresis Chemistry Guide ("Applied Biosystems Manual") was available in May 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Applied Biosystems Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

Cornish-Bowden, A. (1985). Nomenclature for incompletely specified bases in nucleic acid sequences: recommendations 1984. *Nucleic acids research*, *13*(9), 3021 ("Cornish-Bowden"). Cornish-Bowden was available on May 10, 1985, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

Craig, D. W., et al. (2008). Identification of genetic variants using bar-coded multiplexed sequencing. *Nature methods*, *5*(10), 887 ("Craig"). Craig was available on October 1, 2008, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

Fraiture, M. A., Herman, P., Taverniers, I., De Loose, M., Deforce, D., & Roosens, N. H. (2013). An innovative and integrated approach based on DNA walking to identify unauthorised GMOs. *Food chemistry*, *147*, 60-69 ("Fraiture"). Fraiture was available on September 29, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Fraiture qualifies as prior art under at least 35 U.S.C. § 102(a).

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The Illumina Application Note: DNA Analysis (2013). High-speed, multiplexed 16S amplicon sequencing on the MiSeq system ("Illumina DNA Analysis"). Illumina DNA Analysis was available May 28, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Illumina 16S Metagenomic Sequencing Library Preparation (2013). Preparing 16S ribosomal RNA gene amplicons for the Illumina MiSeq system ("Illumina Sequencing Library Preparation"). Illumina Sequencing Library Preparation was available November 27, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Genomic Sequencing Data Sheet ("Illumina Genomic Sequencing Data Sheet") was available in 2010 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Sequencing Technology – Tech Spotlight ("Illumina Sequencing") was available October 11, 2010 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina TruSeq RNA and DNA Sample Preparation Kits Data Sheet ("Illumina TruSeq Data Sheet") was available November 2, 2010 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Kircher et al.. "Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform." 40 Nucleic acids research e3:1-8 (2011) ("Kircher"). Kircher was published on October 21, 2011. Thus, Kircher qualifies as prior art under 35 U.S.C. § 102(a).

Liu, L., et al. (2012) ("Liu"). Comparison of next-generation sequencing systems. *J. Biomed. Biotechnol. 2012*, 251364, 1-11. Liu was published in 2012. Liu qualifies as prior art at least under 35 U.S.C. § 102(a).

Martin-Harris, M. H., Bartley, P. A., & Morley, A. A. (2010). Gene walking using sequential hybrid primer polymerase chain reaction. *Analytical biochemistry*, *399*(2), 308-310 ("Martin-Harris"). Martin-Harris was available January 13, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Martin-Harris qualifies as prior art under at least 35 U.S.C. § 102(a).

McCarty, D. R., Latshaw, S., Wu, S., Suzuki, M., Hunter, C. T., Avigne, W. T., & Koch, K. E. (2013). Mu-seq: sequence-based mapping and identification of transposon induced mutations. *PLoS One*, *8*(10), e77172 ("McCarty"). McCarty was available October 23, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, McCarty qualifies as prior art under at least 35 U.S.C. § 102(a).

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Meuzelaar, L. S., Lancaster, O., Pasche, J. P., Kopal, G., & Brookes, A. J. (2007). MegaPlex PCR: a strategy for multiplex amplification. *Nature methods*, *4*(10), 835 ("Meuzelaar"). Meuzelaar was available September 16, 2007, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Meuzelaar qualifies as prior art under at least 35 U.S.C. § 102(a).

Quail, M. A. et al. (2012). A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers. *BMC genomics*, *13*(1), 341. Quail was published on July 24, 2012. Quail qualifies as prior art at least under 35 U.S.C. § 102(a).

Skerra, A. (1992). Phosphorothioate primers improve the amplification of DNA sequences by DNA polymerases with proofreading activity. *Nucleic Acids Research*, *20*(14), 3551-3554. Skerra was published in 1992. Skerra qualifies as prior art at least under 35 U.S.C. § 102(a).

U.S. Patent Publication No. 2010/0248310 ("Morley"). Morley was available September 30, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Morley qualifies as prior art under at least 35 U.S.C. § 102(a).

U.S. Patent Application Publication No. 2013/0303461 ("the '461 Publication"). The '461 Publication was published on November 14, 2013. The '461 Publication qualifies as prior art at least under 35 U.S.C. § 102(a).

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THE ASSERTED CLAIMS OF U.S. PATENT 10,450,597 ARE ANTICIPATED AND/OR OBVIOUS OVER MARTIN-HARRIS

U.S. Patent No. 10,450,597	
Claim No.	**Martin-Harris (2010)**
1[pre]. A method of preparing nucleic acids for analysis, the method comprising:	The methods of the '597 patent for preparing nucleic acids for analysis were invented by multiple independent research groups, beginning years before the earliest priority date of the '597 patent, and were also previously published by inventors of the '597 patent. These include Martin-Harris (2010), Morley (2010), Fraiture (2013), McCarty (2013), and U.S. Patent Application Publication No. 2013/0303461 (2013). The preamble is not a limitation. Regardless, to the extent that the preamble is a limitation, the prior art discloses the preamble. Martin-Harris discloses this claim element. For example, Martin-Harris discloses methods for preparing nucleic acids for analysis, such as methods for gene walking. *See, e.g.*, Martin-Harris at 308 ("Numerous methods have been described for gene walking, that is, the identification of unknown regions flanking a known DNA sequence . . . We have developed a simple variation of PCR, termed sequential hybrid primer PCR (SHP-PCR) for brevity, which has proven to be very effective in minimizing nonspecific amplification and facilitating gene walking using a degenerate primer."), *see also* Martin-Harris at Abstract ("We developed a simple and robust method for removing nonspecific amplification produced during gene walking with a gene-specific primer and a degenerate primer. The primary walking polymerase chain reaction (PCR) was followed by two or three PCR rounds, each incorporating a low concentration of a reverse hybrid primer, where the 3' end was bound to a target sequence generated in the preceding PCR round and the 5' end was a new sequence that generated a target sequence for the next PCR round. The low concentration of the hybrid primer and the extent of amplicon stem–loop formation inhibited nonspecific amplification and enabled successful walking along three genes."). Martin-Harris also discloses using these methods for preparing nucleic acids for analysis for diagnostic testing. *See, e.g.*, Martin-Harris at 310 ("In conclusion, SHP-PCR has proven to be a simple adjunctive technique for removing undesired amplification products produced by a primary PCR that performs gene walking with a degenerate primer. It should also be of more general value as a tool for removing nonspecific products produced by a PCR in which a primer or primers directed to one end of a target sequence act bidirectionally and produce unwanted nonspecific amplification. For example, we have successfully applied it to isolate translocation breakpoints in

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INVALIDITY OF U.S. PATENT NO. 10,450,597

EXHIBIT B

U.S. Patent No. 10,450,597 ("the '597 Patent") has an effective filing date after March 16, 2013 and therefore is subject to the provisions of the Leahy-Smith America Invents Act. The earliest possible effective filing date listed on the face of the '597 Patent is the provisional filing date of January 27, 2014. The utility application was filed on January 26, 2015. The references listed below qualify as prior art at least under AIA 35 U.S.C. § 102(a).

The below prior art references, individually or in combination with each other and/or other references render each claim element/claim anticipated and/or obvious, as detailed below by exemplary citation. A person of ordinary skill in the art would be motivated to combine these references together because they are within the same or similar field of endeavor, in particular, methods of preparing nucleic acids for sequencing.

The APAgene Gold-RT Genome Walking Kit Manual ("APAgene Manual") was available September 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, APAgene Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

The Applied Biosystems DNA Sequencing by Capillary Electrophoresis Chemistry Guide ("Applied Biosystems Manual") was available in May 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Applied Biosystems Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

Cornish-Bowden, A. (1985). Nomenclature for incompletely specified bases in nucleic acid sequences: recommendations 1984. *Nucleic acids research*, *13*(9), 3021 ("Cornish-Bowden"). Cornish-Bowden was available on May 10, 1985, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

Craig, D. W., et al. (2008). Identification of genetic variants using bar-coded multiplexed sequencing. *Nature methods*, *5*(10), 887 ("Craig"). Craig was available on October 1, 2008, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

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Fraiture, M. A., Herman, P., Taverniers, I., De Loose, M., Deforce, D., & Roosens, N. H. (2013). An innovative and integrated approach based on DNA walking to identify unauthorised GMOs. *Food chemistry*, *147*, 60-69 ("Fraiture"). Fraiture was available on September 29, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Fraiture qualifies as prior art under at least 35 U.S.C. § 102(a).

The Illumina Application Note: DNA Analysis (2013). High-speed, multiplexed 16S amplicon sequencing on the MiSeq system ("Illumina DNA Analysis"). Illumina DNA Analysis was available May 28, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Illumina 16S Metagenomic Sequencing Library Preparation (2013). Preparing 16S ribosomal RNA gene amplicons for the Illumina MiSeq system ("Illumina Sequencing Library Preparation"). Illumina Sequencing Library Preparation was available November 27, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Genomic Sequencing Data Sheet ("Illumina Genomic Sequencing Data Sheet") was available in 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Illumina Genomic Sequencing Data Sheet qualifies as prior art under at least 35 U.S.C. §102(a).

The Illumina Sequencing Technology – Tech Spotlight ("Illumina Sequencing") was available October 11, 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Illumina Sequencing qualifies as prior art under at least 35 U.S.C. §102(a).

The Illumina TruSeq RNA and DNA Sample Preparation Kits Data Sheet ("Illumina TruSeq Data Sheet") was available November 2, 2010 and thus qualifies as prior art under at least 35 U.S.C. §102(a).

Kircher et al.. "Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform." 40 Nucleic acids research e3:1-8 (2011) ("Kircher"). Kircher was published on October 21, 2011. Thus, Kircher qualifies as prior art under at least 35 U.S.C. § 102(a).

Liu, L., et al. (2012) ("Liu"). Comparison of next-generation sequencing systems. *J. Biomed. Biotechnol. 2012*, 251364, 1-11. Liu was published in 2012. Liu qualifies as prior art at least under 35 U.S.C. § 102(a).

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Martin-Harris, M. H., Bartley, P. A., & Morley, A. A. (2010). Gene walking using sequential hybrid primer polymerase chain reaction. *Analytical biochemistry*, *399*(2), 308-310 ("Martin-Harris"). Martin-Harris was available January 13, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Martin-Harris qualifies as prior art under at least 35 U.S.C. § 102(a).

McCarty, D. R., Latshaw, S., Wu, S., Suzuki, M., Hunter, C. T., Avigne, W. T., & Koch, K. E. (2013). Mu-seq: sequence-based mapping and identification of transposon induced mutations. *PLoS One*, *8*(10), e77172 ("McCarty"). McCarty was available October 23, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, McCarty qualifies as prior art under at least 35 U.S.C. § 102(a).

Meuzelaar, L. S., Lancaster, O., Pasche, J. P., Kopal, G., & Brookes, A. J. (2007). MegaPlex PCR: a strategy for multiplex amplification. *Nature methods*, *4*(10), 835 ("Meuzelaar"). Meuzelaar was available September 16, 2007, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Meuzelaar qualifies as prior art under at least 35 U.S.C. § 102(a).

Quail, M. A. et al. (2012). A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers. *BMC genomics*, *13*(1), 341. Quail was published on July 24, 2012. Quail qualifies as prior art at least under 35 U.S.C. § 102(a).

Skerra, A. (1992). Phosphorothioate primers improve the amplification of DNA sequences by DNA polymerases with proofreading activity. *Nucleic Acids Research*, *20*(14), 3551-3554. Skerra was published in 1992. Skerra qualifies as prior art at least under 35 U.S.C. § 102(a).

U.S. Patent Publication No. 2010/0248310 ("Morley"). Morley was available September 30, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Morley qualifies as prior art under at least 35 U.S.C. § 102(a).

U.S. Patent Application Publication No. 2013/0303461 ("the '461 Publication"). The '461 Publication was published on November 14, 2013. The '461 Publication qualifies as prior art at least under 35 U.S.C. § 102(a).

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THE ASSERTED CLAIMS OF U.S. PATENT 10,450,597 ARE ANTICIPATED AND/OR OBVIOUS OVER FRAITURE

U.S. Patent No. 10,450,597	
Claim No.	**Fraiture**
1[pre]. A method of preparing nucleic acids for analysis, the method comprising:	The methods of the '597 patent for preparing nucleic acids for analysis were invented by multiple independent research groups, beginning years before the earliest priority date of the '597 patent, and were also previously published by inventors of the '597 patent. These prior art references include Martin-Harris (2010), Morley (2010), Fraiture (2013), McCarty (2013), and U.S. Patent Application Publication No. 2013/0303461 (2013). The preamble is not a limitation. Regardless, to the extent that the preamble is a limitation, the prior art discloses the preamble. Fraiture discloses this claim element. For example, Fraiture discloses that the goal of the method described is to prepare nucleic acids for analysis to identify genetic markers to determine whether an organism has been genetically modified. *See* Fraiture at 63 ("The aim of the present study is to supply an integrated approach to identify unauthorised GMOs: A first real-time PCR screening allows the detection of the terminator 35S (t35S) of the pCAMBIA family vectors to indicate the potential presence of unauthorised GMOs in food matrices (Fig. 3). Then, an appropriate DNA walking method, anchored on the sequence used for the screening followed by two semi-nested PCRs to identify the junction, confirms the GMO presence"); *see also id.* at 68 ("With regard to the previous articles describing methods characterising the junction sequences of GMOs, the present DNA walking approach possesses the substantial advantage to be easily implementable in semi-routine use thanks to the simplicity of a method exclusively based on PCR. In addition, its short time frame to get the results (less than three days including DNA walking method, DNA purification and direct sequencing) and its relatively low cost clearly represent a crucial benefit for the enforcement laboratories").
1[a]. (a) contacting a first nucleic acid template comprising a sequence of a first strand of a double-stranded target	Fraiture discloses this limitation. For example, Fraiture teaches contacting a first nucleic acid template comprising a sequence of a first strand of a double-stranded target nucleic acid with a complementary target-specific primer that comprises a target-specific hybridization sequence, under conditions to promote template-specific hybridization and extension of the target-specific primer. Fraiture discloses in Figures 1A and 1B (reproduced below) contacting a first

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INVALIDITY OF U.S. PATENT NO. 10,450,597

EXHIBIT C

U.S. Patent No. 10,450,597 ("the '597 Patent") has an effective filing date after March 16, 2013 and therefore is subject to the provisions of the Leahy-Smith America Invents Act. The earliest possible effective filing date listed on the face of the '597 Patent is the provisional filing date of January 27, 2014. The utility application was filed on January 26, 2015. The references listed below qualify as prior art at least under AIA 35 U.S.C. § 102(a).

The below prior art references, individually or in combination with each other and/or other references render each claim element/claim anticipated and/or obvious, as detailed below by exemplary citation. A person of ordinary skill in the art would be motivated to combine these references together because they are within the same or similar field of endeavor, in particular, methods of preparing nucleic acids for sequencing.

The Applied Biosystems DNA Sequencing by Capillary Electrophoresis Chemistry Guide ("Applied Biosystems Manual") was available in May 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Applied Biosystems Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

Cornish-Bowden, A. (1985). Nomenclature for incompletely specified bases in nucleic acid sequences: recommendations 1984. *Nucleic acids research*, *13*(9), 3021 ("Cornish-Bowden"). Cornish-Bowden was available on May 10, 1985, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

Craig, D. W., et al. (2008). Identification of genetic variants using bar-coded multiplexed sequencing. *Nature methods*, *5*(10), 887 ("Craig"). Craig was available on October 1, 2008, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

Fraiture, M. A., Herman, P., Taverniers, I., De Loose, M., Deforce, D., & Roosens, N. H. (2013). An innovative and integrated approach based on DNA walking to identify unauthorised GMOs. *Food chemistry*, *147*, 60-69 ("Fraiture"). Fraiture was available on September 29, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Fraiture qualifies as prior art under at least 35 U.S.C. § 102(a).

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The Illumina Application Note: DNA Analysis (2013). High-speed, multiplexed 16S amplicon sequencing on the MiSeq system ("Illumina DNA Analysis"). Illumina DNA Analysis was available May 28, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Illumina 16S Metagenomic Sequencing Library Preparation (2013). Preparing 16S ribosomal RNA gene amplicons for the Illumina MiSeq system ("Illumina Sequencing Library Preparation"). Illumina Sequencing Library Preparation was available November 27, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Genomic Sequencing Data Sheet ("Illumina Genome Sequencing Data Sheet") was available in 2010 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Sequencing Technology – Tech Spotlight ("Illumina Sequencing") was available October 11, 2010 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina TruSeq RNA and DNA Sample Preparation Kits Data Sheet ("Illumina TruSeq Data Sheet") was available November 2, 2010 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Kircher et al.. "Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform." 40 Nucleic acids research e3:1-8 (2011) ("Kircher"). Kircher was published on October 21, 2011. Thus, Kircher qualifies as prior art at least under 35 U.S.C. § 102(a).

Liu, L., et al. (2012) ("Liu"). Comparison of next-generation sequencing systems. *J. Biomed. Biotechnol. 2012*, 251364, 1-11. Liu was published in 2012. Liu qualifies as prior art at least under 35 U.S.C. § 102(a).

Martin-Harris, M. H., Bartley, P. A., & Morley, A. A. (2010). Gene walking using sequential hybrid primer polymerase chain reaction. *Analytical biochemistry*, *399*(2), 308-310 ("Martin-Harris"). Martin-Harris was available January 13, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Martin-Harris qualifies as prior art under at least 35 U.S.C. § 102(a).

McCarty, D. R., Latshaw, S., Wu, S., Suzuki, M., Hunter, C. T., Avigne, W. T., & Koch, K. E. (2013). Mu-seq: sequence-based mapping and identification of transposon induced mutations. *PLoS One*, *8*(10), e77172 ("McCarty"). McCarty was available October

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23, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. McCarty qualifies as prior art under at least 35 U.S.C. § 102(a).

Meuzelaar, L. S., Lancaster, O., Pasche, J. P., Kopal, G., & Brookes, A. J. (2007). MegaPlex PCR: a strategy for multiplex amplification. *Nature methods*, *4*(10), 835 ("Meuzelaar"). Meuzelaar was available September 16, 2007, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Meuzelaar qualifies as prior art under at least 35 U.S.C. § 102(a).

Quail, M. A. et al. (2012). A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers. *BMC genomics*, *13*(1), 341. Quail was published on July 24, 2012. Quail qualifies as prior art at least under 35 U.S.C. § 102(a).

Skerra, A. (1992). Phosphorothioate primers improve the amplification of DNA sequences by DNA polymerases with proofreading activity. *Nucleic Acids Research*, *20*(14), 3551-3554. Skerra was published in 1992. Skerra qualifies as prior art at least under 35 U.S.C. § 102(a).

U.S. Patent Publication No. 2010/0248310 ("Morley"). Morley was available September 30, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Morley qualifies as prior art under at least 35 U.S.C. § 102(a).

U.S. Patent Application Publication No. 2013/0303461 ("the '461 Publication"). The '461 Publication was published on November 14, 2013. The '461 Publication qualifies as prior art at least under 35 U.S.C. § 102(a).

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THE ASSERTED CLAIMS OF U.S. PATENT 10,450,597 ARE ANTICIPATED AND/OR OBVIOUS OVER MORLEY

U.S. Patent No. 10,450,597	
Claim No.	**MORLEY**
1[pre]. A method of preparing nucleic acids for analysis, the method comprising:	The methods of the '597 patent for preparing nucleic acids for analysis were invented by multiple independent research groups, beginning years before the earliest priority date of the '597 patent, and were also previously published by inventors of the '597 patent. These prior art references include Martin-Harris (2010), Morley (2010), Fraiture (2013), McCarty (2013), and U.S. Patent Application Publication No. 2013/0303461 (2013). The preamble is not a limitation. Regardless, to the extent that the preamble is a limitation, the prior art discloses the preamble. Morley discloses this claim element. For example, Morley discloses methods of preparing nucleic acids for a range of applications including, but not limited to, diagnosis and monitoring of genetic diseases, analysis of gene regions of interest, and isolation of gene sequences of interest only the nucleotide sequence at one end of the gene sequence of interest is known. *See* Morley at Abstract ("The present invention relates generally to a method of amplifying a nucleic acid region of interest and, more particularly, to a method of amplifying a nucleic acid region of interest using a PCR method designed to minimise the generation of amplicons from primers which have bound to nucleic acid regions other than the specific region of interest . . . The provision of a selective means of amplifying a nucleic acid region of interest is useful in a range of applications including, but not limited to, the diagnosis and/or monitoring of disease conditions which are characterised by specific gene sequences, the characterisation or analysis of gene regions of interest, the identification or characterisation of DNA breakpoint regions and the isolation of gene sequences of interest where only the nucleotide sequence at one end of the gene sequence of interest is known").
1[a]. (a) contacting a first nucleic acid template comprising a sequence of a first strand of a double-	Morley discloses this limitation. For example, Morley discloses in Figure 4 contacting a first nucleic acid template comprising a sequence of a first strand of a double-stranded target nucleic acid with a complementary target-

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INVALIDITY OF U.S. PATENT NO. 10,450,597

EXHIBIT D

U.S. Patent No. 10,450,597 ("the '597 Patent") has an effective filing date after March 16, 2013 and therefore is subject to the provisions of the Leahy-Smith America Invents Act. The earliest possible effective filing date listed on the face of the '597 Patent is the provisional filing date of January 27, 2014. The utility application was filed on January 26, 2015. The references listed below qualify as prior art at least under AIA 35 U.S.C. § 102(a).

The below prior art references, individually or in combination with each other and/or other references render each claim element/claim anticipated and/or obvious, as detailed below by exemplary citation. A person of ordinary skill in the art would be motivated to combine these references together because they are within the same or similar field of endeavor, in particular, methods of preparing nucleic acids for sequencing.

The Applied Biosystems DNA Sequencing by Capillary Electrophoresis Chemistry Guide ("Applied Biosystems Manual") was available in May 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Applied Biosystems Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

Cornish-Bowden, A. (1985). Nomenclature for incompletely specified bases in nucleic acid sequences: recommendations 1984. *Nucleic acids research*, *13*(9), 3021 ("Cornish-Bowden"). Cornish-Bowden was available on May 10, 1985, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

Craig, D. W., et al. (2008). Identification of genetic variants using bar-coded multiplexed sequencing. *Nature methods*, *5*(10), 887 ("Craig"). Craig was available on October 1, 2008, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

Fraiture, M. A., Herman, P., Taverniers, I., De Loose, M., Deforce, D., & Roosens, N. H. (2013). An innovative and integrated approach based on DNA walking to identify unauthorised GMOs. *Food chemistry*, *147*, 60-69 ("Fraiture"). Fraiture was available on September 29, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Fraiture qualifies as prior art under at least 35 U.S.C. § 102(a).

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The Illumina Application Note: DNA Analysis (2013). High-speed, multiplexed 16S amplicon sequencing on the MiSeq system ("Illumina DNA Analysis"). Illumina DNA Analysis was available May 28, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Illumina 16S Metagenomic Sequencing Library Preparation (2013). Preparing 16S ribosomal RNA gene amplicons for the Illumina MiSeq system ("Illumina Sequencing Library Preparation"). Illumina Sequencing Library Preparation was available November 27, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Genomic Sequencing Data Sheet ("Illumina Genomic Sequencing Data Sheet"). Illumina Genomic Sequencing Data Sheet was available in 2010 and thus qualifies as prior art under 35 U.S.C. §102(a).

The Illumina Sequencing Technology – Tech Spotlight ("Illumina Sequencing") was available October 11, 2010 and thus qualifies as prior art under 35 U.S.C. §102(a).

The Illumina TruSeq RNA and DNA Sample Preparation Kits Data Sheet ("Illumina TruSeq Data Sheet") was available November 2, 2010 and thus qualifies as prior art under 35 U.S.C. §102(a).

Kircher et al.. "Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform." 40 Nucleic acids research e3:1-8 (2011) ("Kircher"). Kircher was published on October 21, 2011. Thus, Kircher qualifies as prior art under 35 U.S.C. § 102(a).

Liu, L., et al. (2012) ("Liu"). Comparison of next-generation sequencing systems. *J. Biomed. Biotechnol. 2012*, 251364, 1-11. Liu was published in 2012. Liu qualifies as prior art at least under 35 U.S.C. § 102(a).

Martin-Harris, M. H., Bartley, P. A., & Morley, A. A. (2010). Gene walking using sequential hybrid primer polymerase chain reaction. *Analytical biochemistry*, *399*(2), 308-310 ("Martin-Harris"). Martin-Harris was available January 13, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Martin-Harris qualifies as prior art under at least 35 U.S.C. § 102(a).

McCarty, D. R., Latshaw, S., Wu, S., Suzuki, M., Hunter, C. T., Avigne, W. T., & Koch, K. E. (2013). Mu-seq: sequence-based mapping and identification of transposon induced mutations. *PLoS One*, *8*(10), e77172 ("McCarty"). McCarty was available October 23, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, McCarty qualifies as prior art under at least 35 U.S.C. § 102(a).

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Meuzelaar, L. S., Lancaster, O., Pasche, J. P., Kopal, G., & Brookes, A. J. (2007). MegaPlex PCR: a strategy for multiplex amplification. *Nature methods*, *4*(10), 835 ("Meuzelaar"). Meuzelaar was available September 16, 2007, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Meuzelaar qualifies as prior art under at least 35 U.S.C. § 102(a).

Quail, M. A. et al. (2012). A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers. *BMC genomics*, *13*(1), 341. Quail was published on July 24, 2012. Quail qualifies as prior art at least under 35 U.S.C. § 102(a).

Skerra, A. (1992). Phosphorothioate primers improve the amplification of DNA sequences by DNA polymerases with proofreading activity. *Nucleic Acids Research*, *20*(14), 3551-3554. Skerra was published in 1992. Skerra qualifies as prior art at least under 35 U.S.C. § 102(a).

U.S. Patent Publication No. 2010/0248310 ("Morley"). Morley was available September 30, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Morley qualifies as prior art under at least 35 U.S.C. § 102(a).

U.S. Patent Publication No. 2013/0303461 ("the '461 Publication"). The '461 Publication was published on November 14, 2013. The '461 Publication qualifies as prior art at least under 35 U.S.C. § 102(a).

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THE ASSERTED CLAIMS OF U.S. PATENT 10,450,597 ARE ANTICIPATED AND/OR OBVIOUS OVER MCCARTY

U.S. Patent No. 10,450,597	
Claim No.	**McCarty**
1[pre]. A method of preparing nucleic acids for analysis, the method comprising:	Defendants note that, to the extent that Plaintiffs continue to contend that the '597 patent asserted claims can be read to cover the Accused QIAGEN products, contrary to the Court's Memorandum Order Regarding Claim Construction ('597 Patent) (D.I. 254), McCarty anticipates or renders obvious those asserted claims. Defendants, nonetheless, disagree with Plaintiffs' overbroad interpretation and application of the asserted claims of the '597 patent to the Accused QIAGEN products, which do not infringe any asserted claim of the '597 patent, as construed by the Court in its Memorandum Order Regarding Claim Construction ('597 Patent) (D.I. 254). The methods of the '597 patent for preparing nucleic acids for analysis were invented by multiple independent research groups, beginning years before the earliest priority date of the '597 patent and were also previously published by inventors of the '597 patent. These prior art references include Martin-Harris (2010), Morley (2010), Fraiture (2013), McCarty (2013), and U.S. Patent Application Publication No. 2013/0303461 (2013). The preamble is not a limitation. Regardless, to the extent that the preamble is a limitation, McCarty discloses this limitation. For example, McCarty teaches methods for preparing nucleic acids for analysis, such as mapping and identifying mutations tagged by transposon insertions in organisms with sequenced genomes. *See*, *e.g.*, McCarty at 1 ("Mutations tagged by transposon insertions can be readily mapped and identified in organisms with sequenced genomes. Collections of such mutants allow a systematic analysis of gene function, and can be sequence-indexed to build invaluable resources. Here we present Mu-seq (Mutant-seq), a high-throughput NextGen sequencing method for harnessing high-copy transposons. We illustrate the efficacy of Mu-seq by applying it to the Robertson's Mutator system in a large population of maize plants. A single Mu-seq library, for example, constructed from 576 different families (2304 plants), enabled 4,723 novel, germinal, transposon insertions to

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INVALIDITY OF U.S. PATENT NO. 10,450,597

EXHIBIT E

U.S. Patent No. 10,450,597 ("the '597 Patent") has an effective filing date after March 16, 2013 and therefore is subject to the provisions of the Leahy-Smith America Invents Act. The earliest possible effective filing date listed on the face of the '597 Patent is the provisional filing date of January 27, 2014. The utility application was filed on January 26, 2015. The references listed below qualify as prior art at least under AIA 35 U.S.C. § 102(a).

The below prior art references, individually or in combination with each other and/or other references render each claim element/claim anticipated and/or obvious, as detailed below by exemplary citation. A person of ordinary skill in the art would be motivated to combine these references together because they are within the same or similar field of endeavor, in particular, methods of preparing nucleic acids for sequencing.

The APAgene Gold-RT Genome Walking Kit Manual ("APAgene Manual") was available September 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, APAgene Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

The Applied Biosystems DNA Sequencing by Capillary Electrophoresis Chemistry Guide ("Applied Biosystems Manual") was available in May 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Applied Biosystems Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

Craig, D. W., et al. (2008). Identification of genetic variants using bar-coded multiplexed sequencing. *Nature methods*, *5*(10), 887 ("Craig"). Craig was available on October 1, 2008, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Craig qualifies as prior art under at least 35 U.S.C. § 102(a).

Cornish-Bowden, A. (1985). Nomenclature for incompletely specified bases in nucleic acid sequences: recommendations 1984. *Nucleic acids research*, *13*(9), 3021 ("Cornish-Bowden"). Cornish-Bowden was available on May 10, 1985, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

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Fraiture, M. A., Herman, P., Taverniers, I., De Loose, M., Deforce, D., & Roosens, N. H. (2013). An innovative and integrated approach based on DNA walking to identify unauthorised GMOs. *Food chemistry*, *147*, 60-69 ("Fraiture"). Fraiture was available on September 29, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Fraiture qualifies as prior art under at least 35 U.S.C. § 102(a).

The Illumina Application Note: DNA Analysis (2013). High-speed, multiplexed 16S amplicon sequencing on the MiSeq system ("Illumina DNA Analysis"). Illumina DNA Analysis was available May 28, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Illumina 16S Metagenomic Sequencing Library Preparation (2013). Preparing 16S ribosomal RNA gene amplicons for the Illumina MiSeq system ("Illumina Sequencing Library Preparation"). Illumina Sequencing Library Preparation was available November 27, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Genomic Sequencing Data Sheet ("Illumina Genomic Sequencing Data Sheet") was available in 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Illumina Genomic Sequencing Data Sheet qualifies as prior art under at least 35 U.S.C. §102(a).

The Illumina Sequencing Technology – Tech Spotlight ("Illumina Sequencing") was available October 11, 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Illumina Sequencing qualifies as prior art under at least 35 U.S.C. §102(a).

The Illumina TruSeq RNA and DNA Sample Preparation Kits Data Sheet ("Illumina TruSeq Data Sheet") was available November 2, 2010 and thus qualifies as prior art under at least 35 U.S.C. §102(a).

Kircher et al.. "Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform." 40 Nucleic acids research e3:1-8 (2011) ("Kircher"). Kircher was published on October 21, 2011. Thus, Kircher qualifies as prior art under at least 35 U.S.C. § 102(a).

Liu, L., et al. (2012) ("Liu"). Comparison of next-generation sequencing systems. *J. Biomed. Biotechnol. 2012*, 251364, 1-11. Liu was published in 2012. Liu qualifies as prior art at least under 35 U.S.C. § 102(a).

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Martin-Harris, M. H., Bartley, P. A., & Morley, A. A. (2010). Gene walking using sequential hybrid primer polymerase chain reaction. *Analytical biochemistry*, *399*(2), 308-310 ("Martin-Harris"). Martin-Harris was available January 13, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Martin-Harris qualifies as prior art under at least 35 U.S.C. § 102(a).

McCarty, D. R., Latshaw, S., Wu, S., Suzuki, M., Hunter, C. T., Avigne, W. T., & Koch, K. E. (2013). Mu-seq: sequence-based mapping and identification of transposon induced mutations. *PLoS One*, *8*(10), e77172 ("McCarty"). McCarty was available October 23, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, McCarty qualifies as prior art under at least 35 U.S.C. § 102(a).

Meuzelaar, L. S., Lancaster, O., Pasche, J. P., Kopal, G., & Brookes, A. J. (2007). MegaPlex PCR: a strategy for multiplex amplification. *Nature methods*, *4*(10), 835 ("Meuzelaar"). Meuzelaar was available September 16, 2007, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Meuzelaar qualifies as prior art under at least 35 U.S.C. § 102(a).

Quail, M. A. et al. (2012). A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers. *BMC genomics*, *13*(1), 341. Quail was published on July 24, 2012. Quail qualifies as prior art at least under 35 U.S.C. § 102(a).

Skerra, A. (1992). Phosphorothioate primers improve the amplification of DNA sequences by DNA polymerases with proofreading activity. *Nucleic Acids Research*, *20*(14), 3551-3554. Skerra was published in 1992. Skerra qualifies as prior art at least under 35 U.S.C. § 102(a).

U.S. Patent Publication No. 2010/0248310 ("Morley"). Morley was available September 30, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Morley qualifies as prior art under at least 35 U.S.C. § 102(a).

U.S. Patent Application Publication No. 2013/0303461 ("the '461 Publication"). The '461 Publication was published on November 14, 2013. The '461 Publication qualifies as prior art at least under 35 U.S.C. § 102(a).

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THE ASSERTED CLAIMS OF U.S. PATENT 10,450,597 ARE ANTICIPATED AND/OR OBVIOUS OVER APAGENE MANUAL

U.S. Patent No. 10,450,597	
Claim No.	**APAgene Manual and System**
1[pre]. A method of preparing nucleic acids for analysis, the method comprising:	The methods of the '597 patent for preparing nucleic acids for analysis were invented by multiple independent research groups, beginning years before the earliest priority date of the '597 patent, and were also previously published by inventors of the '597 patent. These prior art references include Martin-Harris (2010), Morley (2010), Fraiture (2013), McCarty (2013), and U.S. Patent Application Publication No. 2013/0303461 (2013). The preamble is not a limitation. Regardless, to the extent that the preamble is a limitation, the prior art manual discloses and the system, the APAgene GOLD Genome Walking Kit ("the System"), uses the method described in the preamble. The APAgene Manual discloses and the System practices this claim element. For example, APAgene Manual discloses and the System practices preparing nucleic acids for analysis for sequencing, cloning or as probes. *See* APAgene Manual at 2 (Introduction) ("The APAgene™ GOLD Genome Walking Kit can enable rapid isolation of unknown sequences which flank known gene sequences. Examples include: • Genomic sequences flanking transgenes (including T-DNAs, gene traps, transposons), sequence-tagged sites (STSs) or expressed sequence tags (ESTs); • Insert ends of large clones such as P1, YAC and BAC DNAs; • 5' promoter control regions and 3' transcriptional terminators of cDNAs; • cDNA walking, 5' and 3' RACE from first-strand cDNAs; • Other localized sequences flanking known sequences from large clones and genomic DNAs. PCR products can directly be used for sequencing, cloning or as probes").
1[a]. (a) contacting a first nucleic acid template comprising a	The APAgene Manual discloses and the System practices this limitation. The APAgene manual teaches and the System practices contacting a first nucleic acid template comprising a

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INVALIDITY OF U.S. PATENT NO. 10,450,597

EXHIBIT F

The below prior art references, individually or in combination with each other and/or other references render each claim element/claim obvious, as detailed below by exemplary citation. A person of ordinary skill in the art would be motivated to combine these references together because they are within the same or similar field of endeavor, in particular, methods of preparing nucleic acids for sequencing.

U.S. Patent No. 10,450,597 ("the '597 Patent") has an effective filing date after March 16, 2013 and therefore is subject to the provisions of the Leahy-Smith America Invents Act. The earliest possible effective filing date listed on the face of the '597 Patent is the provisional filing date of January 27, 2014. The utility application was filed on January 26, 2015. The references listed below qualify as prior art at least under AIA 35 U.S.C. § 102(a).

The below prior art references, individually or in combination with each other and/or other references render each claim element/claim anticipated and/or obvious, as detailed below by exemplary citation. A person of ordinary skill in the art would be motivated to combine these references together because they are within the same or similar field of endeavor, in particular, methods of preparing nucleic acids for sequencing.

The APAgene Gold-RT Genome Walking Kit Manual ("APAgene Manual") was available September 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, APAgene Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

The Applied Biosystems DNA Sequencing by Capillary Electrophoresis Chemistry Guide ("Applied Biosystems Manual") was available in May 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Applied Biosystems Manual qualifies as prior art under at least 35 U.S.C. § 102(a).

Cornish-Bowden, A. (1985). Nomenclature for incompletely specified bases in nucleic acid sequences: recommendations 1984. *Nucleic acids research*, *13*(9), 3021 ("Cornish-Bowden"). Cornish-Bowden was available on May 10, 1985, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Cornish-Bowden qualifies as prior art under at least 35 U.S.C. § 102(a).

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Fraiture, M. A., Herman, P., Taverniers, I., De Loose, M., Deforce, D., & Roosens, N. H. (2013). An innovative and integrated approach based on DNA walking to identify unauthorised GMOs. *Food chemistry*, *147*, 60-69 ("Fraiture"). Fraiture was available on September 29, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Fraiture qualifies as prior art under at least 35 U.S.C. § 102(a).

The Illumina Application Note: DNA Analysis (2013). High-speed, multiplexed 16S amplicon sequencing on the MiSeq system ("Illumina DNA Analysis"). Illumina DNA Analysis was available May 28, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

Illumina 16S Metagenomic Sequencing Library Preparation (2013). Preparing 16S ribosomal RNA gene amplicons for the Illumina MiSeq system ("Illumina Sequencing Library Preparation"). Illumina Sequencing Library Preparation was available November 27, 2013 and thus qualifies as prior art at least under 35 U.S.C. §102(a).

The Illumina Genomic Sequencing Data Sheet ("Illumina Genomic Sequencing Data Sheet") was available in 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, the Illumina Genomic Sequencing Data Sheet qualifies as prior art under at least 35 U.S.C. §102(a).

The Illumina Sequencing Technology – Tech Spotlight ("Illumina Sequencing") was available October 11, 2010, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Illumina Sequencing qualifies as prior art under at least 35 U.S.C. §102(a).

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Kircher et al.. "Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform." 40 Nucleic acids research e3:1-8 (2011) ("Kircher"). Kircher was published on October 21, 2011. Thus, Kircher qualifies as prior art under at least 35 U.S.C. § 102(a).

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Martin-Harris, M. H., Bartley, P. A., & Morley, A. A. (2010). Gene walking using sequential hybrid primer polymerase chain reaction. *Analytical biochemistry*, *399*(2), 308-310 ("Martin-Harris"). Martin-Harris was available January 13, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Martin-Harris qualifies as prior art under at least 35 U.S.C. § 102(a).

McCarty, D. R., Latshaw, S., Wu, S., Suzuki, M., Hunter, C. T., Avigne, W. T., & Koch, K. E. (2013). Mu-seq: sequence-based mapping and identification of transposon induced mutations. *PLoS One*, *8*(10), e77172 ("McCarty"). McCarty was available October 23, 2013, prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, McCarty qualifies as prior art under at least 35 U.S.C. § 102(a).

Meuzelaar, L. S., Lancaster, O., Pasche, J. P., Kopal, G., & Brookes, A. J. (2007). MegaPlex PCR: a strategy for multiplex amplification. *Nature methods*, *4*(10), 835 ("Meuzelaar"). Meuzelaar was available September 16, 2007, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Meuzelaar qualifies as prior art under at least 35 U.S.C. § 102(a).

Quail, M. A. et al. (2012). A tale of three next generation sequencing platforms: comparison of Ion Torrent, Pacific Biosciences and Illumina MiSeq sequencers. *BMC genomics*, *13*(1), 341. Quail was published on July 24, 2012. Quail qualifies as prior art at least under 35 U.S.C. § 102(a).

Skerra, A. (1992). Phosphorothioate primers improve the amplification of DNA sequences by DNA polymerases with proofreading activity. *Nucleic Acids Research*, *20*(14), 3551-3554. Skerra was published in 1992. Skerra qualifies as prior art at least under 35 U.S.C. § 102(a).

U.S. Patent Publication No. 2010/0248310 ("Morley"). Morley was available September 30, 2010, more than a year prior to January 27, 2014, the date of the earliest provisional application listed on the face of the '597 patent. Thus, Morley qualifies as prior art under at least 35 U.S.C. § 102(a).

U.S. Patent Application Publication No. 2013/0303461 ("the '461 Publication"). The '461 Publication was published on November 14, 2013. The '461 Publication qualifies as prior art at least under 35 U.S.C. § 102(a).

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U.S. Patent No. 10,017,810 ("'810") claims the benefit of U.S. Provisional Application Nos. 61/645,364 (filed May 10, 2012) and 61/679,302 (filed August 3, 2012). To the extent that '810 is entitled to its claim for priority, '810 qualifies as prior art at least under 35 U.S.C. § 102(a).

U.S. Patent No. 9,487,828 ("'828") claims the benefit of U.S. Provisional Application Nos. 61/645,364 (filed May 10, 2012) and 61/679,302 (filed August 3, 2012). '828 was published on November 14, 2013, '828 qualifies as prior art at least under 35 U.S.C. § 102(a).

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THE ASSERTED CLAIMS OF U.S. PATENT 10,450,597 ARE ANTICIPATED AND/OR OBVIOUS OVER U.S. PATENT NOS. 9,487,828, 10,017,810, AND PUBLISHED APPLICATION US 2013/0303461

U.S. Patent No. 10,450,597	
Claim No.	U.S. Patent Nos. 9,487,828 and 10,017,810 and Published Application US 2013/0303461
1[pre]. A method of preparing nucleic acids for analysis, the method comprising:	U.S. Patent Nos. 10,017,810 ("'810") and 9,487,828 ("'828"), as well as Published Application No. US 2013/0303461, Application No. 13/793,564 (the "'564 App."). describe a method of preparing nucleic acid samples for sequencing. '810 Col. 1:33-2:2; '828 Col. 1:30-67; '564 App. ¶¶ [0004]-[0006]. They describe methods to create sequencing libraries for various NGS sequencing platforms. *See, e.g.*, '810 Col. 5:44-65; '828 Col. 5:44-63 (describing Fig. 1); '564 App. ¶ [0026]; *see also* '810 Claims 1 and 16 (A method for preparing a nucleic acid for sequencing, the method comprising."); '828 Claims 1 and 40 ("a method for determining the nucleotide sequence contiguous to a known target nucleotide sequence of 10 or more nucleotides, the method comprising"); '564 App. Claim 1. Defendants note that, to the extent that Plaintiffs continue to contend that the '597 patent asserted claims can be read to cover the Accused QIAGEN products contrary to the Court's Memorandum Order Regarding Claim Construction ('597 Patent) (D.I. 254), the '810 patent, the '828 patent, and the '564 App. anticipate or render obvious those asserted claims. Defendants, nonetheless, disagree with Plaintiffs' overbroad interpretation and application of the asserted claims of the '597 patent to the Accused QIAGEN products, which do not infringe any asserted claim of the '597 patent, as construed in the Court's in its Memorandum Order Regarding Claim Construction ('597 Patent) (D.I. 254).
1[a]. (a) contacting a first nucleic acid template comprising a sequence of a first strand of a double-stranded target nucleic acid with a complementary target-specific primer that comprises a target-specific hybridization	Plaintiffs allege that the set in QIAGEN's process of ligating a universal oligonucleotide tail adaptor to a target nucleotide sequence, and then using a first adaptor primer that anneals to that universal oligonucleotide tail adaptor and initiates a PCR reaction satisfies this element. The '810 and '828 specifications and claims make that same disclosure. See e.g., '810 Col. 2:1-9; '828 Col. 2:1-9 ("(a) ligating a target nucleic acid comprising the known target nucleotide sequence with a universal oligonucleotide tail-adaptor; (b) amplifying a portion of the target nucleic acid and the amplification strand of the universal oligonucleotide tail adaptor with a first adaptor primer and a first target-specific primer…"); '564 App. ¶ [0007]. The specifics of the sequence of the universal

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EXHIBIT 19

Each limitation of claim 1 of the ’597 Patent (Ex. 1) is disclosed in the ’943 Provisional (Ex. 15) and ’959 Provisional (Ex. 14) in substantively identical terms.

’597 Patent, claim 1	**Exemplary disclosures in the ’943 and ’959 Provisionals**
A method of preparing nucleic acids for analysis, the method comprising:	“Aspects of the technology disclosed herein relate to methods for preparing and analyzing nucleic acids.” **’943 [0012]; ’959 [0013]** “For example, [FIGS. 1A-B / FIG. 4] present[s] schematics of exemplary methods of amplifying target nucleic acids that have a known target region 5' to an adjacent region (e.g., for purposes of sequencing the adjacent region).” **’943 [0014]; ’959 [0016]**
(a) contacting a first nucleic acid template comprising a sequence of a first strand of a double-stranded target nucleic acid with a complementary target-specific primer that comprises a target-specific hybridization sequence, under conditions to promote template-specific hybridization and extension of the target-specific primer;	“In step [102 / 103] DNA molecules produced by reverse transcription are contacted by one or more initial target-specific primers which may or may not be the same as the first target-specific primer. In step [103 / 104], hybridization of the initial target-specific primer to a portion of the target nucleic acid […] primes an extension reaction using a DNA molecule as a template to produce a complementary DNA strand. Extension products are purified in step [104 / 105].” **’943 [0017]; ’959 [0016]**
(b) contacting a second nucleic acid template comprising a sequence of a second strand that is complementary to the sequence of the first strand of the double-stranded target nucleic acid with a plurality of different primers that share a common sequence that is 5' to different hybridization sequences, under conditions to promote template-specific hybridization and extension of at least one of the plurality of different primers,	“At step 101, initial RNA is obtained or provided in a sample and is used as a template. RNA template is exposed to a plurality of tailed primers (*e.g.*, tailed random primers) that comprise a common sequence that is 5' to different hybridization sequences and shared between all of the tailed primers of the population. In some embodiments, at least one primer hybridizes to an RNA molecule and primes a reverse transcriptase reaction to produce a complementary DNA strand.” **’943 [0016]; ’959 [0014]**

’597 Patent, claim 1	Exemplary disclosures in the ’943 and ’959 Provisionals
wherein the different hybridization sequences have different 3' ends, and wherein each primer of the plurality of different primers does not anneal to the same sequence of the double-stranded target nucleic acid as any other primer of the plurality of different primers,	“In some embodiments, the plurality of primers (e.g., a plurality of sets of first and second target-specific primers) can specifically anneal to known target sequences comprised by separate genes. In some embodiments, at least two sets of primers (e.g., at least two sets of first and second target-specific primers) can specifically anneal to different portions of a known target sequence. In some embodiments, at least two sets of primers (e.g., at least two sets of first and second target-specific primers) can specifically anneal to different portions of a known target sequence comprised by a single gene. In some embodiments, at least two sets of primers (e.g., at least two sets of first and second target-specific primers) can specifically anneal to different exons of a gene comprising a known target sequence.” **’943 [0087]; ’959 [0102]**
wherein, following (a) and (b), an extension product is generated to contain both a sequence that is characteristic of the target-specific primer and a sequence that is characteristic of the at least one of the plurality of different primers; and	**’943, Fig. 4, step 103** **’959, Fig. 1A, step 104**

’597 Patent, claim 1	Exemplary disclosures in the ’943 and ’959 Provisionals
(c) subjecting the extension product to an amplification reaction comprising successive rounds of polymerase extension of i) a tail primer that comprises a 3' sequence that specifically anneals to the complement of the common sequence and that comprises a 5' tail sequence, and ii) a primer that specifically anneals to the complement of the target-specific hybridization sequence.	“In [Figure 4 / FIGS. 1A and 1B], a first tail primer hybridizes to at least a portion of a DNA molecule provided by the tail portion of the tailed primer of step 101. In some embodiments, the first tail primer hybridizes to the common sequence provided by the tail of the one or more primers of step 101. In some embodiments, a nested target specific primer (nested with respect to the target specific primer of step [102 / 103]) is used in step [105 / 106]. In some embodiments, a first tail primer may comprise an additional sequence 5' to the hybridization sequence that may include barcode, index, adapter sequences, or sequencing primer sites, for example. In step [106 / 107], hybridization of the first target-specific primer and the first tail nucleic acid molecule allows for amplification of a product in a polymerase chain reaction (PCR).” **’943 [0019]; ’959 [0018]**

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on March 1, 2021 on the following counsel in the manner indicated:

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