

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTEGRATED DNA TECHNOLOGIES, INC.,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

Case IPR2024-01502
U.S. Patent 9,546,399

**PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT 9,546,399**

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EXHIBIT LIST

Exhibit	Short Name	Document
Ex. 1001		Reserved
Ex. 1002		Reserved
Ex. 1003	'399 patent	U.S. Patent No. 9,546,399
Ex. 1004	'357 patent	U.S. Patent No. 11,098,357
Ex. 1005	'241 patent	U.S. Patent No. 11,725,241
Ex. 1006		Reserved
Ex. 1007	Siebert	Siebert et al., <i>An improved PCR method for walking in uncloned genomic DNA</i> , NUCLEIC ACIDS RES. 23(6) 1087–1088 (1995)
Ex. 1008	Caruccio	Caruccio, <i>Preparation of Next-Generation Sequencing Libraries using Nextera™ Technology: Simultaneous DNA Fragmentation and Adaptor Tagging by In Vitro Transposition</i> , HIGH-THROUGHPUT NEXT GENERATION SEQUENCING: METHODS AND APPLICATIONS, METHODS IN MOLECULAR BIOLOGY, Ch. 17 (2011)
Ex. 1009	Bronner	Bronner et al., <i>Improved Protocols for Illumina Sequencing</i> , CURR PROTOC HUM GENET. (2009)
Ex. 1010		Reserved
Ex. 1011	Iafrate	U.S. Patent Application Publication No. 2013/0303461
Ex. 1012	Kivioja	Kivioja et al., <i>Counting absolute numbers of molecules using unique molecular identifiers</i> , NATURE METHODS (2011)

Exhibit	Short Name	Document
Ex. 1013	Bielas	International Publication No. WO 2013/123442 A1
Ex. 1014	Masoudi-Nejad	Masoudi-Nejad et al., <i>Next Generation Sequencing and Sequence Assembly Methodologies and Algorithms</i> (2013)
Ex. 1015	Zheng	Zheng et al., <i>Anchored multiplex PCR for targeted next-generation sequencing</i> , NATURE MEDICINE (2014)
Ex. 1016		Reserved
Ex. 1017		Reserved
Ex. 1018		File History for U.S. Patent No. 9,546,399
Ex. 1019		File History for U.S. Patent No. 11,098,357
Ex. 1020		File History for U.S. Patent No. 11,725,241
Ex. 1021	Miner	Miner et al., <i>Molecular barcodes detect redundancy and contamination in hairpin-bisulfite PCR</i> , NUCLEIC ACID RESEARCH 32:17 (2004)
Ex. 1022	McCloskey	McCloskey et al., <i>Encoding PCR Products with Batch-stamps and Barcodes</i> , BIOCHEM GENET 45:761–767 (2007)
Ex. 1023	Hiatt	Hiatt et al., <i>Parallel, tag-directed assembly of locally derived short sequence reads</i> , NAT METHODS 7(2):119–122 (2010)
Ex. 1024	König	König et al., <i>iCLIP reveals the function hnRNP particles in splicing at individual nucleotide resolution</i> , NAT STRUC MOL BIOL. 17(7):909–915 (2010)

Exhibit	Short Name	Document
Ex. 1025	Kinde	Kinde et al., <i>Detection and quantification of rare mutations with massively parallel sequencing</i> , PNAS 108(23):9350–9535 (2011)
Ex. 1026	Casbon	Casbon et al., <i>A method for counting PCR template molecules with application to next-generation sequencing</i> , NUCLEIC ACIDS RESEARCH 39:12 (2011)
Ex. 1027	Fu	Fu et al., <i>Counting individual DNA molecules by the stochastic attachment of diverse labels</i> , PNAS 108(22):9026–9031 (2011)
Ex. 1028	Jabara	Jabara et al., <i>Accurate sampling and deep sequencing of the HIV-1 protease gene using a Primer ID</i> , PNAS 108(50):20166–20171 (2011)
Ex. 1029	Tollervey	Tollervey et al., <i>Characterising the RNA targets and position-dependent splicing regulation by TDP-43; implications for neurodegenerative diseases</i> , NAT NEUROSCI. 14(4):452–458 (2011)
Ex. 1030	Shiroguchi	Shiroguchi et al., <i>Digital RNA sequencing minimizes sequence-dependent bias and amplification noise with optimized single-molecule barcodes</i> , PNAS 109(4):1347–1352 (2012)
Ex. 1031	Schmitt	Schmitt et al., <i>Detection of ultra-rare mutations by next-generation sequencing</i> , PNAS 109(36):14508–14513 (2012)

Exhibit	Short Name	Document
Ex. 1032	De Luca	De Luca and Dono, <i>The Opportunities and Challenges of Molecular Tagging Next-Generation Sequencing in Liquid Biopsy</i> , MOLECULAR DIAGNOSIS & THERAPY 25:537–547 (2021)
Ex. 1033	Samuels	U.S. Patent Application Publication No. 2012/0220494
Ex. 1034		Reserved
Ex. 1035		Reserved
Ex. 1036		Reserved
Ex. 1037		Reserved
Ex. 1038		Reserved
Ex. 1039		Reserved
Ex. 1040		Reserved
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Ex. 1042		Reserved
Ex. 1043		Reserved
Ex. 1044		Reserved
Ex. 1045		Reserved
Ex. 1046		Reserved
Ex. 1047		Reserved
Ex. 1048		U.S. Provisional Patent Application 61/645,364

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Ex. 1049		U.S. Provisional Patent Application 61/679,302
Ex. 1050	Moorthie	Moorthie et al., <i>Review of massively parallel DNA sequencing technologies</i> , HUGO JOURNAL 5:1–12 (2011)
Ex. 1051		Reserved
Ex. 1052		Reserved
Ex. 1053	Syed	Syed, <i>Chapter 19: Second-Generation Sequencing Library Preparation: In Vitro Tagmentation via Transposome Insertion</i> , in TAG-BASED NEXT GENERATION SEQUENCING (Matthias Harbers and Günter Kahl, eds., 2011)
Ex. 1054	Loeb	Loeb et al., <i>Transcriptome-wide miR-155 Binding Map Reveals Widespread Noncanonical MicroRNA Targeting</i> , MOLECULAR CELL 760–770 (2012)
Ex. 1055	Kircher	Kircher et al., <i>Double indexing overcomes inaccuracies in multiplex sequencing on the Illumina platform</i> , NUCLEIC ACIDS RESEARCH 40:1 (2012)
Ex. 1056	Illumina Letter	Illumina Customer Letter (Sept. 7, 2012)
Ex. 1057	Nextera Prep Guide	Nextera® XT DNA Sample Preparation Guide (Oct. 2012)
Ex. 1058	Troutt	Troutt et al., <i>Ligation-anchored PCR: A simple amplification technique with single-sided specificity</i> , PNAS, USA 9823–9825 (1992)

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Ex. 1059	Hug & Schuler	Hug and Schuler, <i>Measurement of the Number of Molecules of a Single mRNA Species in a Complex mRNA Preparation</i> , J. THEOR. BIOL. 221:615–624 (2003),
Ex. 1060	Meyer & Kircher	Meyer and Kircher, <i>Illumina Sequencing Library Preparation for Highly Multiplexed Target Capture and Sequencing</i> , COLD SPRING HARBOR PROTOCOLS (2010)
Ex. 1061	Kircher Thesis	Kircher Thesis, <i>Understanding and improving high-throughput sequencing data production and analysis</i> , LEIPZIG UNIVERSITY, Germany (2011)
Ex. 1062	Smith Thesis	Smith Thesis, <i>Low-Level Variant Detection in Human Mitochondrial DNA Using The Illumina® MiSeq™ Next-Generation Sequencing (NGS) Platform</i> , WESTERN CAROLINA UNIVERSITY (2013)
Ex. 1063	Won	Won et al., <i>Detecting Somatic Genetic Alterations in Tumor Specimens by Exon Capture and Massively Parallel Sequencing</i> , J. VISUALIZED EXPERIMENTS (2013)
Ex. 1064	Kozich	Kozich et al., <i>Development of a Dual-Index Sequencing Strategy and Curation Pipeline for Analyzing Amplicon Sequence Data on the MiSeq Illumina Sequencing Platform</i> , APPLIED AND ENVIRONMENTAL MICROBIOLOGY 79:17, 5112–5120 (2013)
Ex. 1065	Pray	Pray, <i>Major Molecular Events of DNA Replication</i> , NATURE EDUCATION (2008)

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Ex. 1066	Mackenzie	Mackenzie, <i>DNA vs. RNA – 5 Key Differences and Comparison</i> , TECHNOLOGY NETWORKS (2020)
Ex. 1067	Clancy	Clancy and Brown, <i>Translation: DNA to mRNA to Protein</i> , NATURE EDUCATION (2008)
Ex. 1068	Gauthier Thesis	Gauthier Thesis, <i>Simulation of polymer translocation through small channels</i> , UNIVERSITY OF OTTAWA, Canada (2008)
Ex. 1069	Lohman	Lohman et al., <i>DNA Ligases</i> , CURRENT PROTOCOLS IN MOLECULAR BIOLOGY 3.14.1-3.14.7 (2011)
Ex. 1070	Margulies	Margulies et al., <i>Genome sequencing in microfabricated high-density picolitre reactors</i> , NATURE 376–380 (2005)
Ex. 1071		DNA Sequencing Costs: Data, https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data
Ex. 1072	Craig	Craig et al., <i>Identification of Genetic Variants Using Barcoded Multiplexed Sequencing</i> , NAT. METHODS 5(10) 887–893 (2008)
Ex. 1073	Parameswaran	Parameswaran et al., <i>A pyrosequencing-tailored nucleotide barcode design unveils opportunities for large-scale sample multiplexing</i> , NUCLEIC ACIDS RESEARCH 35:19 (2007)

Exhibit	Short Name	Document
Ex. 1074	Lonigro	Lonigro et al., <i>Detection of Somatic Copy Number Alterations in Cancer Using Targeted Exome Capture Sequencing</i> , NEOPLASIA 13(11) 1019–1025 (2011)
Ex. 1075	Bielas Annotated Figure	Annotated Figure
Ex. 1076	Bielas Illumina P5	Annotated Figure
Ex. 1077	Bielas Read 1 Primer	Annotated Figure
Ex. 1078	Bielas i5 Index	Annotated Figure
Ex. 1079	Sims Declaration	Declaration of Peter A. Sims, Ph.D.

Integrated DNA Technologies, Inc. (“IDT” or “Petitioner”) respectfully requests *inter partes* review of claims 1-3, 5-11, and 14-17 of U.S. Patent No. 9,546,399 (the “Challenged Claims” of the “’399 patent”). EX1003. Petitioner is a market leader in assay solutions for next-generation DNA sequencing (“NGS”), and sells NGS products and software under the Archer brand name. These products use Petitioner’s anchored multiplex PCR (“AMP”) technology, which is based on chemistry developed at Massachusetts General Hospital and in-licensed to Petitioner. This technology is used in hundreds of laboratories and hospitals across the country for a variety of research applications, especially cancer research.

In October 2023, Patent Owner Tecan Genomics, Inc. (“Tecan”) sued IDT, alleging that IDT’s products induce infringement of the ’399 patent, among others. Based on its disclosures in district court as of the date of this petition, Tecan does not market a competing product or practice the ’399 patent.

The ’399 patent claims a method for “detecting a duplicate sequencing read” in NGS. The method involves preparing a library of DNA fragments for NGS by (1) attaching synthetic “adaptors” containing a random DNA sequence, called an “identifier site,” to nucleic acid fragments via a chemical process called ligation, (2) generating copies of the adaptor-ligated fragments, (3) sequencing the adaptor-ligated fragments, and (4) using the identifier site and the sequence of the fragment

from each sequencing read to identify duplicate sequences created during the library preparation process.

By 2013, when the priority application was filed, the '399 patent's method was well known. Scientists in the DNA sequencing field had long recognized—and solved—the problem of determining whether an observed sequence was a copy created during NGS library preparation or a copy contained in the original sample. The solution, as reflected in multiple prior art publications, was to label DNA fragments with random identifier sequences prior to NGS and use the labels to identify and remove duplicate sequences created during library preparation. The remaining elements recited in the claims were also well known at the time. Adaptors with the other features recited in the claims were conventional by that point, as were methods of attaching them to DNA fragments via ligation. The remainder of the method recites conventional steps performed in any NGS reaction.

This Petition's first ground begins with U.S. 2013/0303461 ("Iafrate"), EX1011, which discloses the foundational technology for Petitioner's Archer products. Iafrate teaches ligation of adaptors for NGS that have every element of the adaptors recited in the '399 except for the random identifier sequence and explains that those adaptors can be used to prepare a library for NGS. Kivioja, a 2011 article in *Nature Methods*, EX1012, provides the only missing element (and also teaches nearly every element of the claimed method itself). It teaches a random

identifier sequence that “can improve accuracy of almost any next-generation sequencing method,” EX1012.0001, and uses the random identifier sequence and fragment to differentiate original fragment sequences from duplicates—precisely the same use as in the later ’399 claims. It would have been obvious in 2013 to incorporate Kivioja’s random identifiers into Iafrate’s adaptors to arrive at a method that practices every step of the ’399 claims.

The obviousness of the ’399 methods is also shown in the Petition’s second and third grounds, which are based on WO 2013/123442 (“Bielas”). EX1013. Bielas discloses every element of the ’399 method. Bielas teaches a method of using ligated adaptors with exactly the features claimed in the ’399 patent using those adaptors in an NGS method that permits each sequenced fragment to be “connected back to the original molecule.” EX1013.0009. It anticipates or, at a minimum, renders obvious the ’399 claims.

Accordingly, Petitioner respectfully requests that the Board institute *inter partes* review and cancel the Challenged Claims.

I. BACKGROUND

The ’399 patent relates to methods for preparing libraries of nucleic acids for NGS and information processing. EX1079.¶30. NGS was introduced for commercial use around 2005 and revolutionized sequencing by dramatically cutting down sequencing time and cost. EX1079.¶¶80-83; EX1050.0001-02;

EX1071.0002. While NGS harnessed new advances in computer technology and molecular fabrication to increase throughput and efficiency, the biology and chemistry underlying NGS was decades old. EX1079.¶¶62-66, ¶¶80-84; EX1070.0001-06; EX1009.0001, 0002-03; EX1014.0022; EX1050.0001-02; EX1060.0009; EX1062.0034-35; EX1068.0020; EX1008.0001. NGS was rapidly adopted across academia and industry, and there was an explosion of articles and patent applications for NGS-related processes based on applying those old molecular biology tools to NGS, often covering methods that were simultaneously being described elsewhere. EX1079.¶¶80-84; EX1070.0001-06; EX1009.0002-03; EX1014.0022; EX1050.0002; EX1060.0009; EX1062.0034-35.

A. Technical Background

The following primer is based on EX1079, the Declaration of Dr. Peter Sims, a professor at Columbia, who has been teaching and researching in the NGS field for years.

1. Biological Roles of DNA and RNA

i. DNA

DNA encodes genetic information in the sequence of four repeated nucleotides: adenine (“A”), cytosine (“C”), guanine (“G”), and thymine (“T”). EX1079.¶¶31-35, ¶46, ¶50; EX1014.0011-12. Two strands of nucleotides in DNA are “annealed” to one another based on a specific interaction between the nucleotides in each strand. EX1079.¶36; EX1014.0012. Based on this pairing, two paired DNA

strands are said to be “complementary” to one another. EX1079.¶¶36-37; EX1014.0012.

Each strand of DNA is directional with each nucleotide attached from the 3' end of one to the 5' end of the next, and thus each strand of DNA has a 5' and a 3' end. EX1079.¶35, ¶38; EX1014.0011-12. The two DNA strands run in the opposite direction to one another—the 5' end of one strand is complementary to the 3' end of the other. EX1079.¶38.

DNA is generally synthesized one strand at a time by a “polymerase” that starts from a short strand called a “primer” annealed to a template strand. EX1079.¶¶42-45; EX1014.0011-12; EX1065.0001-02.

DNA sequencing has long been an important goal of biological research to study the relationship between genotype and phenotype and the underlying process of genetic heritability. EX1079.¶¶57-59; EX1009.0001. DNA sequencing is thus useful in fields from archaeology to zoology. EX1079.¶57.

ii. RNA

RNA is a polymer related to DNA that is generally single stranded and plays a critical translational function. EX1079.¶¶39-41; EX1066.0001. DNA in cells is transcribed to make RNA by a “transcriptase.” EX1079.¶47. RNA in turn can be translated into the proteins that make up the basic building blocks of a cell. EX1079.¶¶48-49; EX1067.0001.

RNA can also be “reverse transcribed” back to complementary DNA (“cDNA”) by a “reverse transcriptase.” EX1079.¶52, ¶61.

Because RNA also plays a critical biological role and reflects the intermediate step between genetic information and proteins, scientists have also been interested in RNA sequencing. EX1079.¶51, ¶60.

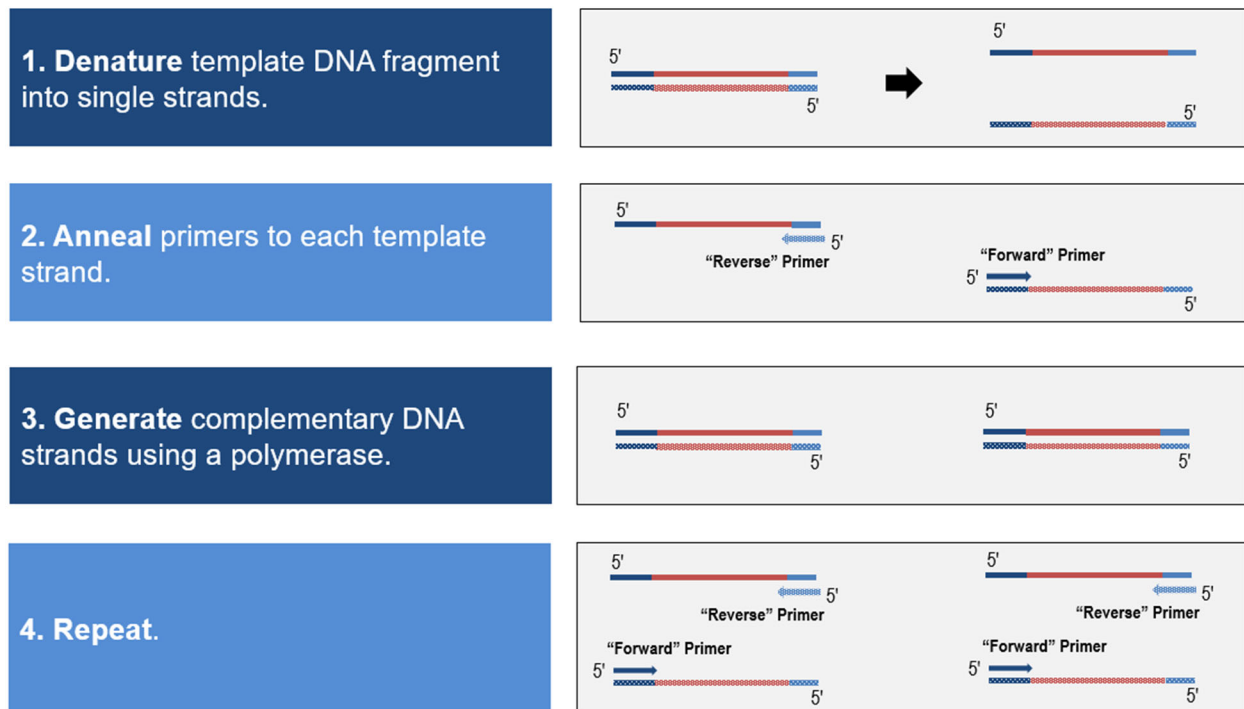
2. Pre-NGS DNA and RNA Research Tools

Beginning in the second half of the 20th century, scientists began to use the cell’s biological tools, such as polymerases and transcriptases, for research purposes, including to manipulate and sequence DNA and RNA. EX1079.¶¶67-79.

i. Polymerase Chain Reaction

Discovered in the 1980s, a polymerase chain reaction (“PCR”) is a method of exponentially copying DNA (including cDNA) and thus is a frequently-used tool to increase DNA concentration for various purposes, e.g., prior to sequencing. EX1079.¶67, ¶¶71-72. In a PCR reaction, DNA fragments are denatured to single strands and combined with a polymerase, free nucleotides, and primers. EX1079.¶68. The primers anneal to the single-stranded DNA fragments and the DNA polymerase regenerates a complementary strand. EX1079.¶¶69-70. The double-stranded products are denatured again and the process repeats. EX1079.¶¶69-70.

Because each strand can be a template in the next round of the reaction, PCR is said to “amplify” DNA because the process is exponential and each round of the reaction doubles the number of DNA molecules. EX1079.¶¶67-70. For a PCR reaction to proceed exponentially, one “forward” primer anneals on one side of the fragment on one strand and one “reverse” primer anneals to a sequence on the other side of the fragment on the complementary strand, as shown in the figure¹ below. EX1079.¶¶68-69.



¹ This figure uses a standard convention to depict DNA strands as colored bars that is discussed in further detail in Dr. Sims’s declaration. EX1079.¶69.

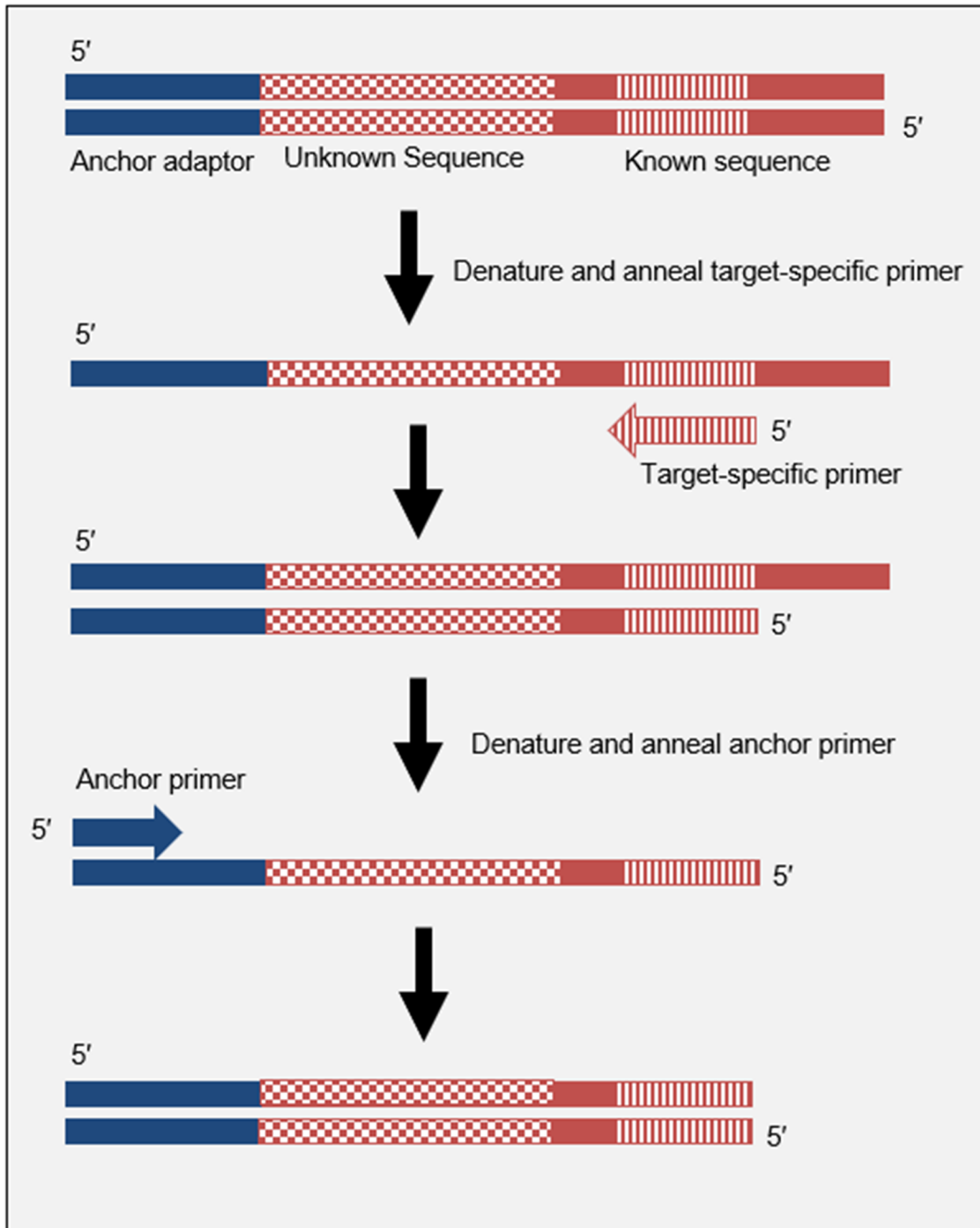
ii. Anchored PCR

One challenge with traditional PCR is that amplification requires knowing at least a portion of the sequence to be amplified at the beginning and the end so that specific forward and reverse primers can be made (as opposed to using random primers to amplify all of the DNA). EX1079.¶¶73-79; EX1058.0001-02; EX1007.0001-02. But for some research applications, being able to amplify an unknown sequence is desirable, e.g., for genetic mutations implicated in cancer. EX1079.¶73.

Beginning in the 1990s, scientists developed a technique, called anchored PCR, to amplify such sequences. EX1079.¶73-79; EX1058.0001-02; EX1007.0001-02. In anchored PCR, a synthetic sequence, called an “adaptor,” is added to one or both ends of the DNA prior to PCR. EX1079.¶56. One known method of adding an adaptor was to use an enzyme called a “ligase.” EX1079.¶53. Ligases directly join two pieces of DNA or RNA together via a process called “ligation.” EX1079.¶¶53-55; EX1069 at 0001-06. One common application was to join a synthetic sequence to a naturally occurring sequence, e.g., as an adaptor sequence for anchored PCR. EX1079.¶56.

The anchored PCR technique is summarized in the figure below. EX1079.¶74. Once the anchor sequence is added, a PCR reaction is conducted with two primers: one complementary to the anchor sequence, and one complementary to

a known sequence. EX1079.¶¶74-79; EX1058.0002. The result of this PCR reaction is to amplify fragments with the known sequence on one side and the anchor on the other, with potentially unknown sequence between the two. EX1079.¶74, ¶79; EX1007 at 0002.



iii. Sequencing By Synthesis (“SBS”)

In the 1970s, Frederick Sanger developed an eponymous method of sequencing DNA by using the natural action of DNA polymerase. EX1079.¶62-66; EX1068.0020; EX1050.0001; EX1009.0001-02. Sanger sequencing, or “sequencing by synthesis” (“SBS”) involved denaturing double-stranded DNA, annealing primers, and using a polymerase to synthesize a complementary strand. EX1079.¶¶63-64; EX1068.0020. The addition of each nucleotide to the growing strand in the DNA synthesis reaction was measured using radioactive or fluorescently-labeled nucleotides. EX1079.¶63.

3. Next Generation Sequencing (“NGS”)

Beginning in the mid-2000s, sequencing technology was revolutionized by the introduction of NGS. EX1079.¶80, ¶86; EX1050.0001-02; EX1008.0001; EX1014. While NGS used sequencing by synthesis chemistry, NGS devices incorporated modern fabrication and imaging techniques to permit exponentially higher throughput using many parallel reactions. EX1079.¶80; EX1050.0001-02; EX1008.0001. Multiple different NGS platforms were launched in the mid-2000s, but the ones that were most widely adopted incorporated a few common features. EX1079.¶84; EX1009.0003; EX1050.0001-02; EX1060.0009; EX1062.0034-35. Specifically, these NGS platforms used a microscopic solid support, such as a chip or a bead, to which fragments of DNA were attached. EX1079.¶82, ¶84;

EX1050.0002. NGS platforms then performed millions of parallel SBS reactions, which were each measured individually using modern microscopy or other analytical techniques. EX1079.¶84-85. NGS platforms permitted millions of SBS reactions to be conducted and measured in much less space and using far less reagents than before, which led to much greater throughput at a lower cost. EX1079.¶81, ¶85; EX1050.0001-02; EX1071.0002.

The first NGS platform, Roche/454 pyrosequencing (“454”), was introduced in 2004 and became the first commercially available NGS platform in 2005. EX1079.¶83, ¶¶87-91; EX1070.0001-06; EX1009.0002; EX1014.0022. By 2013, several other NGS platforms were available, including, among others, Life Technologies/Ion Torrent “semiconductor sequencing,” EX1079.¶¶98-99; EX1014.0027-28, and Solexa/Illumina “reversible terminator sequencing,” which by 2013 was the dominant NGS platform, EX1079.¶¶92-97; EX1050.0002; EX1014.0023-24; EX1060.0009; EX1062.0034-38; EX1063.0003-04; EX1054.0012-15.

4. Library Preparation And Adaptors for NGS

In 2013, 454, Illumina, and Ion Torrent all attached fragments to be sequenced to a solid support prior to sequencing. EX1079.¶82, ¶84, ¶¶100-103; EX1008 at 0001-02; EX1009.0003. All three platforms did this by annealing the fragments to short DNA strands of known sequence that were fixed to the support.

EX1079.¶¶100-101; EX1008.0001-02; EX1009.0003. In addition, all three platforms required a primer binding site for the SBS reaction primers. EX1079.¶102. In order to add these synthetic sequence adaptors as “handles” to the fragments for sequencing, NGS required a “library preparation” process before sequencing. EX1079.¶103.

During library preparation, DNA is fragmented and adaptors are attached that contain, at minimum, a sequence complementary to the strand on the solid support and a binding site for the SBS primer. EX1079.¶100. To ensure sufficient concentration of sample for NGS, following attachment of the adaptors, the fragments are often amplified in one or more PCR steps. EX1079.¶101-102.

By 2013, scientists recognized that adaptors could be modified to incorporate additional synthetic sequences serving other functions, such as sample indexes for multiplex sequencing and random identifier sequences to distinguish original fragment sequences from PCR copies generated during library preparation. EX1079.¶103.

5. Sample Indexes

For certain NGS applications, the number of fragments in a particular sample was much smaller than the available space on an NGS device. EX1079.¶104. With NGS’s capability of sequencing numerous fragments in a single run, scientists began

to simultaneously sequence multiple samples, by “multiplexing” pooled samples. EX1079.¶¶104-112; EX1073.0001-09; EX1072; EX1055.0001-02; EX1064.0003.

With certain modifications to the adaptors added during library preparation, an NGS platform could simultaneously sequence DNA or cDNA from multiple samples. EX1079.¶¶104-112. By 2013, matching a sequence to its sample was generally accomplished by using synthetic sequences called “sample indexes” or “sample barcodes” unique to a particular sample. EX1079.¶¶110-111; EX1064.0003; EX1055.0002. When pooled samples are sequenced, a particular sequence read can be “demultiplexed” to its original sample using the sample index. EX1079.¶¶104-107. Sample indexes for Illumina sequencers were in use at least as of 2008. EX1079.¶107; EX1079.0001-09. By the priority date, some Illumina devices sequenced the sample index in an SBS reaction independently from the fragment sequence, while others sequenced them as part of the main read. EX1079.¶¶110-111.

NGS platforms output sequencing data in certain file formats. EX1079.¶84, ¶97; EX1060.0009; EX1062.0034-35; EX1061.0080-81. For example, one file format output by an Illumina device is called FASTQ. EX1079.¶84; EX1060.0009; EX1062.0034-35. The files contain data for each sequencing read performed and by 2013, it was customary for FASTQ files to be separated by sample, or “demultiplexed,” using the sample index prior to further analysis. EX1079.¶97;

EX1060.0009; EX1062.0034-38; EX1061.0080-81; EX1063.0003-04;
EX1054.0012-15.

6. Molecular Tags

Because PCR was a standard component of NGS library preparation, scientists realized they needed a way to ascertain whether a particular group of seemingly identical sequencing reads were copies of the same original fragment from the sample, or if there were actually fragments in the original sample with the same sequence. EX1079.¶113. The solution multiple research groups independently discovered was to add sequences, sometimes called “molecular tags,” “unique molecular identifiers,” “molecular barcodes,” or “cyphers” to NGS adaptors prior to amplification so that PCR copies that originated from the same DNA fragment could be identified as duplicates. EX1012; EX1021; EX1022; EX1023; EX1024; EX1025; EX1026; EX1027; EX1028; EX1029; EX1030; EX1031; EX1032, EX1059; EX1079.¶¶118-170.

By 2013, scientists understood that library preparation and subsequent sequencing could introduce errors due to, *inter alia*, polymerase’s natural error rate, or because of nonspecific priming. EX1079.¶109, ¶¶114-117, ¶135, ¶456; EX1025.0001; EX1013.0004. Molecular tags allowed scientists to determine whether a change observed in a sequence (compared to other fragments or a

reference genome) was the result of a mutation in the original fragment or an error introduced during PCR or sequencing. EX1079.¶¶117-118.

Molecular tags also permitted researchers to count the number of original fragments in a sample, e.g., to count the number of copies of a gene in a patient sample. EX1079.¶113. This was of particular interest for cancer research because cancer cells often have too many copies of particular oncogenic genes. EX1079.¶231; EX1074.0001-11.

For these reasons, even prior to widespread adoption of NGS, scientists recognized the benefit of being able to identify PCR copies that originated from the same DNA fragment. EX1079.¶103, ¶113. A 2003 paper proposed random molecular tags added via PCR or ligation “to count the number of individual molecules pertaining to the same molecular species.” EX1059.0001-09; EX1079.¶¶119-120. And as early as 2004, scientists began tagging “individual genomic fragments” prior to PCR amplification with random sequences called “molecular sequence barcodes” to identify “redundant and contaminant sequences.” EX1021.0001-03; EX1079.¶¶121-123. These random sequences allowed scientists “to evaluate cloned sequences for redundancy and contamination,” quantify original sample molecules, and correct “for skewing that can arise from PCR amplification or the cloning” of the sample. EX1021.0002-03; EX1079.¶¶121-123. This method

served “as a highly accurate method for positive identification of desired sequences.”

EX1021.0002; EX1079.¶¶121-123.

The prior art also taught how to modify the length of the random sequence to account for the number of fragments in the original sample. EX1079.¶128. Because there are four different nucleotides that can be incorporated into any one “spot” in a polynucleotide, there are 4^n possibilities for uniquely labeling original fragments where “n” is the number of nucleotides in the random sequence. EX1022.0004; EX1079.¶128. The prior art made clear that as long as there were a sufficient number of tags compared to the number of original fragments, each fragment could be made unique by combining the molecular tag and fragment sequence. EX1079.¶¶125-129, ¶¶143-145; EX1022.0004; EX1027.0002.

Once Illumina released its HiSeq 2000 instrument in 2010, greatly increasing the availability of NGS, the field exploded. EX1079.¶86, ¶89, ¶129. Scientists simultaneously, and frequently, began publishing papers on the use of random sequence tags to identify duplicate copies created by PCR and attribute observed sequences to original fragments:

- In 2010, Hiatt proposed randomized 20-nucleotide tags in adaptor-ligated fragments “to identify molecules that are clonally derived” from the same fragment following PCR. EX1023.0001-04; EX1079.¶¶130-132.
- In 2010, König incorporated random three-nucleotide tags in cDNA during

reverse transcription to “discriminate between unique cDNA products and PCR duplicates.” EX1024.0007; EX1079.¶¶133-134.

- In 2011, Kinde added 12-14-nucleotide tags via PCR to identify PCR duplicates, enhance the accuracy of NGS, and detect rare mutations. EX1025.0001, 0004-06; EX1079.¶¶135-138.
- In 2011, Casbon ligated adaptors with partially random 12-nucleotide tags to fragments prior to PCR. EX1026.0001-06. The tags were “used to determine whether a putative variant is associated with a single template molecule or, alternatively, multiple template molecules and hence the probability that it derives from a polymerase error or true variant.” EX1026.0001; EX1079.¶¶139-142.
- In 2011, Fu ligated adaptors with 14-nucleotide tags to fragments prior to PCR to count the absolute number of original molecules in a sample. EX1027.0001-02, 0004-05; EX1079.¶¶143-145.
- In 2011, Jabara added 8-nucleotide tags to cDNA libraries of viral RNA to “directly remove error, correct for PCR resampling, and capture the fluctuation of minor variants in the viral population within a host.” EX1028.0002; EX1079.¶¶146-149.
- In 2011, Kivioja described a method of using random tags in combination with the sequences of the fragments to which they were attached as a

- “unique molecular identifier” associated with a particular original fragment to enable removal of copies from sequencing data and counting of original fragments. EX1012.0001-03, 0005; EX1079.¶¶150-159.
- In 2011, Tollervey used König’s protocol of random molecular tags prior to PCR to identify “3.7 million reads representing unique cDNA molecules.” EX1029.0002; EX1079.¶¶160-161.
 - In 2012, Shiroguchi ligated adaptors containing 20-nucleotide pre-defined tags to cDNA prior to PCR in order to count the number of fragments in the original sample. EX1030.0001-05; EX1079.¶¶162-163.
 - In 2012, Schmitt reported a method of ligating “standard Illumina sequencing adapters” containing 12-nucleotide tags to fragments to detect and remove PCR errors and thereby discover rare genetic variants. EX1031.0001-06; EX1079.¶¶164-169.
 - In 2013, Bielas filed a patent application disclosing a method of ligating adaptors with random molecular tags prior to PCR to differentiate “true mutations” in the original fragments from PCR artifacts. EX1013.0027, 0032; EX1079.¶¶455-486.

B. Petitioner’s Anchored Multiplex PCR Technology

Petitioner markets and sells NGS library preparation kits for research use under the Archer brand based on a technology called anchored multiplex PCR or

“AMP.” These products are widely used by oncologists to selectively enrich DNA and RNA samples for certain target genes prior to NGS.

Petitioner’s AMP products are based on technology developed by researchers at Massachusetts General Hospital (“MGH”). In 2012 and 2013, MGH pathologists John Iafrate, Long Phi Le, and Zongli Zheng filed patent applications directed to methods of using AMP for NGS (“the MGH method”). EX1011; EX1048; EX1049. The MGH method was designed to detect unknown mutations adjacent to known sequences, which are of particular interest to cancer researchers and doctors because certain types of unexpected gene fusions and rearrangements were known tumor biomarkers. EX1011; EX1015.0001. The MGH inventors further elaborated on that work in a 2014 *Nature Medicine* paper describing using the AMP method to detect novel cancer gene fusions. EX1015; EX1079.¶¶176-182.

MGH’s nonprovisional patent application, EX1011 (Iafrate), on this process predates the priority date of the ’399 patent and forms part of the basis of Ground I in this petition. *Infra* §IV.

II. THE ’399 PATENT

The ’399 patent claims priority to a provisional application filed November 13, 2013, after the MGH inventors filed their patent on the AMP technology. The ’399 patent’s claims are directed to a “method for detecting a duplicate sequencing

read from a population of sample sequencing reads.” EX1003 at 25:37-38. Claim 1 recites four steps.

1. Adaptors are ligated to the 5' end of a plurality of nucleic acid fragments, wherein each adaptor comprises (1) “an indexing primer binding site;” (2) “an indexing site;” (3) “an identifier site;” and (4) “a target sequence primer binding site.” *Id.* at 25:42-46.
2. The adaptor-ligated products are amplified by PCR. *Id.* at 25:47-48.
3. The adaptor-ligated products are sequenced. *Id.* at 25:49-51.
4. The resulting reads are used in a data analysis step in which duplicate reads are identified by “the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads.” *Id.* at 25:52-55.

A. Prosecution History

The '399 patent issued from an application filed by Tecan's predecessor-in-interest NuGEN Technologies, Inc. EX1018.0063. Initially, the Examiner rejected the claims as obvious over Samuels (EX1033) and McCloskey (EX1022). EX1018.0430-33. The Examiner explained that it “would have been *prima facie* obvious” to the POSA to use an adaptor with sample indexes and molecular tags “to eliminate PCR-originating artefacts.” EX1018.0432-33.

In response, the Applicant conceded that McCloskey “disclose[d] a method of identifying and removing duplicate reads through incorporating an adaptor comprising a batch stamp, a barcode, a primer-binding site for PCR, and extra bases that serve to minimize nonspecific annealing, wherein the barcodes comprise 7 random nucleotides,” but argued that it did not render obvious an identifier site of “at least 8 nucleotides” and did not teach the target sequence primer binding site. EX1018.0767-68.

The Examiner again rejected the claims as obvious over Samuels and McCloskey. EX1018.0775-78, 0780-84. Rejecting the “7-vs.-8” argument, the Examiner stated that Samuels taught “unique N-mers which contain barcodes 2-21 nucleotides in length” and “barcodes contain[ing] 4-20 nucleotides which uniquely encode library members.” EX1018.0776-78.

After an interview, EX1018.0795, the applicant argued that even if Samuels taught “detection of PCR-introduced errors in sequencing,” it did not teach, among other things, “identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads.” EX1018.0797-98 (emphasis original). Similarly, the applicant argued that while McCloskey taught “a method of identifying redundant sequences,” it did not do so via a “method of ‘identifying a duplicate sequencing read as the sequencing read comprising the same identifier site”

and nucleic acid fragment.” EX1018.0799 (emphasis original). The applicant argued the claimed method used “the identifier site and the sequence of the fragment that is amplified . . . in combination to discern duplication.” EX1018.0799. In summary, having conceded the prior art taught the use of adaptors containing identifier sites to de-duplicate, the applicant distinguished the prior art based on (1) the length of the identifier site and (2) the use of both the identifier and the fragment sequence together to de-duplicate.

Once again, the Examiner rejected the claims on non-prior art grounds, and did not address obviousness. EX1018.0822-30.

On July 29, 2016, after the applicant’s next response, EX1018.0857-1251, the Examiner raised the obviousness grounds again, rejecting the claims over Samuels and McCloskey, EX1018.1271-77. On August 24, the applicant contacted the Examiner about the non-final rejection mailed on July 29, EX1018.1294, and on August 25, the Examiner noted that the non-final obviousness rejection was issued in error and that it would be withdrawn and replaced with a notice of allowability, EX1018.1291-94. The record does not explain why the Examiner withdrew the obviousness rejections.

None of the three references relied on herein, Iafrate, Kivioja, and Bielas, were before the Examiner.

B. The Person Of Ordinary Skill In The Art

Because the '399 patent is directed to library preparation and data interpretation methods for NGS, the POSA could have had academic training in any of a variety of fields that used NGS, including chemistry, molecular biology, biochemistry, or medicine. EX1079.¶184. The POSA would have a PhD or equivalent training in one of those fields and several years of work experience (or commensurately less education and more work experience). EX1079.¶184. The POSA further would have had specific experience with implementing and designing library preparation methods for Illumina, the leading NGS platform in 2013. EX1079.¶185. This would have included specific experience with, and understanding of, the sequences contained in adaptors for Illumina sequencing at the priority date, and the chemistry used to attach those adaptors to DNA fragments prior to sequencing. EX1079.¶184.

As a professor of systems biology and director of the Sequencing Core at Columbia University, Dr. Sims exemplifies the POSA in this case. EX1079.¶¶4-14. Dr. Sims has been using NGS platforms, including Illumina, and NGS library preparation techniques continuously since the late 2000s. EX1079.¶186. In addition to using NGS regularly in his research, Dr. Sims has published papers and received patents relating to his own innovative NGS techniques. EX1079.¶¶184-186.

C. Claim Construction

Where relevant terms are defined in the patent, *see* EX1003 at 4:33-67, Petitioner applies those definitions. All claims of the '399 patent require the use of an adaptor with certain features that are expressly defined in the specification, as elaborated below. EX1003 at 4:33-67, 25:36-27:27.

1. “indexing site”

The '399 patent defines “indexing site” as a sample index, specifically, “a nucleic acid sequence that acts as an index for multiple polynucleotide samples, thus allowing for the samples to be pooled together into a single sequencing run, which is known as multiplexing.” EX1003 at 4:34-38.

2. “indexing primer binding site”

The '399 patent defines “indexing primer binding site” as the binding site for a primer used to read the indexing site/sample index, specifically, “a nucleotide sequence for binding a primer for an indexing site.” EX1003 at 4:33-34.

The patent discloses that this site can be a conventional Illumina sequence compatible with an Illumina primer for an SBS reaction to read the indexing site/sample index, and the examples all use an Illumina device. EX1003 at 12:36-29, 16:26-22:46. In fact, the only sequence disclosed for the indexing read priming site is a conventional Illumina sequence known in the prior art, EX1003.0020 (SEQ ID No. 2), EX1079.¶202, and the patent otherwise directs the POSA to use

sequences compatible with an Illumina device, EX1003 at 12:36-39, 16:44-52. EX1079.¶202.

3. “identifier site”

The '399 patent defines “identifier site” as a molecular tag attached to fragments prior to amplification, specifically, “a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.” EX1003 at 4:43-45. An “identifier site” “can be designed as a set of sequences, or it can be semi-random, or it can be completely random.” *Id.* at 4:49-51. An “identifier site” can also “be a fixed length, or it can be a variable length.” *Id.* at 4:51-54.

4. “target sequence primer binding site”

The '399 patent defines “target sequence primer binding site” as a binding site for a primer used to read the fragment sequence, specifically, a “nucleotide sequence for binding a primer for a target sequence.” EX1003 at 4:62-65.

The '399 patent expressly discloses that this site can be a standard Illumina sequence compatible with an Illumina primer for an SBS reaction to read the DNA fragment. EX1003 at 16:48-51; EX1003.0020 (SEQ ID No. 3). In fact, the only sequence disclosed for the target sequence primer site is a conventional Illumina sequence known in the prior art, EX1003.0020; EX1079.¶201, and the patent

otherwise directs the POSA to use sequences compatible with an Illumina device, EX1003 at 12:36-29, 16:44-52.

**III. IDENTIFICATION OF THE CHALLENGE (37 C.F.R. §42.104(b))
AND STATEMENT OF PRECISE RELIEF REQUESTED (37 C.F.R.
§42.22(a))**

Petitioner respectfully requests institution of IPR and cancellation of claims 1-3, 5-11, and 14-17, for the reasons in the table below and explained further below. In support of the proposed grounds, this Petition includes the declaration of Dr. Peter Sims, EX1079, and is further supported by the references cited herein.

Ground	References	Basis	Claims Challenged
1	Iafrate, EX1011, and Kivioja, EX1012	§103	1-3, 5-11, 14-17
2	Bielas, EX1013	§102	1-2, 5-11, 15-17
3	Bielas	§103	1-3, 5-11, 14-17

A. Priority Date

Petitioner assumes the earliest claimed priority date of November 13, 2013, in this Petition only, without prejudice to its right to challenge that priority date in other proceedings.

B. The References In the Grounds Are Prior Art

Iafrate was filed on March 11, 2013, and published on November 14, 2013. Iafrate names different inventors and is §102(a)(2) prior art. EX1079.¶205.

Kivioja published online on November 20, 2011 and included supplemental materials available on the journal's website. EX1012.0001, 0003. The online

supplemental material was made available contemporaneously with the article and is cited extensively in the article such that the POSA would have considered them one reference. EX1079.¶¶206-207. To the extent the article and supplemental material are not a single reference, the supplemental material is incorporated by reference. *See Arbutus Biopharma Corp. v. ModernaTX, Inc.*, 65 F.4th 656, 662-63 (Fed. Cir. 2023); *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1283-84 (Fed. Cir. 2000). Kivioja is §102(a)(1) prior art.

Bielas, published on August 22, 2013, EX1013.0001, is prior art under at least §102(a)(1).

IV. GROUND I: OBVIOUSNESS OVER IAFRATE AND KIVIOJA

Iafrate and Kivioja render claims 1-3, 5-11, and 14-17 obvious. Iafrate teaches a method of NGS library preparation using an adaptor with all but one of the features recited in claim 1 of the '399 patent. EX1011.0011; EX1079.¶¶208-224. Iafrate's method would have been attractive to the POSA because it disclosed benefits for specific research applications, e.g., oncology. EX1079.¶¶209-210, 225-227, 233-234. Kivioja discloses how to enhance the accuracy of Iafrate's method by adding the remaining feature—a random molecular tag—and teaches that random molecular tags are used in combination with a fragment sequence as a “unique molecular identifier” (“UMI”) for the identification of duplicate sequencing reads. EX1012.0001, 0005, 0014. Together, Iafrate and Kivioja teach the remainder of the

conventional steps recited in claim 1 and the limitations of claims 2-3, 5-11, and 14-17. The POSA would have been motivated to combine the teachings of Iafrate and Kivioja, and would have had a reasonable expectation of success in doing so, given the interchangeability of the standard Illumina sequences used in both, the demonstrated benefits of Iafrate's methods, and the broad applicability of Kivioja's UMI method. EX1079.¶¶208-253.

A. The POSA Would Have Been Motivated To Use Iafrate's Method And Adaptor For NGS Library Preparation.

Iafrate teaches a method of NGS library preparation to selectively enrich a sequence of interest prior to sequencing, and allows determination of sequences adjacent to a known sequence of interest, such as a cancer gene. EX1011.0012, 0022-23, 0028-30; EX1079.¶¶208-210, 225-228. The method uses a customized Illumina adaptor that incorporates all but one of the features recited in claim 1 of the '399 patent. Specifically, the Iafrate adaptor includes (i) an indexing primer binding site (referred to as a "barcode sequencing primer binding site") (**blue**), (ii) an indexing site/sample index (referred to as a "barcode") (**orange**), and (iii) a target sequence primer binding site (referred to as a "sequencing primer binding site") (**green**).

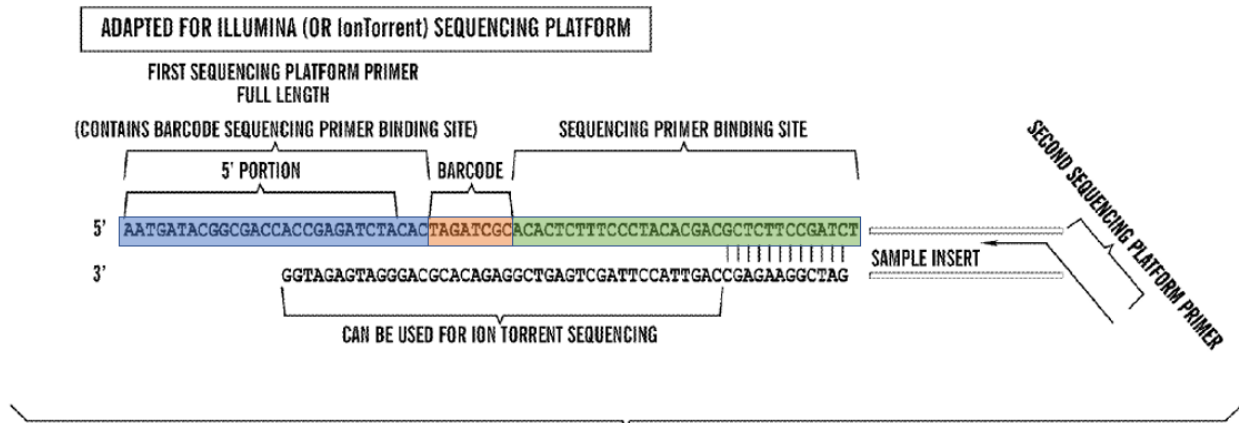


FIG. 9

EX1079.¶211; EX1011.0011, 0013.

Consistent with the general industry trend towards Illumina by 2013, Iafrate teaches that Illumina is a preferred NGS platform, particularly when “higher accuracy” is required. EX1011.0029; EX1079.¶¶ 212, 215. To ensure compatibility with Illumina, Iafrate’s adaptors incorporate the conventional sequences (annotated in the figure above) taught in the Illumina literature for binding to the solid support and allowing SBS primers to bind. EX1079.¶¶211-212, 214.

With respect to the “indexing site,” EX1003 at 25:43, or the “barcode” in Figure 9, EX1011.0011, Iafrate teaches that incorporating the sample index “allow[s] for multiplex sample pooling” because each sample is “ligated with unique barcode adapters,” EX1011.0029. Based on this disclosure and consistent with the general use of sample indexes in 2013, the POSA would have known that Iafrate’s sample index would have been “unique amongst a subset of the plurality of nucleic

acid fragments and [would have been] an index for multiple polynucleotides,” EX1003 at 25:56-58. EX1079.¶¶213-218.

Beyond the adaptor’s features, Iafrate teaches each of claim 1’s library preparation and sequencing steps. As in claim 1, step (a), Iafrate ligated the adaptors to the 5’ end of the fragments in one or more samples, EX1011.0023, 0051, as shown in Figure 9 above, EX1079.¶¶219-220; EX1011.0011.

As in claim 1, step (b), Iafrate amplified the adaptor-ligated nucleic acid fragments, as would have been routine during NGS sample preparation. EX1011.0051; EX1079.¶221.

As in claim 1, step (c), Iafrate then sequenced the fragments using NGS to “generate a population of sequencing reads.” EX1011.0051, EX1079.¶¶222-223.

In sum, Iafrate teaches nearly every element recited in claim 1, except for the use of molecular tags. EX1079.¶¶208-224.

B. The POSA Would Have Been Motivated To Modify Iafrate’s Method To Incorporate Molecular Tags And Use UMIs As Taught By Kivioja.

Iafrate explains that its method is particularly suited for cancer research and diagnostics. EX1011.0013, 0023-25, 0029; EX1079.¶¶225-228. By 2013, scientists knew the development of cancer was associated with mutations like translocations and gene fusions where a known gene appears at an unexpected place in the genome. EX1011.0023-25; EX1079.¶226. Iafrate’s method facilitates sequencing these types

of mutations where an unknown sequence appears adjacent to a known gene. EX1011.0012, 0029-30; EX1079.¶¶225-227. By selectively amplifying target gene sequences prior to NGS, the Iafrate method greatly increases the number of copies of fragments from a particular gene of interest and thus the chance of sequencing a particular point mutation in that gene. EX1079.¶¶225-227. This permits more sensitive detection of low-frequency mutations, “a critical feature for evaluating somatic mutations in cancer.” EX1011.0029. The process also “enables wider dynamic range for allele counting (in gene expression and copy number assessment),” which is important to cancer research. EX1011.0029; EX1079.¶¶210, 225-228, 234; EX1074.0001-11. Because of the principal application of the Iafrate method to cancer-related applications, the POSA would have been motivated to enhance its accuracy, both in terms of counting fragments in the original sample and ensuring original fragments were correctly sequenced. EX1079.¶¶229-233.

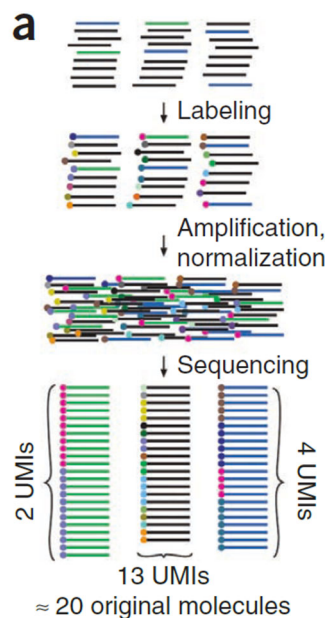
The Iafrate method can include as many as 40 rounds of PCR. EX.1011.0014-15, 0019, 0027; EX1079.¶229. Because each round of PCR can cause errors in a particular fragment that can propagate in later rounds of PCR, PCR-induced errors can confound sequencing results by making it difficult to determine if a particular mutation was present in the original sample. EX1079.¶¶230-231. PCR also confounds counting the original number of fragments, which have been amplified into copies. EX1079.¶¶230-232. Accordingly, the POSA would have been

motivated to modify Iafrate's method to permit accurate fragment counting and mitigate PCR-induced error. EX1079.¶¶229-234.

The prior art taught a method to improve NGS accuracy and mitigate PCR error by using the only feature recited in the '399 patent that Iafrate did not include—a random molecular tag. EX1079.¶235; EX1022.0006; EX1026.0001-07; EX1028.0001-06; EX1030.0001-05; EX1031.0005; *supra* §I.A.6. Specifically, Kivioja disclosed a way to “improve the accuracy of almost any next-generation sequencing method.” EX1012.0001. Kivioja explained that PCR prevented accurate counting and “errors introduced during amplification” hindered interpretation of sequencing data. EX1012.0002; EX1079.¶236. Kivioja solved this problem by adding a random molecular tag sequence prior to amplification and sequencing, and using that tag sequence in combination with the fragment sequence to associate observed sequences with a particular original fragment. EX1012.0001, 0005; EX1079.¶¶237-240.

Kivioja showed its method diagrammatically in Figure 1(a), reproduced below. EX1012.0001; EX1079.¶237. Kivioja fragmented a sample and then labeled the fragments with random molecular tags. EX1012.0001; EX1079.¶238. After amplification and sequencing, Kivioja taught that duplicate reads with the same unique label-fragment combination corresponded to a single “UMI” or unique original sequence. EX1012.0001; EX1079.¶239. As shown in Figure 1(a), Kivioja

collapsed the amplification products to 20 original molecules, i.e., they identified duplicate molecules that were the result of PCR and associated them to a particular original labeled fragment. EX1012.0001; EX1079.¶239. Thus, in Figure 1(a), Kivioja disclosed generally the steps of '399 claim 1: (a) attaching an adaptor with a molecular tag to the 5' end of a DNA fragment, (b) amplifying the tagged fragments, (c) sequencing them, and (d) identifying duplicate sequencing reads based on the UMI, i.e., the unique concatenation of the tag and fragment sequences. EX1012.0001, 0004-05.



Kivioja also provided several proof of concept experiments. Like Iafrate, Kivioja disclosed specific methods for Illumina NGS library preparation, including one experiment using mRNA from *Drosophila*. EX1012.0002-05. In that experiment, the adaptor contained all of the features in the '399 patent's adaptor;

specifically, it contained the same Illumina universal target sequence primer binding site found in Iafrate (**green**), a random sequence UMI (**yellow**), and an indexing site (**orange**):

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

Oligomer	Sequence (5'-3')
Oligo-dT adapter	CAAGCAGAAGACGGCATACGAGCTCTTCCGATCTTTTTTTTTTTTTTTTTTTVN
5'-adapter	ACACTCTTCCCTACACGACGCTCTTCCGATCT(NNN)dU(NNNN)dU(NNN)[GACTT]rGrGrGrG
Paired-end compatible oligo-dT adapter	CTCGGCATTCTGCTGAACCGCTCTTCCGATCTTTTTTTTTTTTTTTTTTTVN

EX1079.¶241-242; EX1012.0003-05, 0014. Kivioja did not specify a separate sample index primer binding site because the sample index, molecular tag, and fragment were all sequenced together on their Illumina device. EX1079.¶243; EX1012.0004-05. The green sequence in the Kivioja adaptor is both the target sequence primer binding site and the index primer binding site. EX1079.¶243.

Thus, Kivioja taught an adaptor with all of the features of the adaptor recited in claim 1, step (a). EX1079.¶242-243. Because Kivioja exemplified the UMI method in RNA, Kivioja used a reaction called an RNA template switch to attach the adaptor to the 5' end of the fragments, rather than a ligation reaction. EX1012.0003-04. However, Kivioja recognized, and the POSA would have understood, that the template switch could only be used with RNA. EX1079.¶244. Kivioja separately disclosed that for applications to DNA or cDNA, adaptors could

be ligated to the DNA fragments. EX1012.0001-03; EX1079.¶244-245. Accordingly, Kivioja expressly contemplated adding its adaptors to the 5' end of DNA fragments by ligation. EX1012.0001-03; EX1079.¶¶244-246. And it would have been obvious to the POSA to ligate the adaptors for an application like Iafrate's that taught a benefit to ligation, e.g., for introducing the anchor sequence needed for the anchored PCR used in Iafrate (but was not required for Kivioja's methods that "shotgun" sequenced all fragments). EX1079.¶¶210-211, 227, 242; EX1012.0001-03.

Kivioja further taught steps (b) and (c) recited in '399 claim 1— amplifying and sequencing the adaptor-ligated fragments. EX1012.0004; EX1079.¶247.

Finally, Kivioja also taught step (d) recited in '399 claim 1 of identifying a duplicate sequencing read comprising the same identifier site and nucleic acid fragment. Kivioja explained that after sequencing, "the mapped reads with the same gene, position, and label were collected to one UMI and the number of such reads was recorded as the copy number of that UMI." EX1012.0005. In other words, Kivioja explained that the combination of the fragment sequences (mapped against known *Drosophila* genes) and the random label sequence were used to determine whether particular sequence reads were unique or PCR duplicates. EX1079.¶248. Kivioja then collected sequence reads with the same random label and fragment sequence to a single UMI, i.e., unique fragment. EX1079.¶¶238-248.

In summary, Kivioja teaches every element of the '399 claims, except it attaches the adaptor using a template switch instead of ligation. But it would have been obvious to modify the Kivioja method for applications starting from DNA or cDNA samples to use adaptor ligation instead of the template switch. EX1079.¶¶225-249.

The POSA would have been motivated to combine Iafrate and Kivioja to practice the claims of the '399 patent. EX1079.¶¶225-249. Iafrate taught a method of target enrichment that promised to unlock understanding of genetic sequences that influence cancer using Illumina's NGS platform, but it required multiple rounds of PCR and demanded accuracy. EX1079.¶¶225-234. Kivioja taught a method of mitigating PCR errors and improving NGS accuracy also on Illumina platforms by using a random molecular tag. To realize the Iafrate method's full potential, the POSA would have been motivated to incorporate the Kivioja molecular tag into the Iafrate adaptor. EX1079.¶¶225-249.

C. The POSA Would Have Had a Reasonable Expectation Of Success In Combining Iafrate and Kivioja to Arrive At The Claimed Method.

The POSA would have had a reasonable expectation of success in modifying Iafrate's method by incorporating Kivioja's teachings. The POSA would have understood that Iafrate's method was "adaptable for any [] [NGS] platform." EX1011.0029; EX1079.¶250. And the POSA would have had further confidence

combining the two methods because both Iafrate and Kivioja taught Illumina as a preferred platform. EX1079.¶250. Both methods relied on universal Illumina sequences and were designed for implementation with Illumina's standard devices and reagents. EX1079.¶250. In fact, the Iafrate adaptor and the Kivioja adaptor incorporated the same universal Illumina sequence, as shown below in green. And Iafrate and Kivioja both taught the other conventional steps recited in the '399 claims, including amplification and sequencing. Based on similarity between the Kivioja and Iafrate adaptors, and the POSA's understanding that NGS methods involved generally interchangeable adaptor sequences, the POSA would have readily understood to insert the Kivioja random molecular tag into the analogous position in the Iafrate adaptor—e.g., on the 3' side of the sequencing primer binding site (annotated with a star below)—and would have had the molecular tools to do so. EX1079.¶¶250-253.

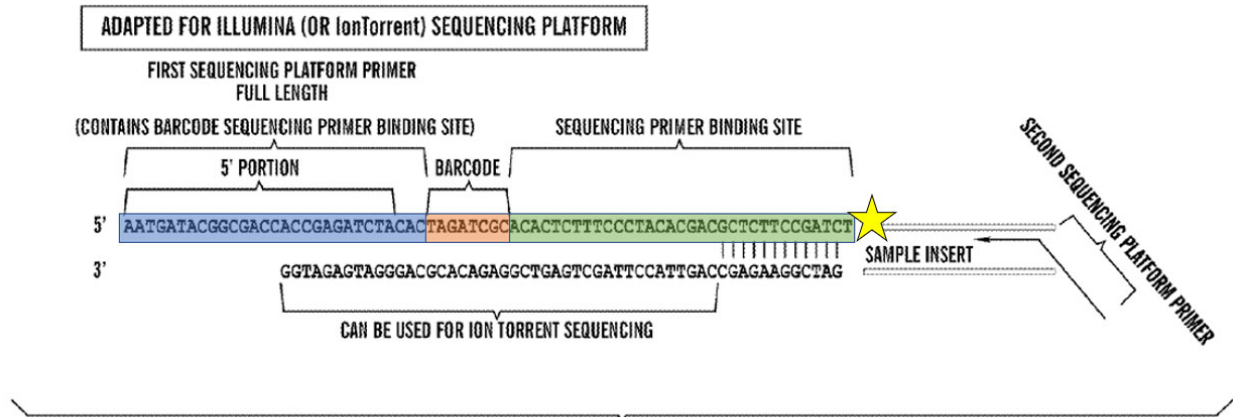


FIG. 9

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

EX1079.¶250.

Given the POSA's understanding that NGS library preparation required attachment of sequences compatible with the NGS device and the fact that both Iafrate and Kivioja exemplified their methods using Illumina, the POSA would have had a reasonable expectation of success in combining the two methods.

EX1079.¶¶250-253.

D. Claims 1-3, 5-11, And 14-17 Would Have Been Obvious Over Iafrate and Kivioja.

1. Claim 1

Based on Iafrate and Kivioja, the POSA would have been motivated to practice claim 1's method. In short—Iafrate disclosed a method of ligating DNA fragments to an adaptor with all of the features except the random molecular tag and

then amplifying and sequencing those ligated fragments on an Illumina NGS device. EX1079.¶¶208-224. Kivioja disclosed a method of using adaptors with all of the recited features (but attached them via template switch instead of ligation), amplifying and sequencing fragments on an Illumina NGS device, and then using the combination of the molecular tag and fragment sequences to differentiate between original fragments and PCR copies. EX1079.¶¶236-248.

All of the other features of claim 1 are also present in Iafrate and/or Kivioja and would have been obvious over those references. In its preamble, claim 1 recites “a method for detecting a duplicate sequencing read.” EX1003 at 25:37-38. To the extent the preamble is limiting and entitled to patentable weight, Kivioja teaches this element in the method of collapsing labeled fragments to a single UMI based on the tag and fragment sequence. EX1012.0001, 0005.

Kivioja expressly contemplated duplicate identification as part of their methods. EX1012.0005; EX1079.¶¶236-240. Kivioja taught that one of the possible applications of the method was for digital karyotyping. EX1012.0001-02. A karyotype is a common method of diagnosis that involves counting the chromosomes in a cell. EX1079.¶257. Kivioja explains that the number of original fragments corresponding to the original chromosomes can be determined by associating all observed sequences with a particular original fragment using the UMI. EX1012.0001-02; EX1079.¶258. Kivioja then exemplifies this by using its

mRNA sequencing method to demonstrate that “one can reproducibly detect the number of molecules after different numbers of PCR cycles without normalization.” EX1012.0002-03; EX1079.¶¶258-259. This method necessarily involves the determination of whether particular observed sequences from the Illumina run were original fragments or PCR copies. EX1079.¶260. Thus while Kivioja does not use the word “duplicate,” the POSA would have recognized that it teaches a method of detecting and removing duplicates from sequencing information. *Id.*

Additionally, claim 1 requires “identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment as another sequencing read.” EX1003 at 25:53-55. This was one of the two bases (the other being the identifier length) on which the Applicant distinguished the prior art. *Supra* §II.A. But Kivioja, which was not before the Examiner, discloses this limitation, as shown in Figure 1(a), where sequences are collapsed to UMIs based on the colored label sequence and the colored fragment sequence together. EX1012.0001; EX1079.¶¶256-260, 274-278. In addition, in its mRNA example, Kivioja describes identifying a duplicate sequencing read as a sequencing read “with the same gene, position and label.” EX1012.0005; EX1079.¶276. For each “gene” of interest, to identify a read with the same “position” Kivioja mapped the fragment portion of the read to known *Drosophila* genes, meaning Kivioja necessarily used the fragment sequence as part of the information used to determine a duplicate.

EX1079.¶276; EX1012.0005. Kivioja combined that mapped position of the fragment with the label sequence. EX1012.0005; EX1079.¶276. Thus, Kivioja discloses identifying as duplicates sequencing reads with the same identifier site (the “label”) and nucleic acid fragment (the “gene” and “position”). EX1079.¶¶274-278.

Additionally, claim 1 requires the identifier site to be “variable in sequence content in the plurality of adapters.” EX1003 at 25:59-61. Consistent with many other prior art references, *supra* §I.A.6, Kivioja taught the use of a random molecular tag that would be variable in sequence content in the adapters. EX1012.0001, 0014; EX1079.¶¶235-236, 261, 282.

Claim 1 also requires the identifier site to be “between 1 and 8 nucleotides.” EX1003 at 25:44-45. This was the other basis on which the Applicant distinguished the prior art during prosecution. But this limitation is rendered obvious by Kivioja. Although Kivioja used a 10-nucleotide molecular tag, Kivioja provided a specific motivation to use a shorter molecular tag, particularly for an application like Iafrate’s. Because the Illumina devices available in 2013 were only able to read fragments up to a certain limited length, the POSA would have been motivated to keep the length of the tag to a minimum in order to maximize the length of fragment sequence that could be read. EX1079.¶263. In Kivioja, the long molecular tag provided “approximately one million random labels” that “were not exhausted in the experiments.” EX1012.0005. In the Iafrate method, in which there would be a

relatively small number of original fragments of the genes of interest (compared to Kivioja's method of sequencing the entire *Drosophila* transcriptome), the POSA would have recognized that a short molecular tag could be used while still ensuring an excess of molecular tags compared to expected unique fragments. EX1079.¶¶262-271. Therefore, the data in Kivioja would have provided a specific motivation to use a shorter molecular tag, and thereby arrive at a tag from 1 to 8 nucleotides in length. EX1079.¶269.

Furthermore, Tecan has never articulated, in the '399 patent or during prosecution, any unexpected properties or criticality of the specific length of the identifier site, let alone of the entire range of 1 to 8 nucleotides, or otherwise suggested that "the general conditions of the claim are not disclosed in the prior art." *See E.I. DuPont v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). Thus, it cannot be the basis for non-obviousness. The length of the molecular tag is a paradigmatic result-effective variable. Optimizing it is simply a function of the known relationship between the number of resulting tags (i.e., 4^n) and the expected number of unique fragments in a particular sample (which is a product of the amount of input DNA and the method of fragmentation used). EX1079.¶¶264-266; EX1022.0004; EX1027.0002. *See Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1348-49 (Fed. Cir. 2024); *In re Applied Materials*, 692 F.3d 1289, 1295-96 (Fed. Cir. 2012); *In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980).

It would have been an obvious design choice for the POSA to use a random sequence of this length. Given the teachings in Kivioja and the prior art that the tag length could be varied based on the expected number of fragments, EX1079.¶¶262-271; EX1012.0005; EX1022.0004; EX1026.0005, the tag length was a “predictable variation” of the methods of Kivioja and would have “amount[ed] to a design choice.” *See Uber Tech., Inc. v. One, Inc.*, 957 F.3d 1334, 1340 (Fed. Cir. 2020); *In re Brandt*, 886 F.3d 1171, 1174, 1175-78 (Fed. Cir. 2018); *Vicor Corp. v. SynQor, Inc.*, 869 F.3d 1309, 1326 (Fed. Cir. 2017).

For the reasons discussed above, Kivioja and Iafrate render the claimed method obvious and the POSA would have been motivated to practice that method with a reasonable expectation of success. EX1079.¶¶208-283.

2. Claim 2

Claim 2 depends from claim 1 and adds that “the method further comprises removing from the population of sequence reads the sequencing read with a duplicate identifier site and target sequence.” EX1003 at 25:62-65. Iafrate and Kivioja also render this claim obvious. EX1079.¶¶284-285. Kivioja teaches identifying a duplicate read based on the tag and fragment sequence, *supra* §IV.B, §IV.D.1; EX1079.¶¶236-248, and further teaches that those duplicate reads are “collected to one UMI” and treated as a single original fragment. EX1012.0005, 0001. The POSA, moreover, would have understood that Kivioja’s method of

counting the original number of molecules in a sample requires deduplication as a predicate step to counting the original fragments. EX1079.¶¶236-239, 284-285.

3. Claim 3

Claim 3 depends from claim 1 and adds that the identifier site is “sequenced with” the indexing site. EX1003 at 25:66-67. Iafrate and Kivioja also render this claim obvious. In Kivioja, the identifier site/molecular tag and indexing site/sample index are both located to the 3’ side of the sequencing primer site and thus would be sequenced in a single SBS reaction. EX1079.¶242. In addition, the POSA would have recognized that the relative position of the adaptor elements was a design choice based on the particular NGS device and application, and it would have been obvious to re-position the tag and sample index in the adaptor to read the identifier site and index site in the same or different sequencing reads as appropriate. EX1079.¶¶171-175, ¶¶287-292.

4. Claim 5

Claim 5 depends from claim 1 and adds that the fragments are “generated from more than one sample.” EX1003 at 26:41-42. This method would have been obvious based on Iafrate and Kivioja’s express disclosure of multiplexing. EX1011.0029; EX1012.0004-05, 0014; EX1079.¶¶293-296.

5. Claim 6

Claim 6 depends from claim 5 and adds that each sample has a unique sample index. EX1003 at 26:43-45. This limitation also would have been obvious based

on Iafrate and Kivioja's disclosure of the use of unique sample indexes for multiplexing, consistent with standard use of sample indexes for Illumina sequencing in 2013. EX1011.0029; EX1012.0004-05, 0014; EX1079.¶¶297-300.

6. Claim 7

Claim 7 depends from claim 6 and adds that sequencing reads are "separated based on the indexing site." EX1003 at 26:46-47. This method would have been obvious based on Iafrate and Kivioja's disclosure of sample indexes, the purpose of which is to distinguish sequence reads based on that sample index sequence. EX1079.¶302. Moreover, the POSA would have recognized that standard demultiplexing processes on Illumina devices in 2013 would have resulted in exporting sequencing reads in data files separated by sample. EX1079.¶¶301-304.

7. Claim 8

Claim 8 depends from claim 7 and adds that the separation of sequencing reads happens prior to step (d) of claim 1. EX1003 at 26:48-49. The POSA would have recognized that claim 8's order of operations was standard, and thus obvious, for the Illumina devices used in Kivioja and Iafrate that demultiplexed samples prior to data export. EX1079.¶¶305-307.

8. Claim 9

Claim 9 depends from claim 1 and specifies the fragments as DNA and/or RNA. EX1003 at 26:50-52. Claim 9 would have been obvious over Iafrate and Kivioja which both teach DNA or RNA as an input. EX1079.¶¶308-310.

9. Claim 10

Claim 10 depends from claim 9 and specifies the fragments as either genomic DNA or cDNA. EX1003 at 26:53-54. This would have been obvious over Iafrate and Kivioja which both teach using these nucleic acids as inputs. EX1079.¶¶311-313; EX1011.0015, 0028; EX1012.0001-04.

10. Claim 11

Claim 11 depends from claim 1 and recites a sample index of 2-8 nucleotides. EX1003 at 26:55-56. Iafrate (8 nucleotides) and Kivioja (5 nucleotides) each taught sample indexes within this range. EX1011.0011; EX1012.0014; EX1079.¶¶314-318.

11. Claim 14

Claim 14 depends from claim 1 and recites the identifier site is 8 nucleotides. EX1003 at 26:61-62. For the reasons discussed above in connection with claim 1's range of 1-8 nucleotides, *supra* §§IV.B, IV.D.1, the POSA would have been motivated to shorten Kivioja's 10 nucleotide tag, including to an 8 nucleotide tag, when adapting Kivioja's method to Iafrate's lower concentration of target fragments, EX1079.¶¶319-327. Moreover, the '399 patent does not disclose any unexpected properties or criticality of an 8-nucleotide identifier, and the POSA would have recognized that selection of the tag length was the product of routine optimization based on the known relationship between the tag length and resulting number of tags (i.e., 4^n), and the expected number of unique fragments in a sample. EX1079.¶¶264-

266. *See Pfizer*, 94 F.4th at 1348-49. The choice of an 8 nucleotide identifier site instead of the 10 nucleotide site used in Kivioja would have been a design choice for the POSA. EX1079.¶¶319-327. *See Uber*, 957 F.3d at 1340. And the POSA would have had a reasonable expectation of success in practicing the methods with an identifier of 8 nucleotides. EX1079.¶326.

12. Claim 15

Claim 15 depends from claim 1 and recites that the indexing primer binding site is “universal.” EX1003 at 26:63-64. The ’399 patent defines a universal primer as “a primer that can be used for amplifying a number of different sequences.” EX1003 at 5:57-58. This claim is obvious based on Iafrate and Kivioja’s use of the same Illumina indexing primer site in all adaptors. *Supra* §IV.A-C; EX1011.0011; EX1012.0014; EX1079.¶¶328-333.

13. Claim 16

Claim 16 depends from claim 1 and recites that the target sequence primer binding site is “universal.” EX1003 at 26:65-67. This claim is obvious based on Iafrate and Kivioja’s use of the same Illumina sequencing primer site in all adaptors. *Supra* §IV.A-C; EX1011.0011; EX1012.0014; EX1079.¶¶334-338.

14. Claim 17

Claim 17 depends from claim 6 and further adds the step of separating fragments or reads based on the indexing site. EX1003 at 27:1-3. This method would have been obvious for the same reason as claim 6 itself, *supra* §IV.D.5, and

claim 7, which is almost identical to claim 17, *supra* §IV.D.6, and the POSA would have recognized such demultiplexing is a standard part of Illumina workflows, EX1079.¶¶339-342.

E. No Secondary Considerations Support Nonobviousness.

IDT is unaware of any relevant secondary considerations of nonobviousness. Should Tecan present evidence of any secondary considerations following institution, IDT reserves the right to respond in its reply.

V. GROUND II: ANTICIPATION OVER BIELAS

A. Bielas Disclosed Methods With All Of The Elements Claimed In The '399 Patent.

Bielas is a published patent application that, like Kivioja, teaches the benefits of using random molecular tags, which Bielas calls “Cyphers,” in NGS library preparation. EX1013. Like Kivioja, Bielas uses Cyphers to identify PCR copies of original fragments after Illumina sequencing. EX1013.0026-32. Examples 1 and 3 of Bielas disclose all of the elements of Claims 1-2, 5-11, and 15-17, as arranged in those claims, and thus anticipate them. EX1013.0026-32; EX1079.¶¶456-486.

Bielas explains that Cyphers are random molecular tags that are ligated to fragments prior to PCR and sequencing. E.g., EX1013.0010, 0026, 0038. Cyphers “allow a person of ordinary skill in the art to more accurately distinguish true mutations (i.e., naturally arising *in vivo* mutations) of a nucleic acid molecule from artifact ‘mutations’ (i.e., *ex vivo* mutations or errors) of a nucleic acid molecule that

may arise for various reasons, such as a downstream amplification error, a sequencing error, or physical or chemical damage.” EX1013.0007. Thus, Bielas teaches a method of using random molecular tags to differentiate between, and deduplicate, PCR copies to determine if a particular mutation is present in the original fragment (a “true mutation”) or created by PCR (an “artifact mutation”). EX1079.¶¶456-486, 487-490.

Bielas attaches Cyphers to DNA fragments by ligating an adaptor with all of the elements recited in the '399 patent. Example 1 of Bielas discloses a method wherein DNA is fragmented and then ligated into a circular piece of DNA called a vector that contained the adaptors. EX1013.0026. Specifically, Bielas states “the end-repaired DNA fragments are ligated into . . . the library of dual cypher vectors shown in Figure 2” EX1013.0026.

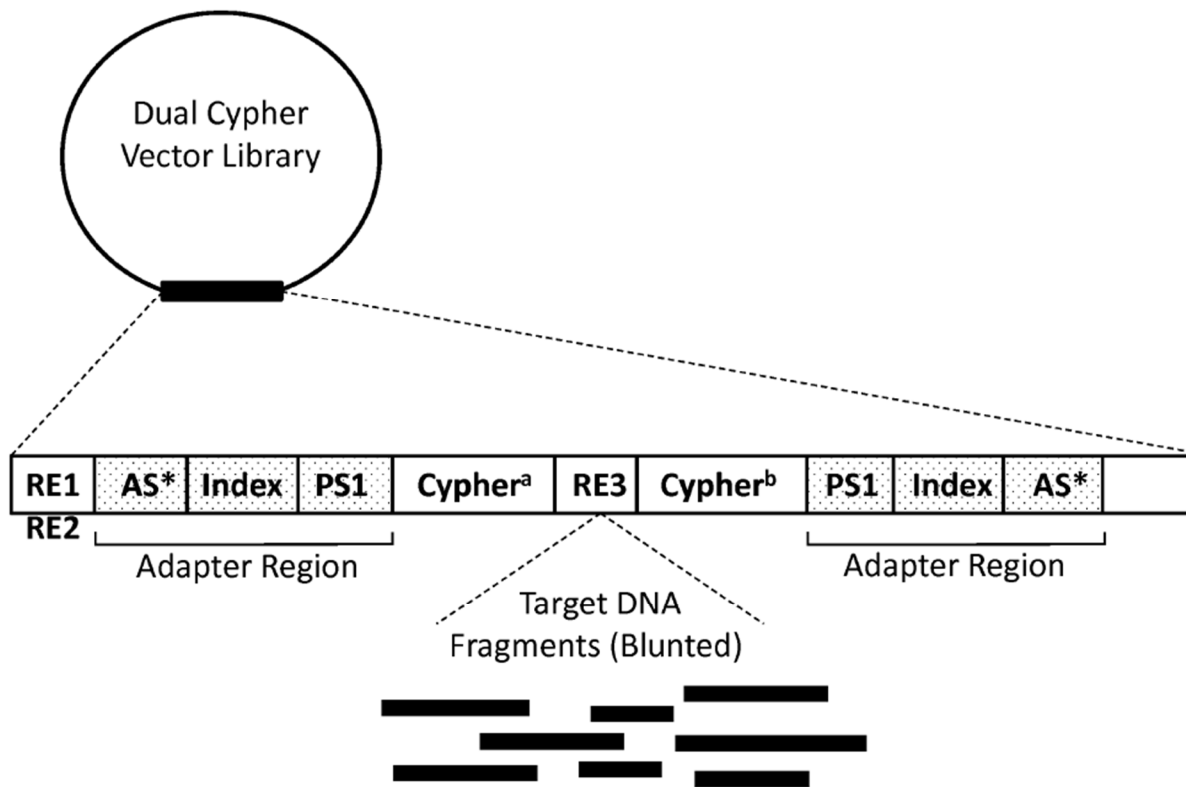
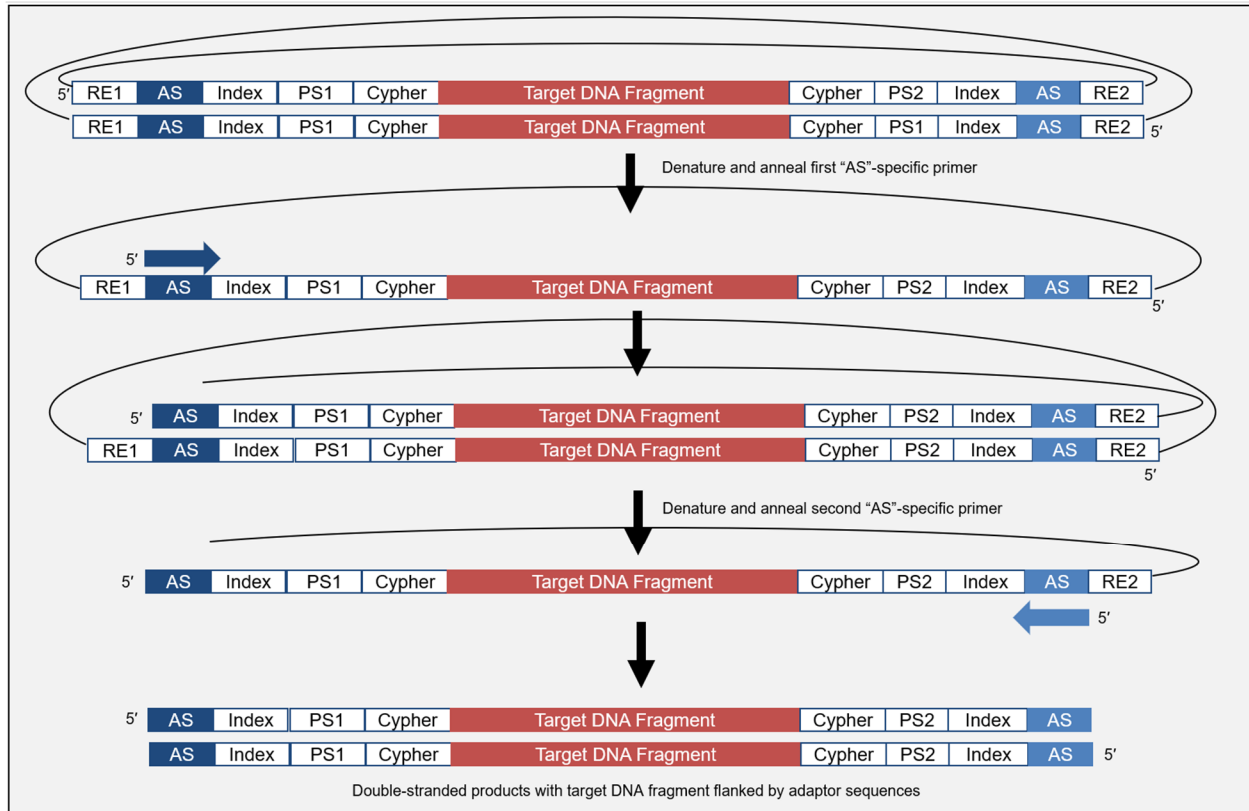


Fig. 2

EX1013.0041.

Bielas cut the vectors at RE3 and inserted the fragments at that site. EX1079.¶¶460-461; EX1013.0026-27. Then, Bielas used a PCR reaction, shown below, to amplify only the adaptor-fragment region out of the vector. EX1079.¶¶462; EX1013.0026-27.



The result of this PCR reaction was a library of double-stranded adaptor-ligated fragments with the structure AS-Index-PS1-Cypher-Fragment-Cypher-PS2-Index-AS. EX1079.¶463; EX1013.0026-27, 0041. For the elements on the 5' side of the fragment, i.e., AS-Index-PS1-Cypher, Bielas explains that "AS" is the Illumina common adaptor sequence used for annealing to the solid support and also used as the primer binding site for sequencing the sample index, EX1013.0023, 0026-27; EX1079.¶464, "Index" is a sample index for multiplexing, EX1013.0027; EX1079.¶465, "PS1" is a primer binding site for the Illumina SBS primer, EX1013.0012, 0022-23, 0027; EX1079.¶¶466-467, and "Cypher" is the random molecular tag sequence, EX1013.0014, 0041; EX1079.¶468. These adaptor-ligated

fragments were then sequenced on an Illumina NGS device. EX1013.0027; EX1079.¶469.

After sequencing, Bielas explains the combined Cypher-fragment sequences are used for de-duplication—“[t]he unique cypher tags are used to computationally deconvolute the sequencing data and map all sequence reads to single molecules (*i.e.*, distinguish PCR and sequencing errors from real mutations).” EX1013.0027; EX1079.¶470. As discussed further below, *infra* §V.B.1, §VI.B.5, this process of deconvoluting sequences necessarily involved de-duplicating PCR copies and collapsing them to an original fragment sequence. EX1079.¶¶489-491, 508-509.

Example 3 of Bielas uses a similar method. EX1013.0028-32. In that example, Bielas created a library of fragments containing pieces of the TP53 gene, EX1013.0028-32, and ligated those fragments into vectors similar to those in Example 1. EX1013.0028-29; EX1079.¶¶471-486. The authors provided the DNA sequence of the circular vector, which the POSA would have recognized contained standard Illumina sequences. EX1013.0028-29; EX1079.¶¶471-480; EX1056; EX1057; EX1075; EX1076; EX1077; EX1078.

Bielas again used PCR to amplify the adaptor-ligated fragments out of the vector. EX1013.0031; EX1079.¶481. The final adaptor-ligated fragments again had the structure AS-Index-PS1-Cypher-Fragment-Cypher-PS2-Index-AS. EX1079.¶481; EX1013.0028-31. The POSA would understand that the AS

sequence was the standard Illumina flow cell sequence that also contains a primer binding site to read the sample index, Index is a sample index, PS1 is the Illumina primer binding site for sequencing the fragment, and Cypher is the random molecular tag. EX1079.¶¶474-480. The authors sequenced the adaptor-ligated fragments on a MiSeq Illumina device. EX1013.0029.

Bielas explains that “all sequencing reads with identical cypher pairs and their reverse complements were grouped into families to create a consensus sequence,” i.e., the adaptor-ligated fragments were de-duplicated using the Cypher and the fragment sequence. EX1013.0031; EX1079.¶¶483-486. Using this process, “true mutations (i.e., those that arise naturally in a cell during replication) are readily detectable using the cypher system of the instant disclosure.” EX1013.0032. As further explained *infra* §V.B.5, Bielas illustrates this process in Figure 3B:

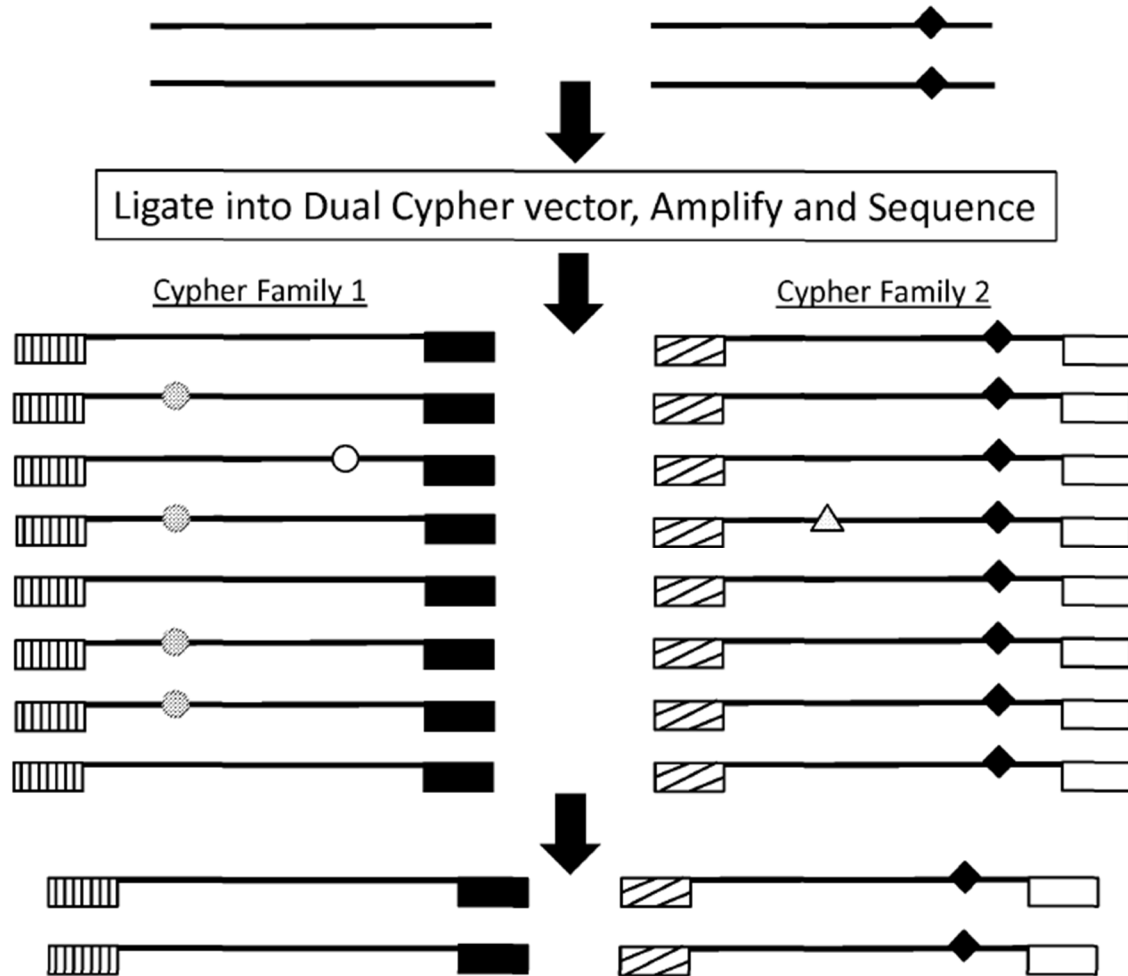


Fig. 3B

EX1013.0031-32, 0043; EX1079.¶¶483-486.

In summary, Bielas disclosed not one, but two, examples of methods that practiced every step of claims 1-2, 5-11, and 15-17.

B. Bielas Anticipates Claim 1.

Bielas discloses every element of claim 1 arranged as in the claim in both Example 1 and Example 3. EX1079.¶¶456-486.

1. Preamble

Bielas discloses a method for detecting a duplicate sequencing read from a population of sample sequencing reads. Despite not using the word “duplicate,” Bielas teaches differentiating between “true mutations” and “artifact ‘mutations’” using the combination of the Cypher/identifier site and the fragment so that each sequence “can be connected back to the original molecule.” EX1013.0007, 0009. In Example 1, Bielas explains that reads were “computationally deconvolute[d]” using the Cypher sequence and the mapped position of the fragment genes. EX1013.0026-27. Likewise, in Example 3, Bielas explains that a consensus sequence was derived by using the Cypher and the fragment sequence, and then “errors introduced during library preparation [] and during sequencing [] were computationally eliminated from the consensus sequence.” EX1013.0028-32. As discussed further below in §V.B.5, the POSA would understand that in order to “deconvolute” sequences to particular original fragments, the sequences were necessarily de-duplicated to remove PCR copies of the same molecule from the data set. EX1079.¶¶489-491.

2. Step a)

Example 1 and Example 3 of Bielas both involved ligation of a fragment into a circular vector, which attached an adaptor made up of AS-Index-PS1-Cypher to

the 5' end of the fragment, as shown in the annotated version of Bielas Figure 2 below. EX1013.0026, 0029-31; EX1079.¶¶492-493.

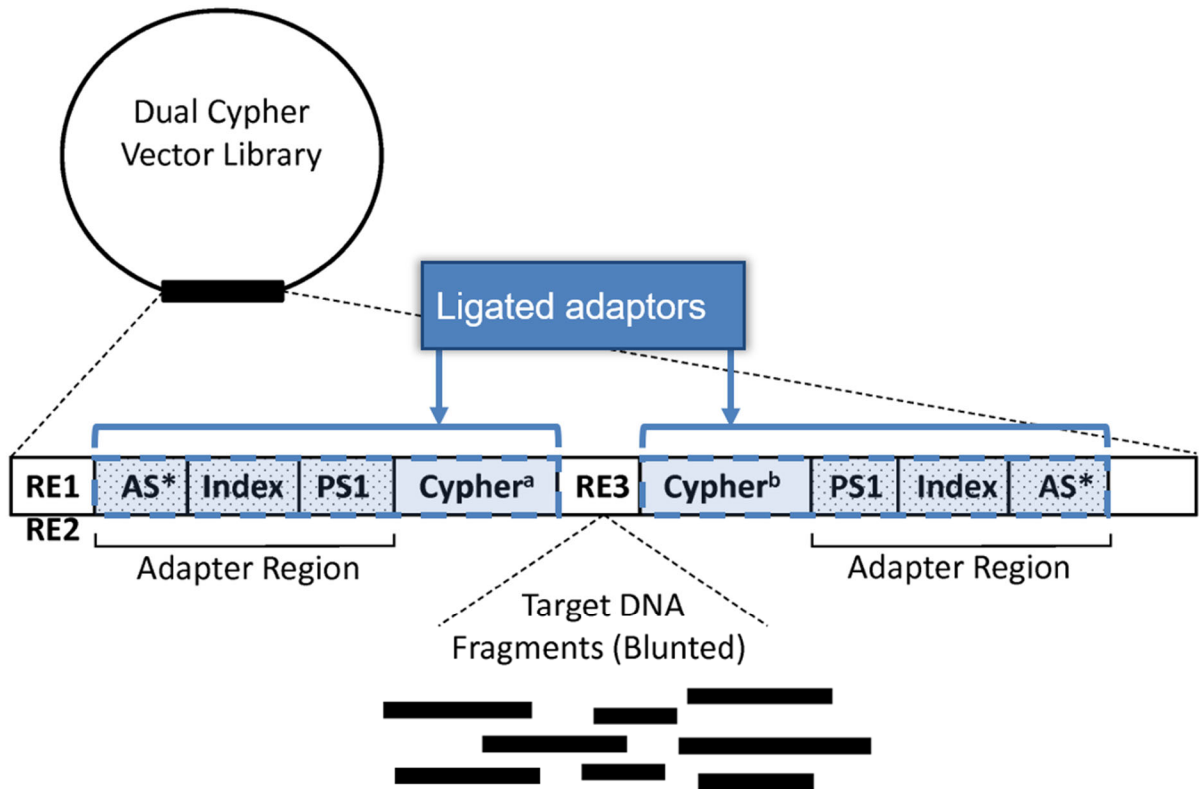


Fig. 2

EX1079.¶492; EX1013.0041.

i. “an indexing primer binding site”

In both Example 1 and Example 3, Bielas’s adaptor includes a site for binding the standard Illumina primer for reading the indexing site, i.e. an indexing primer binding site. EX1079.¶494; EX1013.0026-29.

In Example 1, the adaptor contains “an index sequence if multiplex sequencing is desired” and sequencing was performed on an Illumina Genome

Analyzer II “as specified by the manufacturer.” EX1013.0027. Based on this teaching, the POSA would have understood the adaptor to include the standard Illumina sequence in PS1 that allows the device to read the indexing site in the reverse direction, away from the fragment. EX1079.¶494.

Likewise, in Example 3, the 5′ adaptor sequence disclosed by Bielas includes and indexing primer binding site, which begins at the AS sequence and ends immediately before the Index. EX1079.¶494. The AS sequence (also the standard Illumina P5 sequence for annealing to the solid support) functions as the indexing primer binding site on an Illumina MiSeq, which Bielas used in Example 3. EX1079.¶494; EX1013.0028-29.

Thus, both examples in Bielas used adaptors that contained an indexing primer binding site, as that term is defined in the ’399 patent.

ii. “an indexing site”

In both Example 1 and Example 3, Bielas’s adaptor includes a sample index/indexing site in the 5′ portion of the adaptor. EX1079.¶¶495-497; EX1013.0027-29, 0041.

In Example 1, Bielas states that the adaptor contains “an index sequence if multiplex sequencing is desired.” EX1013.0027. In addition, Bielas shows the structure of the adaptor in Figure 2, which includes an Index site, defined as a sample index, in the 5′ side. EX1013.0027 (citing Figure 2); EX1013.0041 (Figure 2).

In Example 3, Bielas provides the adaptor sequence, which includes at the 5' side a standard Illumina sample index. EX1013.0028-29; EX1079.¶¶478-479. This is consistent with Bielas's Figure 2 and other teachings that Bielas included sample indexes in the adaptors. EX1079.¶¶495-497.

Thus, both examples in Bielas used adaptors that contained an indexing site.

iii. “an identifier site consisting of between 1 and 8 nucleotides”

The '399 patent defines an identifier site as “a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.” EX1003 at 4:43-45. In both Example 1 and Example 3, Bielas discloses an adaptor with a random Cypher that is used as a molecular tag to identify duplicate sequencing reads. EX1013.0026, 0028-29; EX1079.¶¶498-504. Bielas further teaches, as discussed below, that the Cypher sequence and the fragment sequence were used for de-duplication. *Infra* §V.B.5.

In Example 1, the adaptor in Figure 2 was used. EX1013.0026; EX1079.¶499. That adaptor includes a Cypher sequence in the 5' portion of the adaptor. EX1013.0041. Bielas teaches that the Cypher sequence in some embodiments consists of specifically 6, 7, or 8 nucleotides, EX1013.0015, 0005; EX1079.¶500. This disclosure anticipates the claimed range of 1 to 8 nucleotides. Additionally, in discussing a similar construct to that shown in Figure 2, Bielas states that the Cypher is “preferably from about 7 nucleotides to about 9 nucleotides,” EX1013.0023, and

thus discloses the claimed range because the POSA would have understood that “there is no reasonable difference in how the invention operates over the[se] ranges,” *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865 (Fed. Cir. 2015), and because the POSA would “at once envisage” a Cypher of 7 or 8 nucleotides from the range of about 7 to about 9, *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962); EX1079.¶503; *see also Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985).

Likewise, in Example 3, Bielas discloses a 7 nucleotide random Cypher in the 5' portion of the adaptor, designated as NNNNNNN. EX1013.0028, 0016; EX1079.¶504. This disclosure of an adaptor with a 7 nucleotide identifier site falls within the range of “between 1 and 8” and therefore anticipates. *Ineos*, 783 F.3d at 869.

Thus, both examples used an adaptor with an identifier site with a number of nucleotides falling within the claimed range.

iv. “a target sequence primer binding site”

Both Example 1 and Example 3 in Bielas disclose this limitation. EX1079.¶505; EX1013.0027-29.

In Example 1, Bielas used the adaptor in Figure 2 and the adaptor-fragments were sequenced on an Illumina device. EX1013.0027. Figure 2 discloses that the adaptor included “PS,” defined by Bielas as “a nucleic acid molecule priming site”

“used to initiate a sequencing reaction.” EX1013.0012. Based on the combination of these teachings, the POSA would understand PS was a primer binding site for an Illumina sequencing primer. EX1079.¶505; EX1013.0041.

In Example 3, Bielas provides the sequence of the adaptor used in the experiment. The POSA would have recognized the sequence contained an Illumina compatible sequence for the forward read primer. EX1013.0028; EX1079.¶505. This sequence was disclosed in the prior art as the Illumina Nextera read 1 primer. EX1053.0004; EX1008.0005; EX1079.¶¶476-477.

Thus, both examples in Bielas used adaptors that contained a “target sequence primer binding site.”

3. Step b)

In Examples 1 and 3, Bielas amplified the adaptor-ligated fragments using a PCR reaction with primers complementary to the AS sequences on either side of the adaptor to generate copies of the adapter-ligated fragments. *Supra* §V.A; EX1013.0026-27, 0031; EX1079.¶506.

4. Step c)

In Examples 1 and 3, Bielas sequenced the adaptor-ligated fragments to generate a population of sequencing reads in a single run of an Illumina device. EX1013.0027, 0031; EX1079.¶507.

5. Step d)

Bielas discloses that fragments can be “computationally deconvolute[d]” using Cypher-fragment sequences to distinguish “true mutations” found in original fragments from “artifact ‘mutations’” generated during library preparation. EX1013.0024-25, 0027, 0037. This process required Bielas to first identify duplicate sequencing reads as those comprising the same Cypher/identifier site and fragment sequence as other reads. EX1079.¶508.

In Example 1, Bielas explains that “[t]he unique cypher tags are used to computationally deconvolute the sequencing data and map all sequence reads to single molecules (*i.e.*, distinguish PCR and sequencing errors from real mutations)” and that “sequence alignment” was performed using a conventional Illumina software package (called Eland). EX1013.0027. “Sequence alignment” entailed mapping the fragment sequences to their positions in the then-known human genome so as to determine any mutations from the germline. EX1013.0027; EX1079.¶508. In other words, to de-duplicate all of the sequence reads to “single molecules,” *i.e.* original fragment sequences, Bielas relied on the Cypher sequence and the mapped fragment sequence.

Likewise, in Example 3, Bielas explains that “all sequencing reads with identical cypher pairs and their reverse complements were grouped into families to create a consensus sequence” and then “errors introduced during library preparation and during sequencing were computationally eliminated from the consensus

sequence and only mutations present in all reads of a cypher family were counted as true mutations.” EX1013.0031-32. To perform this comparison, Bielas looked at both the Cypher sequence, to group reads, and the fragment sequence, to ascertain whether a particular sequence contained a mutation. EX1013.0031-32, 0043; EX1079.¶509. The authors then de-duplicated reads with the same cypher and fragment sequence to a single consensus read in order to compare those reads to the reference genome and identify “true mutations.” EX1013.0031-32, 0043; EX1079.¶509.

Bielas diagrammed this process in Figure 3B. EX1013.0043. Original double stranded fragments are shown at the top of the figure. EX1079.¶509; EX1013.0043. These fragments are then ligated to the adaptors containing the Cyphers/identifier sequences shown as boxes on either end of the fragment. EX1079.¶509; EX1013.0043. These fragments are then amplified, creating multiple different copies of the same original fragment, annotated as copies 1, 2, and 3 below. EX1079.¶509; EX1013.0043. These copies are then de-duplicated and collapsed to a single fragment in the final step. EX1079.¶509; EX1013.0043.

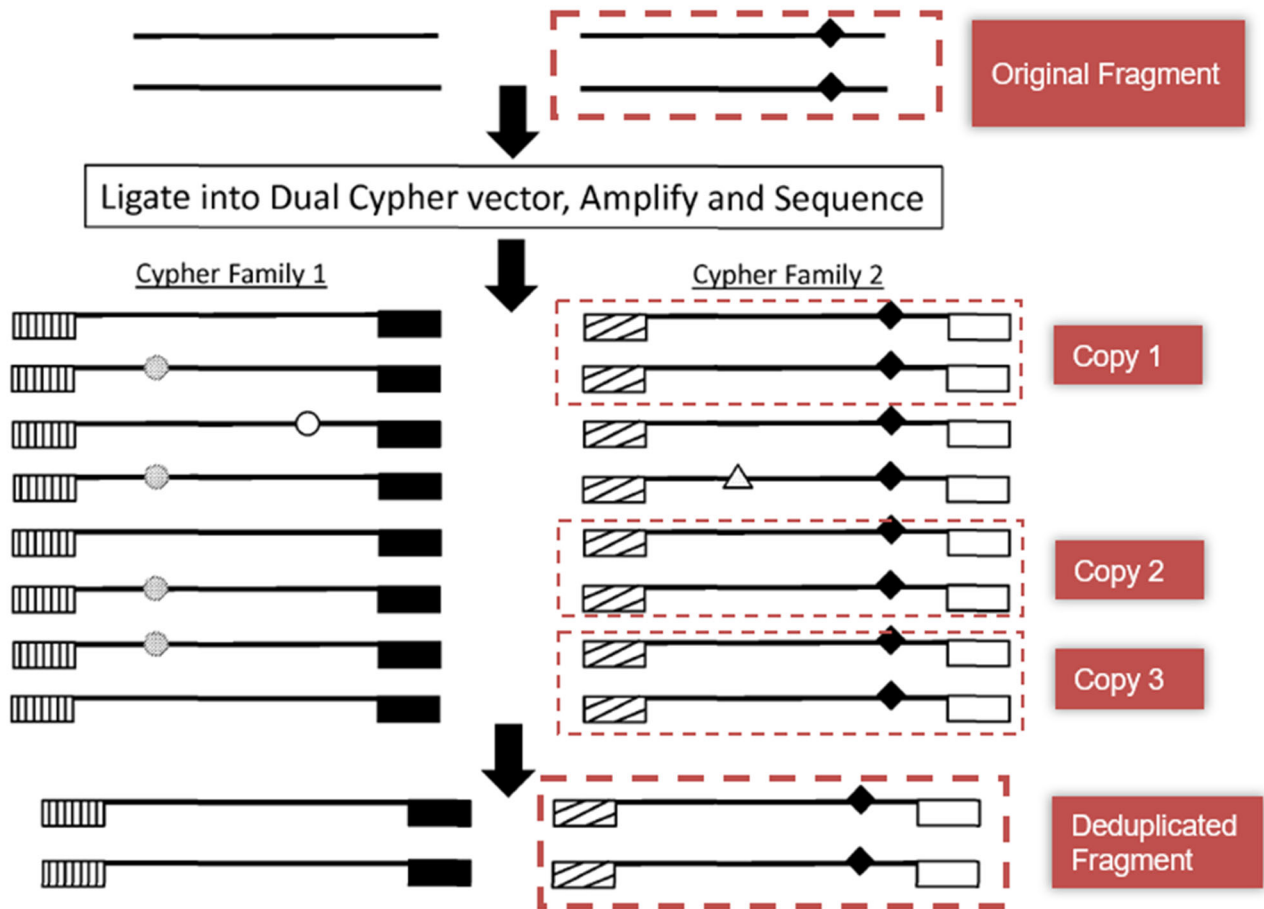


Fig. 3B

Thus, in both Example 1 and Example 3, Bielas identified duplicate sequencing reads by using the Cypher/identifier site and fragment sequence.

6. Indexing site is unique

In both Example 1 and Example 3, Bielas included sample indexes in the adaptors. *Supra* §V.B.2.b; EX1079.¶510. Bielas explains that these indexes are “a unique index sequence . . . specific for a particular sample,” and that if ten samples are pooled, ten different index sequences will be used. EX1013.0015-16. Thus,

Bielas taught that the indexing sites are unique to a subset of fragments, i.e. from a sample, and used as an index for that set of polynucleotides, i.e. for that sample.

7. Identifier site is variable

Bielas teaches that the Cypher sequences used in Examples 1 and 3 were random, *supra* §V.B.2.iii, and thus variable in sequence content across the adaptors. EX1079.¶511.

C. Claim 2

Bielas anticipates dependent claim 2, which adds that duplicate reads are removed after being identified. EX1003 at 25:62-65; EX1079.¶¶520-523. In Examples 1 and 3, reads with duplicate Cypher-fragment sequences were “deconvoluted” to “original molecules,” i.e. they were de-duplicated, as shown in Figure 3B. *Supra* §V.B.5; EX1079.¶¶521-522; EX1013.0043.

D. Claim 5

Bielas anticipates dependent claim 5, which requires that the fragments are “generated from more than one sample.” EX1003 at 26:41-42; EX1079.¶¶527-529. In both Example 1 and Example 3, Bielas discloses that samples were pooled prior to sequencing. EX1079.¶528; EX1013.0027-29.

In Example 1, Bielas explains that the index sequence is included in the adaptor “if multiplex sequencing is desired.” EX1013.0027. Likewise, in Example 3, the adaptor included “adapter sequences, *indices*, and random 7-nucleotide barcodes.” EX1013.0028 (emphasis added). Bielas explains that the purpose of the

index sequence is to allow for multiplex sequencing. EX1013.0015-16. Furthermore, the POSA would understand that the sequence of the adaptor included a standard Illumina sample index. EX1079.¶¶478-479.

E. Claim 6

Bielas anticipates claim 6, which depends from claim 5 and adds that each sample has a unique sample index. EX1003 at 26:43-45; EX1079.¶¶530-532.

Example 1 and Example 3 disclosed that the adaptors contain an indexing site for multiplexing. *Supra* §V.B.2.ii; EX1079.¶531. Bielas further explains that each sample “has a single, unique index sequence identifier.” EX1013.0015-16.

F. Claim 7

Bielas anticipates claim 7, which depends from claim 6 and requires sequencing reads are “separated based on the indexing site.” EX1003 at 26:46-47; EX1079.¶¶533-535.

Both Example 1 and Example 3 of Bielas disclose the use of sample indexes for multiplexing on an Illumina device. *Supra* §V.B.2.ii. The POSA would understand that the Illumina devices used in Example 1 and Example 3 would have separated sequencing data by sample. EX1079.¶¶533-535.

G. Claim 8

Bielas anticipates claim 8, which depends from claim 7 and requires separation of sequencing reads prior to step (d). EX1003 at 26:48-49; EX1079.¶¶536-539.

As discussed with respect to claim 7, *supra* §V.B.F, the Illumina devices used in Bielas de-multiplexed sequence results prior to identifying duplicates based on Cypher sequences. EX1079.¶¶533-539.

H. Claim 9

Bielas anticipates claim 9, which depends from claim 1 and specifies the fragments as DNA and/or RNA. EX1003 at 26:50-52. Both Bielas examples used DNA. EX1013.0026, 0029-31; EX1079.¶¶540-541.

I. Claim 10

Bielas anticipates claim 10, which depends from claim 9 and specifies genomic DNA or cDNA. EX1003 at 26:53-54. Both Bielas examples used genomic DNA. EX1013.0026, 0029-31; EX1079.¶¶542-543.

J. Claim 11

Bielas anticipates dependent claim 11, which recites a sample index of 2-8 nucleotides. EX1003 at 26:55-56; EX1079.¶¶544-550. Bielas used an 8-nucleotide sample index in Example 3. EX1013.0028; EX1079.¶547. Furthermore, Bielas directs the POSA to use standard Illumina sequences, which at the priority date would have included 8-nucleotide sample indexes. EX1079.¶546.

K. Claim 15

Bielas anticipates dependent claim 15, which adds that the indexing primer binding site is “universal,” defined as “a primer that can be used for amplifying a number of different sequences.” EX1003 at 5:57-58, 26:63-64. In both Examples,

Bielas used a standard Illumina index primer binding site that is the same in all the adaptors and is thus “universal.” EX1013.0027-28, 0041; EX1079.¶¶556-557.

L. Claim 16

Bielas anticipates dependent claim 16, which recites that the target sequence primer binding site is “universal.” EX1003 at 65-67. In both Examples, Bielas used a standard Illumina sequencing primer binding site that is the same in all the adaptors and is thus “universal.” EX1013.0027-28, 0041; EX1079.¶¶558-559.

M. Claim 17

Bielas anticipates claim 17, which depends from claim 6 and adds separating fragments or reads based on the indexing site. EX1003 at 27:1-3. As discussed above with respect to claim 7, which recites an almost identical limitation, *supra* §V.B.F, Bielas used conventional Illumina devices that at the priority date would have separated reads by indexing site prior to exporting sequencing data. EX1079.¶¶560-562.

VI. GROUND III: OBVIOUSNESS OVER BIELAS

To the extent that Bielas does not anticipate claims 1-2, 5-11, and 15-17, Bielas renders those claims obvious, as explained below. Bielas also renders claims 3 and 14 obvious.

A. Claim 1

Bielas discloses every element of claim 1 and thus anticipates it. But to the extent that the Board concludes certain elements are not disclosed or arranged as in

the claim, Bielas renders claim 1 obvious for the reasons set forth *supra* §V.A and in this section. EX1079.¶¶512-519

To the extent that Bielas does not disclose adaptors in Examples 1 and 3 that include an indexing site and an indexing primer binding site as recited in claim 1, the method including such features would have been obvious because Bielas teaches the desirability of multiplex sequencing and the use of unique sample indexes to differentiate between samples. EX1079.¶513; EX1013.0015-16, 0027-29, 0041. Moreover, in Example 3, Bielas's adaptor sequence includes a known 8 nucleotide Illumina sample index. EX1079.¶478-479; EX1013.0026-27. The POSA accordingly would have had a motivation to add the 8-nucleotide standard Illumina sample indexes described in Bielas to the adaptors used in Examples 1 and 3 to permit sample multiplexing to save costs and time, and had a reasonable expectation of success in doing so. EX1079.¶513.

Likewise, to the extent that Bielas does not disclose an adaptor in Examples 1 and 3 with an identifier site of 1 to 8 nucleotides as recited in claim 1, Bielas renders claim 1 obvious because Bielas teaches that those adaptors can contain a Cypher. Specifically, Bielas teaches Cypher lengths of 6, 7, and 8 nucleotides, used a Cypher length of 7 nucleotides in Example 3, and disclosed ranges of Cypher lengths that fall within or overlap the claimed range, including 6 to 8 and 7 to 9. EX1079.¶514-519; EX1013.0005, 0010, 0015, 0028. Additionally, as discussed in §IV.D.1 in

connection with Kivioja, it would have been obvious to the POSA to routinely optimize the Cypher length because Bielas likewise teaches that the appropriate Cypher length is based on the predictable relationship between Cypher length and the number of unique tags (4^n) and the expected number of unique fragments in the sample. EX1013.0015-16; EX1022.0004; EX1027.0002; EX1079.¶514-519. *See Pfizer*, 94 F.4th at 1348-49.

B. Claim 2

To the extent claim 2 is not anticipated, *supra* §V.C, it would have been obvious. The POSA would have been motivated to remove duplicate sequencing reads for data analysis, including to distinguish between true and artifact mutations as described in Bielas, and would have had a reasonable expectation of success in doing so. EX1079.¶¶520-523; EX1013.0007-08.

C. Claim 3

Claim 3 depends from claim 1 and adds that the identifier site is “sequenced with” the indexing site. EX1003 at 25:66-67. Bielas discloses every element of claim 1, *supra* §V.A, §VI.A, and renders the additional limitations obvious. In the Illumina devices used by Bielas, the indexing site/sample index was read in a separate SBS reaction from the identifier site and the fragment. EX1079.¶525. The POSA also would have recognized that the position of these sites in the adaptor was a design choice and the POSA could have positioned the identifier site so as to be

read as part of the sample index read. EX1079.¶¶171-175, ¶525. *See Uber*, 957 F.3d at 1340. The patent does not disclose any criticality or unexpected properties of reading the identifier site “with” the indexing site versus reading them separately. EX1079.¶¶524-526.

D. Claim 11

To the extent claim 11 is not anticipated, *supra* §V.J, it would have been obvious. The POSA would have been motivated to use an indexing site/sample index of 8 nucleotides, as Bielas used in Example 3 and was standard in Illumina adaptors at the priority date, and would have had a reasonable expectation of success in doing so. EX1079.¶¶544-550; EX1013.0028.

E. Claim 14

Claim 14 depends from claim 1 and recites that “the identifier site is 8 nucleotides in length.” EX1003 at 26:61-62. The POSA would have been motivated to use a Cypher of 8 nucleotides for certain applications, as expressly taught in Bielas, which states in some embodiments the Cypher “comprises 8 nucleotides.” EX1013.0015. In addition, the POSA would have been motivated to routinely optimize the length of the Cypher/identifier site depending on the number of unique fragments expected in a particular sample because Bielas teaches that Cypher length is a predictable result of the number of Cyphers needed (4^n) to ensure that each unique fragment has a unique Cypher. EX1013.0015-16; EX1079.¶¶551-555; *supra*

§IV.D.1. *See Pfizer*, 94 F.4th at 1348-49. And the use of an 8-nucleotide identifier site instead of the 7-nucleotide identifier site used in Bielas Example 3 would have been a design choice for the POSA. *See Uber*, 957 F.3d at 1340. There is no evidence of unexpected properties or criticality of an 8-nucleotide identifier site. EX1079.¶555. And the POSA would have had a reasonable expectation of success in practicing the methods with an identifier of 8 nucleotides. EX1079.¶554. Thus, Bielas renders this claim obvious.

F. Claims 5, 6, 7, 8, And 17

These claims recite additional limitations relating to multiplexing, including pooling samples (claim 5), using a unique index for each sample (claim 6), separating the sequencing reads by sample index (claim 7), performing separation prior to de-duplication (claim 8), and separating reads based on indexing site (claim 17). To the extent these claims are not anticipated, *supra* §V.D, §V.E, §V.F, §V.G, §V.M, they would have been obvious based on the express teaching that the Bielas methods are compatible with sample pooling and multiplexing, EX1013.0015-16, 0022, 0027, and the use of Illumina devices. EX1079.¶¶527-539, 560-562. All of these dependent elements were standard parts of Illumina demultiplexing and data analysis at the priority date, which involved separation of sequencing reads by unique sample index and export of separate sequencing data files prior to further analysis. EX1079.¶¶527-539, 560-562. The POSA would have been motivated to

pool and multiplex samples to maximize the use of the space on the Illumina device and save costs and time, and thus these limitations would have been obvious to the POSA based on the standard Illumina workflows at the time. EX1079.¶¶527-539, 560-562. The POSA would have had a reasonable expectation of doing so based on the express teachings in Bielas regarding multiplexing and the use of standard Illumina devices. EX1079.¶¶527-539, 560-562.

Moreover, the order of particular data processing steps in sample analysis is a prototypical design choice, *see Uber*, 957 F.3d at 1340, and there is no evidence in the '399 patent that the particular order of steps claimed in these dependent claims has any benefit, let alone unexpected properties.

G. Claims 9, 10, 15, And 16

The limitations of these dependent claims are clearly disclosed in Bielas, *supra* §§V.G-H, §§V.K-L, and thus these claims rise and fall with the anticipation and/or obviousness of claim 1.

H. No Secondary Considerations Support Non-obviousness.

IDT is unaware of any relevant secondary considerations of non-obviousness. Should Tecan present evidence of any secondary considerations following institution, IDT reserves the right to respond in its reply.

VII. DISCRETIONARY DENIAL IS NOT APPROPRIATE

The Board should not deny institution under 35 U.S.C. §325(d), or 35 U.S.C. §314(a) and *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020).

A. Discretionary Denial Under §325(d) Is Not Appropriate

The Petition is based on prior art and arguments that were not before the Examiner or substantially similar to those before the Examiner. First, Iafrate, Kivioja, and Bielas were not cited during prosecution, nor were any related or substantially-similar references. EX1018; EX1079.¶¶654-656. Nor did the Examiner have the benefit of the additional evidence presented by Petitioner here, including Dr. Sims's declaration. Second, to the extent the Examiner allowed the claims on the grounds that the prior art did not teach an identifier site of 8 nucleotides or de-duplicating using both the identifier and fragment sequence, *supra* §II.A, the Examiner materially erred because the prior art, including Kivioja and Bielas, taught both of these features, *supra* §§IV-VI; EX1079.¶¶654-656. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte G.m.b.H.*, IPR2019-01469, Paper 6, at 8-9 (PTAB Feb. 13, 2020).

B. Discretionary Denial Under §314(d) Is Not Appropriate

The parties' litigation in *Tecan Genomics, Inc. v. Invitae Corp., et al.*, C.A. No. 23-cv-1114-GBW (D. Del.) does not warrant discretionary denial under the relevant factors. *See Fintiv*, IPR2020-00019, Paper 11, at 6.

First factor. The first factor is neutral because no party has requested a stay in district court, though Petitioner will promptly seek a stay after filing this Petition.

Second factor. Trial is scheduled for June 22, 2026—after the Board’s projected decision date. This factor weighs in favor of institution.

Third factor. The case is still early in fact discovery, favoring institution.

Fourth and fifth factors. Petitioner and Patent Owner are both parties to the district court action. Petitioner has not presented any grounds, arguments, or evidence in district court, though Petitioner expects to serve initial invalidity contentions soon after the filing of this Petition. ,If this trial is instituted, however, Petitioner stipulates it will not pursue any arguments in district court that could have been raised herein under 35 U.S.C. §311(b). Thus, there is no prospect for conflicting decisions and duplicative efforts, and these factors cannot weigh against institution. Katherine K. Vidal Memorandum 7-8 (June 21, 2022).

Sixth factor. The Petition raises “a compelling unpatentability challenge” and that “alone demonstrates that the PTAB should not discretionarily deny institution under *Fintiv*.” *CommScope Techs. LLC v. Dali Wireless, Inc.*, IPR2022-01242, Paper 23, at 3 (PTAB Feb. 27, 2023). Any doubt should be resolved in favor of institution because it is “highly likely” that Petitioner will “prevail with respect to at least one challenged claim.” *Id.* at 3-4.

VIII. STANDING (37 C.F.R. §42.104(a)) AND PROCEDURAL STATEMENTS

Petitioner certifies the '399 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR on the grounds herein. Petitioner is submitting a Power of Attorney and an Exhibit List pursuant to §42.10(b) and §42.63(e), respectively, as well as all fees required under 37 C.F.R. §42.15(a), concurrently with this Petition. If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Acct. No. DA506403.

IX. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

A. Real Party-in Interest (37 C.F.R. §42.8(b)(1))

The real parties-in-interest are Integrated DNA Technologies, Inc., and its corporate parent, Danaher Corporation.

B. Related Matters (37 C.F.R. §42.8(b)(2))

To the best of Petitioner's knowledge, the '399 patent is, or has been, involved in only one matter. On October 6, 2023, Patent Owner filed a complaint against Petitioner for infringement of the '399 patent in *Tecan Genomics, Inc. v. Invitae Corp.*, C.A. No. 23-cv-1114-GBW (D. Del.) (the "District Court Action").

U.S. Patents 11,098,357, EX1004, and 11,725,241, EX1005, which like the '399 patent also claim priority to U.S. provisional application No. 61/903,826,² are asserted in the District Court Action and in a related district court action: *Tecan Genomics, Inc. v. QIAGEN Sciences, LLC*, C.A. No. 23-cv-1115-GBW (D. Del.).

Petitioner will concurrently file petitions for IPR against U.S. Patents 11,098,357 and 11,725,241.

C. Lead and Backup Counsel and Service Information (37 C.F.R. §42.8(b)(3) and (b)(4))

Lead Counsel	Backup Counsel
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² U.S. Patent 10,570,448 and U.S. Patent Application 2024/0141426 also claim priority to the same provisional application. Neither are the subject of any matters of which Petitioner is aware.

IDT consents to service by e-mail at tfletcher@wc.com, jberniker@wc.com, nvincent@wc.com, and IDT-Tecan-IPRs@wc.com.

X. CONCLUSION

IDT respectfully requests institution and cancellation of claims 1-3, 5-11, and 14-17.

Dated: September 30, 2024

Respectfully submitted,

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CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

I hereby certify that the foregoing complies with the type-volume limitations of 37 C.F.R. § 42.24(d) and contains 13,843 words, excluding those portions exempted under 37 C.F.R. § 42.24(a)(1).

/Thomas S. Fletcher/
Thomas S. Fletcher
Reg. No. 72,383

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105, I hereby certify that on September 30, 2024, I caused the foregoing Petition for *Inter Partes* Review, Power of Attorney, Exhibit List, and the accompanying exhibits to be served on Patent Owner by depositing them for shipment with Federal Express, Standard Overnight delivery, to the following correspondence address of record listed on USPTO Patent Center:

BROWN RUDNICK LLP
One Financial Center
Boston, MA 02111

A courtesy electronic copy has also been sent to Timothy J. Beavers (tbeavers@goodwinlaw.com), Linnea P. Cipriano (lcipriano@goodwinlaw.com), John P. Padro (jpadro@goodwinlaw.com), and Scott T. Weingaertner (sweingaertner@goodwinlaw.com), counsel for Plaintiffs in *Tecan Genomics, Inc. v. Invitae Corp. et al.*, C.A. No. 23-cv-1114-GBW (D. Del.).

Dated: September 30, 2024

/Thomas S. Fletcher/
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