

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 No. IPR2024-01504
U.S. Patent No. 11,098,357

PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	TECHNOLOGY BACKGROUND	3
A.	Development of Sequencing Technology	3
B.	Challenges With Existing Methods of NGS	5
III.	THE '357 PATENT.....	6
A.	Overview	6
B.	Level of Ordinary Skill in the Art	7
C.	Prosecution History	8
D.	Claim Construction.....	9
1.	“indexing site”	9
2.	“identifier site”	9
3.	“identifying sequence reads with identical identifier and target sequences as duplicates”	9
4.	“duplicates”	16
5.	“comprising”	17
IV.	THE CITED REFERENCES	20
A.	Iafrate.....	20
B.	Kivioja	20
C.	Bielas	21

V.	THE ASSERTED GROUNDS.....	23
VI.	GROUND I: PETITIONER’S COMBINATION OF KIVIOJA AND IAFRATE DOES NOT RENDER THE Challenged CLAIMS OBVIOUS.....	24
	A. Neither Kivioja Nor Iafrate Disclose Limitation 1(d).....	25
	B. Neither Iafrate Nor Kivioja Disclose Removing Duplicate Reads (Claim 2).....	29
	C. Petitioner’s Motivation to Combine Kivioja and Iafrate is Deficient.....	30
VII.	GROUND 2 AND 3: PETITIONER HAS NOT SHOWN THAT ANY CHALLENGED CLAIM IS ANTICIPATED BY, OR OBVIOUS OVER, BIELAS	33
	A. Bielas Does Not Disclose Identifying and/or Removing a Duplicate Sequencing Read Based on the Identifier Site and Nucleic Acid Fragment.....	34
	B. Petitioner Has Not Shown a POSA Would Have Been Motivated to Modify Bielas.....	37
VIII.	CONCLUSION	38

TABLE OF AUTHORITIES

	Page(s)
Cases	
<i>Apple, Inc. v. Ameranth, Inc.</i> , 842 F.3d 1229 (Fed. Cir. 2016)	11
<i>Callicrate v. Wadsworth Mfg., Inc.</i> , 427 F.3d 1361 (Fed. Cir. 2005)	11
<i>Dippin' Dots, Inc. v. Mosey</i> , 476 F.3d 1337 (Fed. Cir. 2007)	18
<i>In re Gorman</i> , 933 F.2d 982 (Fed. Cir. 1991)	32
<i>Groove Digital, Inc. v. United Bank</i> , 825 F. App'x 852 (Fed. Cir. 2020).....	10
<i>Johns Manville Co. v. Knauf Insulation, Inc.</i> , IPR2018-00827, Paper 9 (PTAB Oct. 16, 2018).....	31
<i>Johnson Controls, Inc. v. Wildcat Licensing WI, LLC</i> , IPR2014-00305, Paper 45 (PTAB June 22, 2015)	24
<i>In re Magnum Oil Tools Int'l, Ltd.</i> , 829 F.3d 1364 (Fed. Cir. 2016)	30
<i>Markman v. Westview Instruments, Inc.</i> , 52 F.3d 967 (Fed. Cir. 1995) (en banc), <i>aff'd</i> , 517 U.S. 370 (1996).....	10
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005) (en banc)	15
<i>Spectrum Int'l, Inc. v. Sterilite Corp.</i> , 164 F.3d 1372 (Fed. Cir. 1998)	18, 21
<i>William Wesley Carnes, Sr., Inc. v. Seaboard International, Inc.</i> , IPR2019-00133, Paper 10 (PTAB May 8, 2019)	25, 31
<i>Xerox Corp. v. Midwest Athletics and Sports Alliance LLC</i> , IPR2019-00426, Paper 9 (PTAB July 22, 2019).....	35, 37

TABLE OF EXHIBITS

Ex.	Short Name	Description
2001	Alkan 2011	Can Alkan et al., <i>Limitations of next-generation genome sequence assembly</i> , 8 NAT. METHODS 1 (2011)
2002	Chiasson 2015	Mark J.P. Chiasson et al., <i>Genetic variation and the de novo assembly of human genomes</i> , 16 NAT. REV. (2015)
2003	Doan 2022	U.S. Patent Publication No. 2022/0145380 A1 to Doan, et al.
2004	Goodwin 2016	Sara Goodwin et al., <i>Coming of age: ten years of next-generation sequencing technologies</i> , 17 NAT. REV. (2016)
2005	Kanagawa 2003	Takahiro Kanagawa, <i>Bias and Artifacts in Multitemplate Polymerase Chain Reactions (PCR)</i> , 96 J. BIOSCI. & BIOENG 4 (2003)
2006	Mamanova 2010	Lira Mamanova et al., <i>Target-enrichment strategies for next-generation sequencing</i> , 7 NAT. METHODS 2 (2010)
2007	Nakamura 2011	Kensuke Nakamura et al., <i>Sequence-specific error profile of Illumina sequencers</i> , 39 NUCLEIC ACIDS RES. 13 (2011)
2008	Sanger 1977	F. Sanger et al., <i>DNA sequencing with chain-terminating inhibitors</i> , 74 PROC. NATL. ACAD. SCI. USA 12 (1977)
2009	Satam 2023	Heena Satam et al., <i>Next-Generation Sequencing Technology: Current Trends and Advancements</i> , 997 BIOL. 12 (2023)
2010	Whiteford 2009	Nava Whiteford et al., <i>Swift: Primary Data Analysis for the Illumina Solexa Sequencing Platform</i> , 25 BIOINFORMATICS 16 (2009)
2011	Capurro 2015	Alberto Capurro et al., <i>Computational deconvolution of genome wide expression data from Parkinson's and Huntington's disease brain tissues using population-specific expression analysis</i> , 8 FRONTIERS IN SCI. (2015)
2012	Carr 2013	Rogan Carr et al., <i>Reconstructing the Genomic Content of Microbiome Taxa through Shotgun Metagenomic Deconvolution</i> , 9 PLOS COMPUTATIONAL BIOL. 10, (2013)
2013	Wang 2015	Niya Wang et al., <i>UNDO: a Bioconductor R package for unsupervised deconvolution of mixed gene expressions in tumor samples</i> , 31 BIOINFORMATICS 1 (2015)

Ex.	Short Name	Description
2014	Wong 2013	Koon Ho Wong et al., <i>UNDO: a Bioconductor R package for unsupervised deconvolution of mixed gene expressions in tumor samples</i> , CURRENT PROTOCOLS IN MOLECULAR BIOL. (2013)
2015	Mardis 2017	Elaine R. Mardis, <i>DNA sequencing technologies: 2006–2016</i> , 12 NAT. PROTOCOLS 12, (2017)
2016	Sims Deposition	Transcript for the June 26, 2025 Deposition of Dr. Peter A. Sims
2017		<i>Reserved</i>
2018		<i>Reserved</i>
2019		<i>Reserved</i>
2020		<i>Reserved</i>
2021		<i>Reserved</i>
2022		<i>Reserved</i>
2023	Aird 2011	Daniel Aird et al., <i>Analyzing and minimizing PCR amplifications bias in Illumina sequencing libraries</i> , 12 GENOME BIOL. (2011)
2024	Cock 2009	Peter J. A. Cock et al., <i>The Sanger FASTQ file format for sequences with quality scores, and the Solexa/Illumina FASTQ variants</i> , 38 NUCLEIC ACIDS RES. 6 (2009)
2025	McKenna 2010	Aaron McKenna et al., <i>The Genome Analysis Toolkit: A MapReduce framework for analyzing next-generation DNA sequencing data</i> , 20 GENOME RES. 1297 (2010)
2026	Lam 2012	Hugo Y. K. Lam et al., <i>Detecting and annotating genetic variations using the HugeSeq pipeline</i> , 30 NAT. BIOTECH. 3 (2012)
2027	Li 2009	Heng Li et al., <i>The Sequence Alignment/Map format and SAMtools</i> , 25 BIOINFORMATICS 16 (2009)
2028	Flicek 2009	Paul Flicek & Ewan Birney, <i>Sense from sequence reads: methods for alignment and assembly</i> , 6 NAT. METHODS SUPPLEMENT 11 (2009)
2029	IHGSC 2004	International Human Genome Sequencing Consortium, <i>Finishing the euchromatic sequence of the human genome</i> , 431 NAT. 21 (2004)

Ex.	Short Name	Description
2030	Baker 2012	Monya Baker, <i>De novo genome assembly: what every biologist should know</i> , 9 NAT. METHODS 4 (2012)
2031	Church 2011	Deanna M. Church et al., <i>Modernizing Reference Genome Assemblies</i> , 9 PLOS BIOL. 7 (2011)
2032	Horner 2009	David Stephen Horner et al., <i>Bioinformatics approaches for genomics and post genomics applications of next-generation sequencing</i> , 11 BRIEFINGS IN BIOINFORMATICS 2 (2009)
2033	Mullis 1986	K. Mullis et al., <i>Specific Enzymatic Amplification of DNA In Vitro: The Polymerase Chain Reaction</i> , 51 COLD SPRING HARBOR SYMPOSIA QUANTITATIVE BIOL. 1 (1986)
2034	N/A	<i>The Cost of Sequencing a Human Genome</i> , NAT'L INST. OF HEALTH NAT'L HUMAN GENOME RESEARCH INST., https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost (last visited July 11, 2025)
2035	Bustamante Declaration	Declaration of Carlos D. Bustamante, Ph.D.

Patent Owner Tecan Genomics, Inc. (“Tecan”) submits this Patent Owner’s Response (“POR”) to respond to the Petition (Paper 1) for *inter partes* review (“IPR”) of claims 1-4, 6-7, and 9-10 (the “challenged claims”) of U.S. Patent No. 11,098,357 (“the ’357 patent,” EX1004) filed by Integrated DNA Technologies, Inc. (“Petitioner”), and the Board’s institution decision, Paper 7.

I. INTRODUCTION

Petitioner’s obviousness and anticipation arguments are fundamentally flawed, in large part because they all rest on an incorrect reading of the “identifying duplicates” limitation of the challenged claims. The record, including the prosecution history, evidences that the challenged claims are patentably distinct from the prior art, in part because they claim a novel method of identifying duplicate sequence reads that includes a step of comparing **both** the identifier site **and** a portion of the target sequence to identify duplicates. None of the prior art cited in the Petition discloses or teaches a method with this step, as claimed.

Petitioner’s first Ground relies on the combination of Iafrate and Kivioja. As Petitioner admits, and the Board acknowledged, Iafrate does not disclose adapters with all elements of the challenged claims. Importantly, Iafrate does not disclose an adapter with an identifier site—which is necessary both for the limitations that define the adapter and the “identifying” limitation that uses the identifier site with the nucleic acid sequence to identify duplicates. In an attempt to remedy this deficiency,

Petitioner relies on Kivioja, but Kivioja does not use its “label” in the manner that the claims require the identifier site be used. Rather Kivioja discloses a series of data analysis steps, none of which use both the nucleic acid sequence and the label together to identify duplicates. Therefore, Petitioner has failed to show that all the limitations are disclosed in the prior art and has failed to prove that the challenged claims are unpatentable under Ground 1.

Petitioner’s second and third Grounds rely on Bielas, which suffers from the same defects as Kivioja. Namely, Bielas is explicit that its “cyphers,” which Petitioner equates to the identifier site of the claims, are used on their own to sort the data into families. Additionally, Bielas’s method is directed at detecting sequencing errors, which Applicants specifically distinguished from the claimed method of identifying duplicates during prosecution. Bielas lacks any disclosure of a process of identifying duplicates using both an identifier site and the nucleic acid sequence together, and therefore, cannot anticipate or render obvious any challenged claim.

As such, Petitioner has not met its burden of showing that the challenged claims are unpatentable.

II. TECHNOLOGY BACKGROUND

Much of the background technology at issue in this case is not in dispute. Tecan provides some additional background here for context. The fact that a particular topic is not addressed here does not indicate that Tecan accepts Petitioner's representations.

A. Development of Sequencing Technology

Genetic sequencing, the assessment of genetic information through methods that characterize the sequence of an organism's genetic code, is essential for the understanding of biology and medicine. EX2009.0001 ("Satam 2023"). Several methods have been developed over the years to accurately and efficiently sequence DNA, starting with traditional sequencing methods that are now referred to as pre-next-generation sequencing ("NGS") technologies. *Id.*, .0002-03.

Starting in the early 2000s, the field of genetics was revolutionized by the invention of NGS. EX2004.0001 ("Goodwin 2016"). Compared to traditional, pre-NGS sequencing methods, NGS sequencing utilized a new design that no longer relied on disassembling and then piecing together a single original template DNA strand. *Id.*, .0002-03. Instead, NGS sequencing now allowed for hundreds of thousands of original template strands to be sequenced in the same reaction. *Id.* With NGS, a user could perform massively parallel sequencing, allowing for elements of the genome to be sequenced in a fast, scalable manner. *Id.*, .0003. As

compared to pre-NGS sequencing methods, NGS was cheaper, more efficient, and capable of assessing both larger genetic samples and larger portions of the human genome in high fidelity. *Id.*

However, early NGS methods had their drawbacks. NGS was limited to shorter individual sequencing reads than those of Pre-NGS sequencing methods, which made it more difficult to map the sequence reads to a full genome. *Id.*, .0001, 0003. NGS methods also made it difficult to determine whether reads were duplicates generated during amplification, unique but identical sections of a genome, or mutated sequences of the genome. EX2001.0001 (“Alkan 2010”); *see also id.*, .0001-02.

Sample amplification steps prior to NGS sequencing introduced PCR errors, which made it difficult to determine whether changes in nucleotides across similar sequences were due to mutations, or to PCR errors, and confounded the data. EX2005.0005 (“Kanagawa 2003”). There were also errors within the sequencing process, such as signal cross-talk, where signals overlap and do not accurately identify the nucleotide, leading to a sequencing read containing the wrong nucleotide. EX2010.0002-03 (“Whiteford 2009”). Lastly, errors occurred during sequencing strand synthesis, leading to sequence strands containing an incorrect insertion or deletion of a nucleotide. EX2007.0001-02 (“Nakamura 2011”).

B. Challenges With Existing Methods of NGS

Because of the errors inherent in the NGS process, identifying duplicates to accurately map the sequence reads and to distinguish between mutations versus sequencing errors, became an area of interest for both whole genome and targeted enrichment NGS applications. Beyond the scientific issues noted above, the problem of duplicates also had practical implications. For example, large numbers of duplicates in data led to unnecessarily large data sets, making it more difficult to parse the data and more expensive and burdensome to store. EX2015.0003-04 (“Mardis 2017”). Removing duplicates as much as possible would not only allow for more accurate sequencing, but would also save on the time and expense of data analysis associated with sequencing.

One way to identify duplicates was to match the beginning and end of fragments to positions in the reference genome—the odds were higher that fragments with the same beginning and end sequences would be duplicates. EX1003.0009 (“the ’399 patent”). But with this method, there was still a risk that naturally-occurring repetitive sequences would be improperly identified as duplicates. The identification of duplicates was particularly challenging with single primer target enrichment methods, where only the side of the fragment associated with the primer would vary in position across the reference genome. *Id.* The end-

matching method was not usable at all in instances where the reference genome was unknown.

One potential solution involved the use of “barcodes” of nucleotides to tag original sequences prior to sample preparation and amplification. EX1033.0099 (“Samuels”). The presence of the barcode signaled that a fragment was part of an original sequence. *Id.* It could also be used to identify mutations present in the genome versus mutations introduced via PCR, sequencing, or sequence strand synthesis. *Id.* The barcode method, while helpful, also had downsides. Barcodes added extra nucleotides to each fragment, which increased the total number of nucleotides that needed to be sequenced and took up space on the sequence read. EX2014.0008-09 (“Wong 2013”). Shorter barcodes required less space but reduced the number of unique barcodes available and had limited value for samples that contained many unique fragments. EX2003.0041 (“Doan 2022”). As of 2013, researchers in the field struggled to find a method of identifying duplicates that improved on the accuracy of the original barcode method while still allowing for longer sequence reads.

III. THE '357 PATENT

A. Overview

The '357 patent is directed to a method of detecting and subsequently removing duplicate sequencing reads from a sample population. EX1004.0001. The

claimed method is beneficial in overcoming issues related to duplication that arose in previous sequencing methods, such as the problem of distinguishing between mutations and sequencing errors, as described above. *See supra* Section II. The claimed method provides cleaner sequencing data by allowing the identification and removal of unnecessary duplicative data. This is particularly beneficial for sequencing applications where a user seeks to understand the relative amount of starting material where a scientist would want to compare the quantity of the sequenced gene in relation to another gene that might be present in the sample. In addition, as noted above, the accurate removal of duplicates can help to reduce the massive data set generated by sequencing methods, saving both time and money.

B. Level of Ordinary Skill in the Art

In its Institution Decision, the Board adopted Tecan's proposed definition of a POSA with minor modifications. Specifically, the Panel held that a person of ordinary skill in the art ("POSA") would possess the following qualifications:

[A] person of ordinary skill would have had a Ph.D. in the field of chemistry, molecular biology, or biochemistry. Alternatively, a POSA would have had a B.S. or M.S. degree with three to five years of experience working in any of those fields. The person of ordinary skill would have had experience with NGS sequencing methods and a working knowledge of how those methods functioned.

Paper 7, 8-9.

For the purposes of this proceeding, Tecan does not dispute the Board's definition of a POSA.

C. Prosecution History

During prosecution of the '357 patent, Applicants overcame multiple rejections based on the prior art references McCloskey (EX1022) and Samuels (EX1033). To overcome obviousness rejections based on McCloskey, Applicants argued that McCloskey disclosed "methods to identify redundant sequences using ... a 'batch stamp,' and 'barcode,' and a target specific 'genomic target-binding site.'" EX1019.0452 ("File History for the '357 patent"). In contrast, Applicants described the claimed method as "identifying sequence reads with identical identifier and fragment sequences" to "identify redundant or duplicate sequences." *Id.*, .0452-53. Applicants further distinguished the claimed method by arguing that, "in contrast to the claimed methods, McCloskey does not use the sequence of a nucleic acid fragment to identify redundant or duplicate sequences." *Id.*

In overcoming obviousness rejections based on Samuels, Applicants distinguished the claimed method by arguing that "Samuels does not teach detecting duplicate sequence reads. Rather, Samuels reports using barcodes to differentiate sequencing errors from single nucleotide polymorphisms," thus, "Samuels fails to disclose detecting duplicate sequence reads by any means." *Id.*, .0452.

D. Claim Construction1. “indexing site”

The Board construed the term “indexing site” as “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.” Paper 7, 10-11. For the purposes of this proceeding, Tecan does not dispute this construction.

2. “identifier site”

The Board construed the term “identifier site” as “a nucleic acid sequence that comprises random bases and is used to identify duplicate sequencing reads.” Paper 7, 11. For the purposes of this proceeding, Tecan does not dispute this construction.

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

Term (Claims)	Tecan’s Proposed Construction
“identifying sequence reads with identical identifier and target sequences as duplicates” (’357 patent, claim 1)	“identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence”

The term “identifying sequence reads with identical identifier and target sequences as duplicates” appears in claim 1. Tecan agrees with the Panel’s suggestion that construction of this limitation will be helpful, as the parties seem to disagree regarding the meaning of this term. Paper 7, 11-13.

Based on a proper reading of the specification and prosecution history, the term “identifying sequence reads with identical identifier and target sequences as duplicates” should be construed as “identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence.”

When construing the claims of a patent, courts consider the express language of the claims, the patent specification, and the prosecution history. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 977-80 (Fed. Cir. 1995) (en banc), *aff’d*, 517 U.S. 370 (1996). “Claim terms are generally given their ordinary and customary meaning as understood by persons of ordinary skill in the art in view of the specification and prosecution history.” *Groove Digital, Inc. v. United Bank*, 825 F. App’x 852, 855 (Fed. Cir. 2020) (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc)). Here, all intrinsic evidence supports Tecan’s proposed construction.

Starting with the claim, it is clear from the claim language itself that Applicants intended that the claimed method included an independent step of identifying duplicates by using both the identifier and at least a portion of the target sequence. Each of the steps of the claimed method include specific elements necessary for that step, and the identifying step is no different. An interpretation of this term that allows the identification of duplicates with only one of the claimed elements essentially reads out the rest of this limitation. For example, if this claim

is interpreted to read on a method that includes a step of identifying duplicates using only the identifier site, the reference to the target sequence in this limitation is entirely removed from the claim. *Apple, Inc. v. Ameranth, Inc.*, 842 F.3d 1229, 1237 (Fed. Cir. 2016) (holding that, in considering the words of a claim for construction, a court should “give meaning to all of a claim’s terms”). Additionally, reading this limitation expansively to include the use of the identifier site and the target sequence in different parts of the method similarly ignores the plain language of the claim that requires that both of these elements be used in the “identifying” step of the method. *See Callicrate v. Wadsworth Mfg., Inc.*, 427 F.3d 1361, 1369 (Fed. Cir. 2005) (holding that it was error for the district court to read out a limitation clearly required by the claim language and specification).

The specification also supports Tecan’s proposed construction of this term. For example, Example 5 of the ’357 patent, “Identification of Duplicate Sequencing Reads in Determining mRNA Expression Levels,” describes a process of identifying duplicate sequencing reads using both the identifier and a portion of the target sequence. Example 5 explains that each adapter contains a “unique identifier ... that enables libraries made with these adapters to be distinguished.” EX1004, 20:19-21; EX2035.¶¶ 85-88 (“Bustamante Declaration”). After amplification and sequencing, “[t]he first 50 bases of the target sequence read are compared to each other. Any read that has identical sequence to any other read is identified as a duplicate.”

EX1004, 20:58-62. Based on the structure of the adaptor used in Example 5, the “target sequence read” includes **both** the claimed identifier sequence and a portion of the target sequence. EX2035.¶¶ 85-88. Thus, Example 5 describes a method in which the identifier and a portion of the target sequence are used together as part of a process to identify duplicates. Once a “read that has [an] identical sequence to any other read is identified as a duplicate,” it is “removed from the population” such that “only a single copy is retained within the file.” EX1004, 20:60-62. After duplicate reads are removed, Example 5 then instructs that the 8 bases of the identifier are removed from each read, confirming that the comparison to identify duplicates used both the identifier site and a portion of the target sequence. *Id.*, 20:62-64.

The specification of the '357 patent additionally discloses that, “[if] the sequences of two libraries¹ are identical, their duplication status is unknown since this could occur by chance in any library. If an identifier sequence is used in combination with the library reads, the status can be determined (***duplicates if identical***, distinct if different).” *Id.*, 17:64-18:1 (emphasis added). Thus, the

¹ A sequencing library refers to a collection of nucleic acid fragments to be sequenced. EX2035.¶ 50. A POSA would understand that one could have different sequencing libraries for nucleic acid fragments that originate from different biological samples. *Id.*, ¶ 60.

specification makes clear that a critical feature of the claimed method is that both a portion of the target sequence and the identifier sequence are used together to determine whether a sequence is a duplicate.

Tecan's proposed construction is also consistent with Applicants' statements during the prosecution of the '357 patent and its predecessors. The '357 patent issued from an application that was a continuation of Application No. 15/406,002, which was a division of Application No. 14/540,917. During prosecution of the 14/540,917 application, the Examiner rejected McCloskey and Samuels. EX1018.0780-81 ("File History for the '399 patent"). McCloskey is directed to a method of identifying redundant sequences in a sequencing dataset, and discloses the use of 7-nucleotide-length "barcodes" and "batch-stamps" to do so. EX1022.0004. McCloskey further describes identification of sequence reads based only on reads that share the same "barcode" or "batch-stamp." *Id.*, .0006. Samuels is directed to a method of attaching barcodes to a nucleotide sequence to allow a user to differentiate PCR-caused errors from true single nucleotide polymorphisms. EX1033.0086-87, 94, 97, 99. Samuels further discloses amplifying the barcodes and nucleotide sequence via PCR, and sequencing the amplified products. *Id.*

Applicants overcame rejections based on McCloskey and Samuels by amending the claims to add the "identifying" limitation that is similar to that in the issued claims of the '357 patent:

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

EX1018.0807. Applicants explained that the “identifying” step required comparison of both the identifier and a portion of the target sequence in the same identifying step. Specifically, Applicants distinguished Samuels because it “do[es] not teach (1) *the active step* of ‘identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads.’” *Id.*, .0797-78 (emphasis added). Applicants also stated that the claimed method “is very different than the method disclosed in McCloskey” because in the claimed method “the sequence of the

identifier site and the sequence of the fragment that is amplified ***are used in combination*** to discern duplication.” *Id.*, .0799 (emphasis added).

During prosecution of the application which led to the '357 patent, Applicants overcame similar rejections based on Samuels and McCloskey by clarifying that the claimed method was directed to “using the identifier and fragment sequence to identify duplicate reads ... ***[T]he fragment sequence is used in conjunction with the identifier*** to find duplicates.” EX1019.0453. When an inventor has asserted that the invention does or does not include a particular aspect, that intention “is regarded as dispositive.” *Phillips*, 415 F.3d at 1316. Thus, a POSA would understand from the statements made during prosecution that Applicants were directing the claims at a method that includes a step in which duplicates are identified using a combination of the identifier site and at least a portion of the target sequence.

Thus, the claim language, the specification, and the prosecution history all support a conclusion that the term “identifying sequence reads with identical identifier and target sequences as duplicates” means “identifying sequence reads as duplicates through a step that uses both the identifier and at least a portion of the target sequence.”

4. “duplicates”

Term (Claims)	Tecan’s Proposed Construction
“duplicates” (’357 patent, claim 1)	“reads containing identical sequences as the original nucleic acid fragment”

In the Institution decision, the Board suggested that the parties may want to address “whether ‘duplicates’ in claim 1 of the ’357 patent means the sequences possess an identical sequence.” Paper, 11-13. It is Tecan’s position that, based on the intrinsic record, the term “duplicates” should be construed as “reads containing identical sequences as the original nucleic acid fragment.”

Both the specification and the relevant prosecution history support that this term refers to identical sequences. The specification of the ’357 patent explains that “[t]he present invention is based, in part, on ... methods for discerning duplicate sequencing reads from a population of sequencing reads” (EX1004, 2:14-16), and that these “duplicate reads” are those that have identical sequences: “[t]he first 50 bases of the target sequence read are compared to each other. Any read that has *identical sequence* to any other read is identified as a duplicate and removed from the population, thus, only a single copy is retained within the file.” *Id.*, 20:58-62; *see also id.*, 1:46-48 (“Generally, sequencing reads may be determined to be duplicates if both forward and reverse reads have identical starting positions.”).

The prosecution of the application that led to the '357 patent, as well as the prosecution of a related patent in this family of applications, further clarifies that a POSA would understand the term “duplicates” to be those with identical sequences as identified by the recited step, rather than those with sequencing errors. In response to the Examiner’s rejection of the claims over Samuels and McCloskey, Applicants argued that “Samuels does not teach detecting duplicate sequence reads. Rather, Samuels reports using barcodes to differentiate sequencing errors from single nucleotide polymorphisms.” EX1019.0452.

Thus, the term “duplicate sequencing reads” should be construed as “reads containing identical sequences as the original nucleic acid fragment.”

5. “comprising”

The Board construed the term “comprising” as “an open-ended transition that is not limited to the listed steps.” Paper 7, 13. The Board noted that this was based on a “preliminary record” and recommended that the parties address the construction of this limitation, particularly “whether the prior art meets the claim if the prior art discloses a method of identifying as duplicates those sequence reads with identical labels and target fragments and, in addition also identifies other sequence reads as duplicates, including sequence reads with some mutations resulting from PCR or SBS error.” *Id.*

The “comprising” transitional phrase of the challenged claims leaves open the possibility that additional steps can be included in the method. This term, however, cannot be interpreted so broadly as to effectively eliminate the step of identifying duplicates as claimed. *Dippin’ Dots, Inc. v. Mosey*, 476 F.3d 1337, 1343 (Fed. Cir. 2007) (“The presumption raised by the term ‘comprising’ does not reach into each of the six steps to render every word and phrase therein open-ended.”). Use of “comprising” creates a presumption that the list of elements is nonexclusive but “is not a weasel word with which to abrogate claim limitations.” *Spectrum Int’l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1380 (Fed. Cir. 1998).

The Board’s proposed interpretation that allows for the overall method to include identification of both duplicates and sequences that contain PCR or SBS errors aligns with the typical interpretation of a comprising claim. The critical piece, however, is that this broad interpretation of the claims cannot be read to include a method in which the identifying duplicates step only identifies sequences with PCR or SBS errors and does not identify duplicates in the manner claimed. As described above, the specification explains that the goal of the claimed method is to efficiently identify reads that have identical sequences. *See supra* Section III.D. Expanding the claims to include only identification of reads without duplicate sequences (those that contain PCR or SBS errors) makes this limitation superfluous and cannot be the correct interpretation.

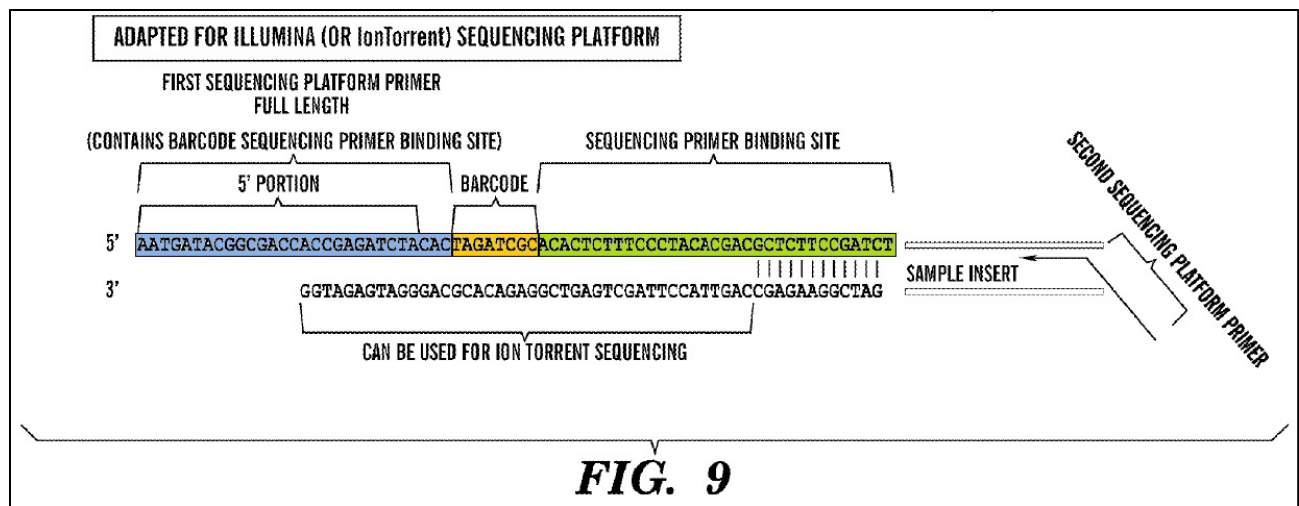
For example, the prosecution history supports that the claim does not cover a method in which the identification step is specifically used to identify sequence reads with PCR errors. During prosecution, Applicants overcame rejections based on prior art that was directed to identifying sequencing errors, not to identifying duplicates using the claimed steps, by clarifying that the claimed method was not directed to identifying sequencing errors. *See, e.g.*, EX1019.0452 (“Samuels does not teach detecting duplicate sequence reads. Rather, Samuels reports using barcodes to differentiate sequencing errors from single nucleotide polymorphisms.”); *id.*, .0453-54 (“Modifying Samuels to use identifiers and fragment sequences to detect duplicate sequences would run counter to the principle of operation of Samuels, which seeks to distinguish between sequence reads with the same barcode/identifier.”); EX2035.¶¶ 76-78. These statements during prosecution made clear that Applicants did not intend for the claims to cover methods in which the identification step was directed at identifying only sequencing errors.

Under the proper construction of the claims, the claims cover a method of identifying sequence reads that are identical as duplicates through a process that uses both the identifier and at least a portion of the target sequence. This method does not exclude methods that include a step of identifying PCR errors in addition to the claimed step of identifying duplicates.

IV. THE CITED REFERENCES

A. Iafrate

Iafrate discloses a sequencing method that uses an adaptor comprising an indexing primer binding site, an indexing site, and a target sequence primer binding site. EX1011.1051 (“Iafrate 2013”). Iafrate teaches the use of a “barcode” as an indexing site/sample index. *See, e.g.*, Figure 9 (reproduced below). As Petitioner’s expert admits, Iafrate does not disclose adaptors that contain an identifier site. EX2016.0030 (116:8-10) (“Sims Deposition”).



EX1011, Fig. 9.

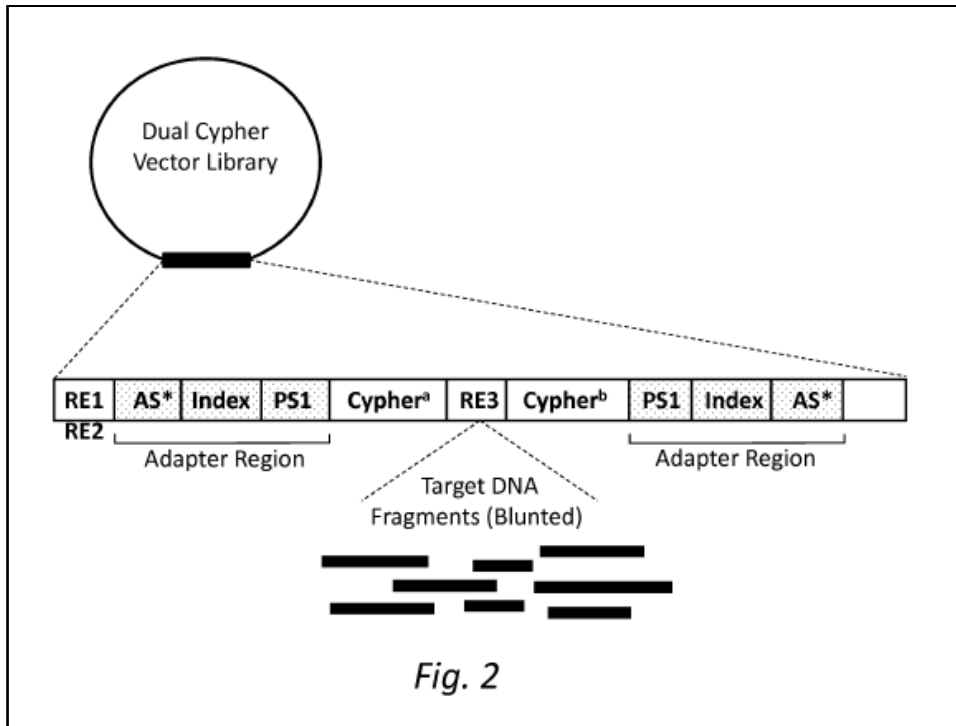
B. Kivioja

Kivioja discloses a method of “[c]ounting absolute numbers of molecules using unique molecular identifiers.” EX1012.0001 (“Kivioja 1012”). Specifically, Kivioja teaches “[c]ounting individual RNA or DNA molecules” using the “gene” (i.e., the proposed chromosomal location of the original genomic sequence) and its

“position” (proposed mapped location of the target sequence to the reference genome), as well as a “label.” *Id.*, .0001, .0005. Kivioja discloses that first, sequence reads are mapped to a reference genome. *Id.*, .0005. After the sequence reads are mapped to the reference genome, Kivioja teaches that the “mapped reads with the same gene, position, and label were collected to one UMI.” *Id.* Lastly, after the sequence reads are mapped to the reference genome, the UMI is used to count the number of unique UMIs present in the sample. *Id.* Since the method described is directed at counting sequencing reads, Kivioja does not describe removing duplicate reads.

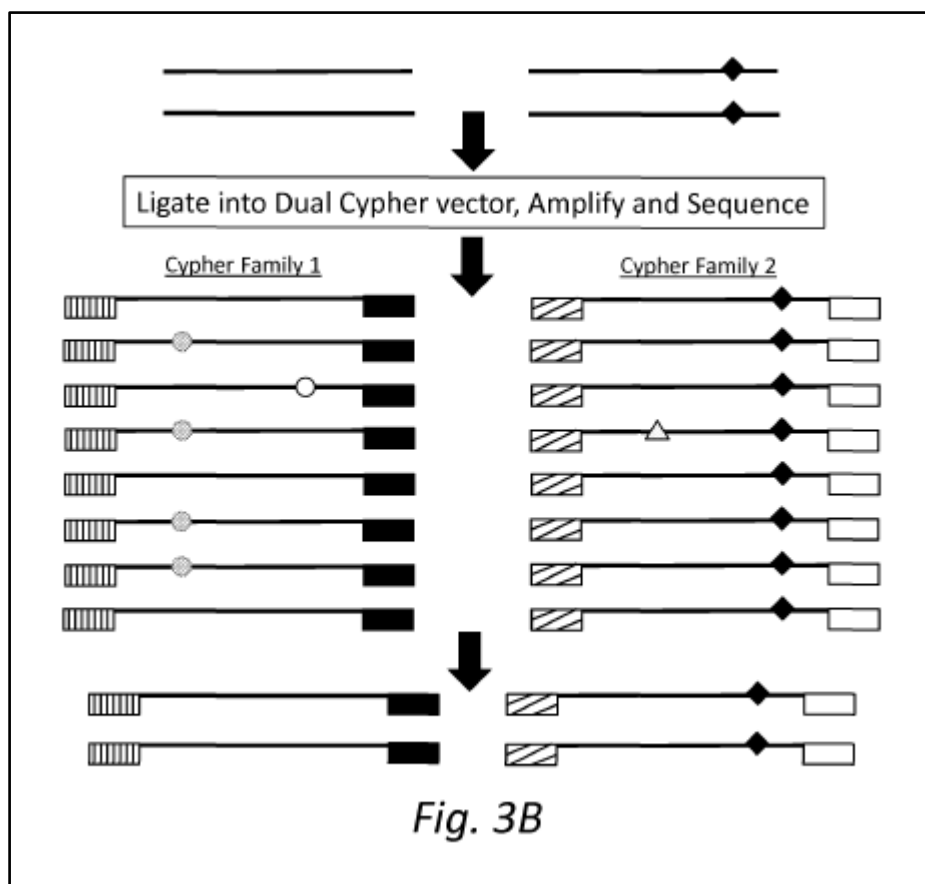
C. Bielas

Bielas discloses a method of using two identifier sites (called “Cyphers”) to sort sequencing reads into families. EX1013, Figure 2 (“Bielas 2013”) (reproduced below).



EX1013, Fig. 2.

Bielas further teaches that “[t]he *unique cypher tags* are used to computationally deconvolute the sequencing data.” *Id.*, .0027 (emphasis added). As shown in Figure 3B (reproduced below), each sequence with the same pair of Cyphers is placed into a family. *See* EX2016.0034 (128:18-129:15).



EX1013, Fig. 3B. Bielas discloses that the sequence reads with mutations are then eliminated from the group, and the remaining sequences in the family are used to create a consensus sequence. EX2035.¶ 117.

V. THE ASSERTED GROUNDS

Petitioner asserts that the challenged claims are unpatentable based on the following grounds:

Ground	Challenged Claims	References
1	1-4, 6-7, 9-10	Kivioja and Iafrate (35 U.S.C. §103)
2	1-4, 6-7, 10	Bielas (35 U.S.C. §102)

Ground	Challenged Claims	References
3	1-4, 6-7, 9-10	Bielas (35 U.S.C. §103)

VI. GROUND I: PETITIONER’S COMBINATION OF KIVIOJA AND IAFRATE DOES NOT RENDER THE CHALLENGED CLAIMS OBVIOUS

Petitioner’s arguments for Ground 1 fail because the Petition does not point to prior art references that disclose all elements of the challenged claims. *Johnson Controls, Inc. v. Wildcat Licensing WI, LLC*, IPR2014-00305, Paper 45 at 28, n. 3 (PTAB June 22, 2015) (holding that “mere attorney argument” will not substitute for objective evidence). Specifically, Petitioner has failed to identify any prior art reference that discloses identifying duplicate sequence reads in the manner described in the challenged claims. Because all challenged claims require this identification of duplicates step, Petitioner’s arguments in Ground 1 are insufficient to show the claims are unpatentable as obvious. Additionally, Petitioner has separately failed to show that the prior art discloses the additional limitation of claim 2, directed at the removal of duplicate sequences. Lastly, Petitioner has not put forward any argument, other than attorney argument, to support a purported motivation to combine. This is insufficient as a matter of law: Petitioner always carries the burden to prove unpatentability (which never shifts to the patentee), and must establish motivation to combine by demonstrating “an articulated reasoning with rationale underpinning sufficient to support a motivation to modify the prior art teachings.”

William Wesley Carnes, Sr., Inc. v. Seaboard International, Inc., IPR2019-00133, Paper 10 at 17 (PTAB May 8, 2019).

A. Neither Kivioja Nor Iafrate Disclose Limitation 1(d)

Petitioner's expert, Dr. Sims, admits that Iafrate does not disclose an adaptor with an identifier site. EX2016.0030 (116:17-18) ("The Iafrate adaptor does not include an molecular tag or identifier site."). As a result, Iafrate cannot disclose a method that uses the identifier site to identify duplicates. Petitioner relies solely on Kivioja for the limitation of claim 1(d), which requires "identifying sequence reads with identical identifier and target sequences as duplicates." EX.1004.0024. Based on the proper claim construction, this limitation requires the use of the identifier label and the target sequence in the same step of identifying duplicate sequence reads. EX2035.¶¶ 126-32; *supra* Section III.D.3-4.

Contrary to Petitioner's interpretation, Kivioja does not teach that a portion of the target sequence must be used in conjunction with the label to identify duplicates. Instead, Kivioja describes a three-step process of counting reads, none of which employ both the target sequence and the label. Petitioner relies on Kivioja's reference to looking to the "gene, position, and label" of mapped reads when collecting sequenced reads, but as explained further below, using the gene and/or position is not the same as using the target sequence and, therefore, Kivioja does not disclose limitation 1(d). EX1012.0005.

The data analysis in Kivioja relevant to this proceeding involved three separate steps. These steps each serve a purpose in Kivioja's experiments, but do not include the claimed step of using both the target sequence and the identifier in a single step to identify duplicates.

KIVIOJA STEP 1: Mapping sequence reads to a known genome. After collecting the sequencing data, Kivioja explains that the reads were mapped to a reference genome. *Id.*, .0004 (“Reads were mapped to the genome using Bowtie.”); *see also* EX2016.0029-30 (109:16-113:09) (agreeing that Kivioja does not describe looking to the actual target sequence itself, but rather teaches the use of the gene position). Mapping sequence reads to a known genome, or Reference Genome Alignment, requires several assumptions and choices. EX2035.¶¶ 54-59. A published available reference genome is identified, then computational aligner tools are used to compare each individual sequence to the entire published reference genome. *Id.*, ¶ 56. The aligner tool finds the best “fit” of sequence to specific gene and position on the reference genome, based on certain criteria that one inputs into the tool. *Id.* The aligner tool then assigns the sequences to a likely gene and position in the reference genome and provides a quality score that indicates the confidence that the alignment assignment is correct. *Id.*

KIVIOJA STEP 2: Discard unmapped data. After mapping the reads to a known reference genome, Kivioja then discards reads that did not map against the

known reference genome. EX1012.0005; EX2016.0029 (110:22-111:16). Specifically, reads were discarded if they did not contain the expected sequence, mapped to the wrong strand, or had a low mapping quality score. EX1012.0005.

KIVIOJA STEP 3: Sorting into families. Once the reads are mapped and the non-mapped reads are discarded, Kivioja explains that reads with the same *mapped gene and position* and label are then “collected to one UMI.” EX1012.0005 (emphasis added). It is thus the mapped gene and position that are used with the label to count the UMI collections in Kivioja. EX2035.¶¶ 107-116; EX2016.0029 (109:20-112:21) (opining that Kivioja first aligns sequence reads to a known genome, then discards reads “based on certain criteria,” and lastly collects reads with the same gene, position, and label to one UMI and records such reads as a copy number of that UMI). Kivioja does not include any disclosure that the target sequence is used in this step.

As Petitioner’s expert admits, the gene and position data is a different piece of data than the nucleic acid sequence of the target sequence. EX2016.0028 (105:15-22). Additionally, Dr. Sims admitted that there can be differences between mapped reads and the actual target sequence, and that “the sequenced nucleic acid fragment can differ from the sequence on the genome from which that nucleic acid fragment originated.” EX2016.0028 (105:15-22); *see also id.* (106:7-12) (explaining that “an observed sequence for a given read” and “a reference sequence that’s known

a priori ... can be different from each other.”). For example, due to natural genetic variation, a nucleic acid sequence from a given individual may contain nucleotide mutations not present in the corresponding sequence in the reference genome. EX2035.¶ 117. In contrast to the “mapping” method taught by Kivioja, claim 1 requires that the target sequence—not data gathered from the use of the target sequence—and the label are used in conjunction to identify duplicates.

A POSA would also have understood that the use of the mapped gene and position is functionally distinct from the use of a portion of the target sequence. Mapping sequence reads to a portion of the reference genome, rather than to a portion of the target sequence itself, lacks the precision of the claimed method. *Id.*, ¶ 57. For example, mapping to a reference genome allows for the inadvertent misassignment of reads to an incorrect location in the genome. *Id.* In addition, for certain applications, determining duplicates based on mapping to a reference genome can be very limited, such as de novo genome sequencing (where no reference genome is available) or when only incomplete contig/scaffold-based genomes are available. *Id.* ¶¶ 57-58. In contrast to the many errors inherent in mapping, looking directly at the fragment nucleic acid sequence removes these potential sources of error, increasing the accuracy of duplicate identification. *Id.* ¶¶ 54-59.

Thus, because Kivioja uses only the gene and position with the label, and not the target sequence, to group the reads into families, Kivioja does not disclose the claimed limitation 1(d), and the combination of Kivioja and Iafrate does not disclose all limitations of the challenged claims. *See supra* Section III.D.3-4.

B. Neither Iafrate Nor Kivioja Disclose Removing Duplicate Reads (Claim 2)

Claim 2 depends from claim 1 and “further compris[es] removing a duplicate read from the sequence reads.” EX1004, cl. 2. As with limitation 1(d), Petitioner relies solely on Kivioja for disclosure of this additional limitation.

Kivioja is directed toward “counting” individual DNA molecules of known genomes, not to removal of duplicate sequence reads. EX1012.0001-02; *see also* EX2016.0030 (113:5-9) (“those UMI are used for quantifying or counting the number of molecules corresponding to a given nucleic acid fragment in the original sample”); *id.*, (113:15-114:3) (explaining that if a pair of reads had the same label and sequence, “you would have two reads, but you would only count them as one.”). For example, Kivioja discloses the use of molecular tags to estimate the number of fragments without directly observing each one. EX1012.0001. Lastly, in the mRNA-seq data analysis example, *see supra* Section IV.A., after the reads are “collected to one UMI,” the reads are then counted by “record[ing] ... the copy number of that UMI.” *Id.*, .0005.

Petitioner admits that Kivioja fails to disclose this limitation. Paper 1, 41. To cure this defect, Petitioner attempts to instead argue that removing duplicates is inherent in the method disclosed by Kivioja. *Id.* In support, Petitioner's expert asserts that the Kivioja method "collapse[s] the labeled and amplified nucleic acid fragments." EX1079, ¶ 239. But Petitioner's interpretation does not match the disclosures of Kivioja, and Petitioner's expert does not dispute that the UMIs are not removed prior to the counting taught in Kivioja. EX2016.0029-30 (111:17-115:1). In fact, Petitioner cannot point to any disclosure in Kivioja that suggests that reads within each UMI family are removed from the data. Instead, Kivioja suggests that this data is *retained*, as to allow for analysis of copy number. EX1012.0005. Additionally, none of the figures on which Petitioner relies in Kivioja show that the members of the UMI families are removed—in each, all members of the families are present, in parallel with the counting of UMIs. *See, e.g., id.*, Fig. 1a. Thus, Petitioner has failed to show that Kivioja discloses the additional limitation of claim 2, and as such cannot show that the combination of Kivioja and Iafrate would have rendered claim 2 obvious.

C. Petitioner's Motivation to Combine Kivioja and Iafrate is Deficient

"To satisfy its burden of proving obviousness, a petitioner cannot employ mere conclusory statements." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380 (Fed. Cir. 2016). But to support its motivation to combine Kivioja and Iafrate

to arrive at the claimed method of 1(d), Petitioner relies heavily on a single bald statement from Kivioja: “[u]se of this method can improve accuracy of almost any next-generation sequencing method.” EX1012.0001; Paper 7, 27. Such a broad and cursory statement is insufficient to establish motivation to combine, which requires a Petitioner to “demonstrate[] ... which of the prior art elements allegedly has a known function, what that function is, and why that function is allegedly predictable.” *Johns Manville Co. v. Knauf Insulation, Inc.*, IPR2018-00827, Paper 9 at 12 (PTAB Oct. 16, 2018) (holding no motivation to combine references from the thermosetting composition field when Petitioner relied on a statement in the prior art that its methods were appropriate wherever a thermosetting composition may be used); *see also William Wesley*, IPR2019-00133, Paper 10 at 17 (holding Petitioner’s obviousness argument based on references being in the same field and directed toward the same objective and process was insufficient; rather, “an articulated reasoning with rationale underpinning sufficient to support a motivation to modify the prior art teachings” was required).

Even assuming that the prior art disclosed all limitations of the challenged claims, Petitioner fails to show that a POSA would have been motivated to combine Iafrate and Kivioja to arrive at the challenged claims, let alone with a reasonable expectation of success. Petitioner relies on improper hindsight, conclusory statements, and the *ipse dixit* of an expert witness, to support its allegations that a

POSA would have been motivated to combine the prior art to arrive at the challenged claims and to have a reasonable expectation of success in achieving them. *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991).

Petitioner claims that a POSA would have been motivated to start with the adapter of Iafrate and modify it according to the disclosures of Kivioja to arrive at the adaptor required in claim 1. Petitioner admits, however, that neither Iafrate nor Kivioja discloses an adapter that contains all elements of the claimed adaptor. Paper 1, 24 (“Iafrate teaches a method of NGS library preparation using an adaptor with all but one of the features recited in claim 1 of the ’357 patent.”), 31 (“[Kivioja] contained a primer binding site (green), which is an Illumina universal target sequence primer binding site and is identical to the one in the Iafrate adapter, a random sequence UMI (yellow), and an indexing site (orange)”). Petitioner glosses over the differences between the Iafrate and Kivioja adapters, on the one hand, and the claimed adapters, on the other, by arguing that Kivioja’s target sequence primer binding site serves the purpose of both of the claimed primer binding sites, but Petitioner provides no explanation on why or how a POSA would combine aspects of the Iafrate and Kivioja adapters. Paper 1, 31. The Petition is, in fact, entirely silent on which aspects of the Iafrate method the POSA would use in any improved sequencing method. Petitioner’s explanation of its obviousness arguments focus solely on the disclosures of Kivioja. *See* Paper 1, 35-41. The only mention of Iafrate

in Petitioner's obviousness argument for claim 1 refers to providing a motivation to use a shorter molecular tag. Paper 1, 38. But, Iafrate does not disclose a molecular tag, so Petitioner cannot rely on Iafrate for the disclosure of that limitation. Nor does Iafrate have any discussion of or suggestion to use a shorter molecular tag. As a result, the Petition lacks any evidence that a POSA would have been motivated to combine aspects of Iafrate with aspects of Kivioja to arrive at the claimed invention. Instead, the manufactured motivation to combine these two references in the Petition is entirely based on improper hindsight.

Petitioner, therefore, has failed to prove that any challenged claim is unpatentable as obvious in light of the combination of Iafrate and Kivioja.

VII. GROUNDS 2 AND 3: PETITIONER HAS NOT SHOWN THAT ANY CHALLENGED CLAIM IS ANTICIPATED BY, OR OBVIOUS OVER, BIELAS

Similar to Petitioner's arguments for Ground 1, its arguments for Grounds 2 and 3 are based on another prior art reference that fails to use both the identifier site and the target sequence together to identify duplicate sequence reads. As Petitioner's expert admits, Bielas discloses a sequencing method with several data analysis steps, but none of these steps use both the target sequence and the identifier site. As such, Petitioner has failed to prove that the challenged claims are unpatentable in light of Bielas.

A. Bielas Does Not Disclose Identifying and/or Removing a Duplicate Sequencing Read Based on the Identifier Site and Nucleic Acid Fragment

Petitioner has failed to show that Bielas discloses or teaches limitation 1(d), requiring “identifying sequence reads as duplicates through a single step that uses both the identifier and the target sequence.” EX1004.0024. As described above, the claim language requires that both the label and the target sequence be used to identify duplicates. *See supra* Section III.D.3. Bielas does not disclose the use of both label and target sequence to identify duplicates. Like Kivioja, Bielas discloses several data analysis steps, some of which use the cyphers disclosed in Bielas, and others that analyze the target sequence. None of these steps use both the cyphers and the target sequence together to identify duplicates.

Petitioner relies on the disclosures of Example 1 and Example 3 in Bielas for its anticipation arguments (Paper 1, 47), but neither of these examples discloses all limitations of the challenged claims.

Example 1. Bielas’s Example 1 states only that “[t]he unique cypher tags are used to computationally deconvolute the sequencing data.” EX1013.0027 (emphasis added). As an initial matter, Bielas does not explain what “computationally deconvolute” means in this context. “Computationally deconvolute” can refer to a number of actions, including sample de-multiplexing, and does not necessarily mean to identify duplicates. EX2035.¶ 122; *see also*

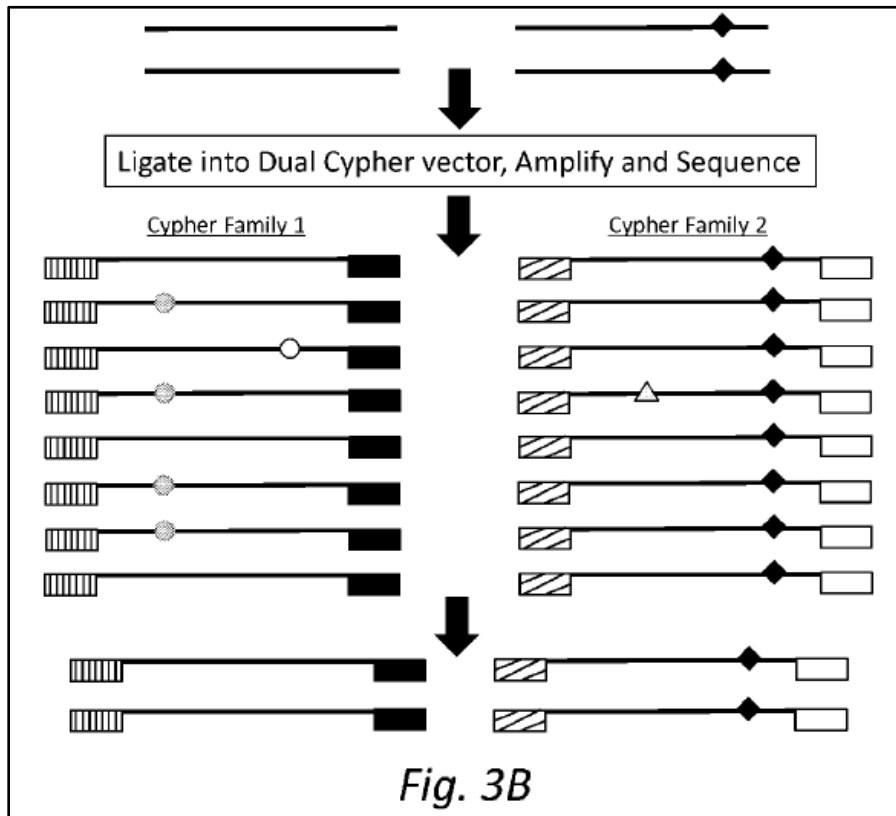
EX2016.0033 (126:5-11). In, fact Dr. Sims has used this term in his publications to mean something very different from deduplication. *See Deconvolution of cell type-specific drug responses in human tumor tissue with single-cell RNA-seq*, 13 GENOME MEDICINE, 82 (2021). There is nothing in Bielas that provides information regarding what analysis is referred to as “computational deconvoluting,” and Dr. Sims does not provide any support for his bald assumption that Bielas meant deduplication. Such unsupported expert testimony cannot supply a limitation that is not found in prior art, and should be rejected. *Xerox Corp. v. Midwest Athletics and Sports Alliance LLC*, IPR2019-00426, Paper 9 at 40 (PTAB July 22, 2019).

Additionally, Example 1 does not teach that both the cyphers *and* the portion of the target sequence were used to “deconvolute” the data. Bielas plainly states that “unique cypher tags” were used to “computationally deconvolute” the data, without any mention of reference to the target sequence. *See* EX1013.0025. Here again, Petitioner relies on unsupported testimony from Dr. Sims to fill in the gaps of the disclosure of Bielas, and these arguments should be rejected. *Xerox Corp.*, IPR2019-00426, Paper 9 at 40.

Based on the actual disclosure of Bielas, Example 1 does not disclose all limitations of the challenged claims.

Example 3. Bielas’s Example 3 similarly uses a series of steps to analyze the sequencing reads. First, Bielas explains that “all sequencing reads with identical

cypher pairs and their reverse complements were grouped into families.”
 EX1013.0031. Figure 3B shows that the sequences are grouped based only on their
 Cypher pairs—without reference to the target sequences.



Id., Fig. 3; EX2016.0033-34 (128:18-129:15) (explaining that in Example 3 of Bielas, “[t]he cypher pairs and their reverse complements are used to group sequencing reads into families”). Bielas does not describe using the target sequence to create the cypher families.

The Bielas method also fails to teach a method of identifying duplicates, as described in the claims. The purpose of Bielas is to determine if a mutation is an artifact of PCR or a true mutation in the sample. EX2016.0032 (121:6-122:7)

(agreeing that “Bielas focused on” whether “a mutation was an artifact of PCR or a true mutation in the sample”); *id.*, .0035 (134:19-22) (“The Bielas technology is designed to remove mutations that occur due to errors made by DNA polymerase during PCR amplification and errors made during sequencing.”); *see also*, EX1013.0001 (“The present disclosure provides compositions and methods for accurately detecting mutations.”); *id.*, .0004-05. Nothing in Bielas discloses that the fragments are used to identify duplicates under the proper construction of the challenged claims; rather, Bielas’s method allows a POSA “to more accurately distinguish true mutations ... from artifact ‘mutations.’” *Id.*, .0007; EX2025.¶¶ 117-124, 143, 144. This is precisely the type of method that Applicants distinguished from the claimed method. *See supra* Section III. As described above, Applicants argued during prosecution that a method that seeks to differentiate between sequencing errors and SNP errors is distinct from the claimed method of identifying duplicates. *See supra* Section III.D.4.

Thus, Bielas does not teach a POSA to identify duplicates using a combination of an identifier sequence and at least a portion of the target sequence, as recited in claim 1.

B. Petitioner Has Not Shown a POSA Would Have Been Motivated to Modify Bielas

Petitioner also does not provide any explanation of how a POSA would modify the method of Bielas to allow for identification of duplicates based on both

the Cypher and a portion of the target sequence, much less why a POSA would have had a reasonable expectation of success in achieving the claimed method. Petitioner points to two possible modifications of Bielas in its obviousness argument (the components of the adaptors and the length of the identifier site), but does not argue that a POSA would have been motivated to modify any other aspect of Bielas to arrive at the challenged claims. Paper 1, 66-67; *see also* EX2016.0036 (140:7-17) (admitting that, in the Sims Declaration, “[t]here isn’t a detailed discussion of Claim 1D in this section, where I’m analyzing obviousness. This section focuses on other limitations.”). Therefore, Petitioner’s obviousness argument cannot cure the deficiencies of Bielas. Petitioner entirely omits any explanation of how or why a POSA would modify the method of Bielas to look instead at the combination of the Cypher and a portion of the target sequence to identify mutations. As a result, Petitioner has not shown by a preponderance of the evidence that any challenged claim is obvious in light of Bielas.

VIII. CONCLUSION

For at least the reasons set forth above, Petitioner’s proposed grounds of unpatentability fail, and Tecan respectfully requests that the Board find all Challenged Claims patentable.

Dated: July 11, 2025

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Response** complies with the type-volume limitation of 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(b)(1). The Response contains 7,730 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system use to prepare the Response.

Dated: July 11, 2025

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on July 11, 2025, a copy of the foregoing **Patent Owner's Response** and all supporting documents were served on the counsel of record for Petitioner by filing the same through the P-TACTS System as well as delivering a copy via electronic mail to the following addresses:

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