

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INTEGRATED DNA TECHNOLOGIES, INC.,
Petitioners,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2024-01506
Patent 11,725,241 B2

Before GEORGIANNA W. BRADEN, ZHENYU YANG, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

BRADEN, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Integrated DNA Technologies, Inc. (“Petitioner”) filed a Petition (Paper 1, “Pet.”) requesting *inter partes* review of claims 1–16 of U.S. Patent No. 11,725,241 B2 (Ex. 1005, “the ’241 patent”). Tecan Genomics, Inc. (“Patent Owner”) filed a Preliminary Response (Paper 6, “Prelim. Resp.”).

Under 35 U.S.C. § 314(a) and 37 C.F.R. § 42.4(a), we have authority to determine whether to institute review.

Based on the current record and for the reasons explained below, Petitioner has shown there is a reasonable likelihood that it would prevail with respect to at least one of the challenged claims. Therefore, pursuant to § 314, we institute an *inter partes* review of claims 1–16 in the ’241 patent on all challenges included in the Petition.

A. *Real Parties-in-Interest*

Petitioner identifies “Integrated DNA Technologies, Inc., and its corporate parent, Danaher Corporation,” as real parties-in-interest. Pet. 76.

Patent Owner identifies “Tecan Group AG (also known as Tecan Group Ltd.)” as a real-party-in-interest. Paper 4 (Patent Owner’s Mandatory Notices), 1.

B. *Related Matters*

The parties indicate that the ’241 patent has been asserted in the following district court litigation: *Tecan Genomics, Inc. v. Invitae Corp.*, C.A. No. 23-cv-1114-GBW (D. Del.). Pet. 76; Paper 4, 1. According to Petitioner, the ’241 patent was also asserted in *Tecan Genomics, Inc. v. QIAGEN Sciences, LLC*, C.A. No. 23-cv-1115-GBW (D. Del.). Pet. 76.

The parties indicate that Petitioner submitted petitions for *inter partes* review of U.S. Patent No. 9,546,399 in IPR2024-01502 and for U.S. Patent

No. 11,098,357 in IPR2024-01504). Pet. 77; Paper 4, 1. Patent Owner also states that Petitioner submitted petitions for *inter partes* review of U.S.

Patent No. 10,036,012 in IPR2025-00015 and for U.S. Patent No. 10,876,108 in IPR2025-00016. Paper 4, 1.

C. The '241 patent

The '241 patent is titled “Compositions and Methods for Identification of a Duplicate Sequencing Read” and it issued on August 15, 2023. Ex. 1005, codes (45), (54). It is a continuation of two U.S. patent applications, it is a divisional of another U.S. patent application, and it claims priority to a provisional application, the earliest of which was filed on November 13, 2013. *Id.* at codes (60), (63).

1. Written Description

The '241 patent “relates generally to the field of high throughput sequencing reactions and the ability to discern artifacts arising through sequence duplications from nucleotide molecules that are unique molecules.” Ex. 1005, 1:26–29. The '241 patent explains that PCR duplicate artifacts may occur in RNA sequencing applications, which hampers accurate gene expression measurements. *Id.* at 1:34–36. The '241 patent also states that paired end sequencing adds cost in expression analysis studies. *Id.* at 1:56–61. In view of this, the '241 patent expresses a need for improved methods of “low-cost, high through-put sequencing of regions of interest, genotyping or simple detection of RNA transcripts without inherent instrument inefficiencies that drive up sequencing costs due to the generation of unusable or non-desired data reads.” *Id.* at 1:64–2:2.

The '241 patent states that its method discerns “duplicate sequencing reads from a population of sequencing reads.” Ex. 1005, 2:13–15. The method includes “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 an indexing primer binding site, an indexing site, an identifier site, and a target sequence primer binding site.” *Id.*

at 2:20–27. The ’241 patent explains that “[t]he ligated adaptor-nucleic acid fragment products can be amplified, thus generating a population of sequencing reads from the amplified adaptor-nucleic acid ligation products.”

Id. at 2:27–30. In addition, “[t]he sequencing reads with a duplicate identifier site and target sequence can then be detected from the population of sequencing reads.” *Id.* at 2:30–32. One embodiment of the ’241 patent is shown in Figures 2A and 2B, reproduced below.

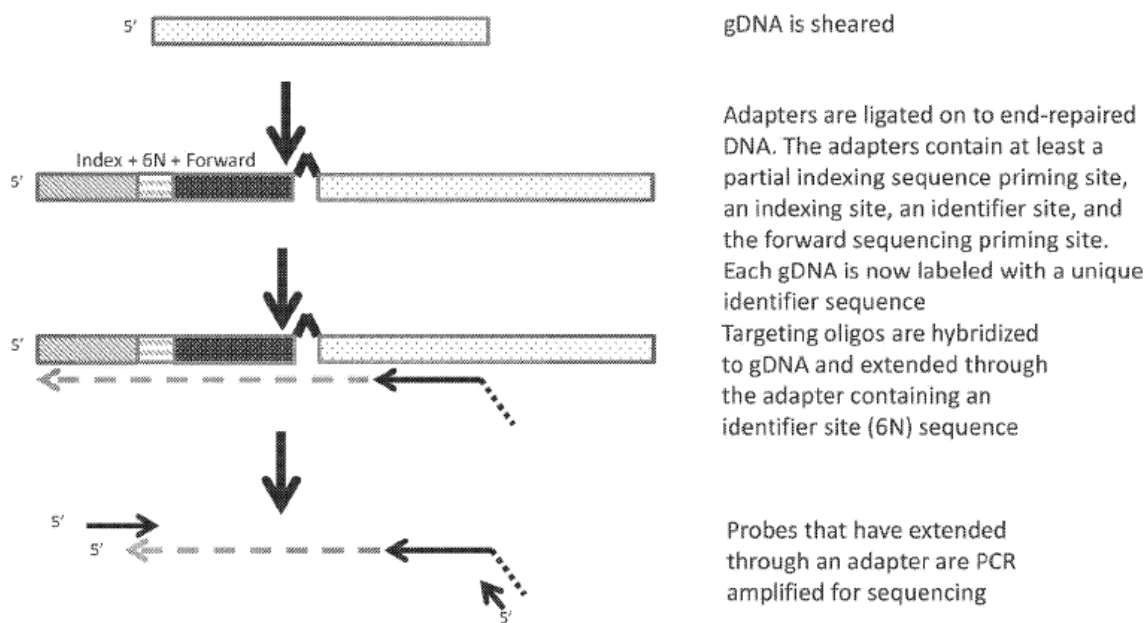
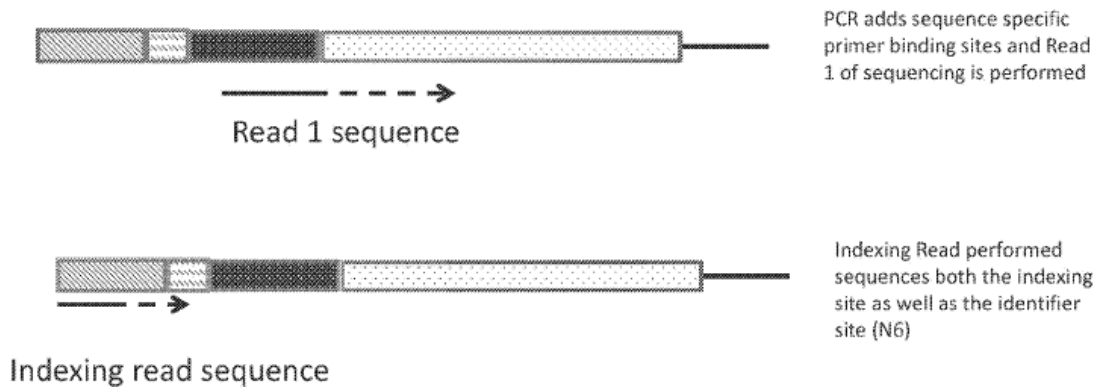


Figure 2A



Figures 2A and 2B (above, partial) are block diagrams depicting a “mechanism of the Single Primer Enrichment Technology (SPET) and how an identifier site is carried over into the final library and how sequencing through the indexing site into the identifier site provides data on which nucleic acid molecule is being identified.” *Id.* at 3:18–23.

The '241 patent further describes an example in which samples were used to generate four libraries that were each from a single amplicon. Ex. 1005, 20:61–21:2. Specifically, “[p]urified libraries were mixed and sequenced as a multiplex on the Illumina MiSeq (Illumina Inc., San Diego, Calif.) to produce 125 nt forward, 8 nt index 1, 8 nt index 2, and 25 nt reverse reads” and “the 0-8nt of random sequence contained in the adaptors ligated to the amplicon were treated as an identifier sequence and used to mark duplicates.” *Id.* at 21:2–6, 10–12. The '241 patent states that “[a]ny paired end reads that shared the same length and sequence of these random bases with any other paired end read was called a duplicate.” *Id.* at 21:12–14. One embodiment of the '241 patent is shown in Figure 4, reproduced below.

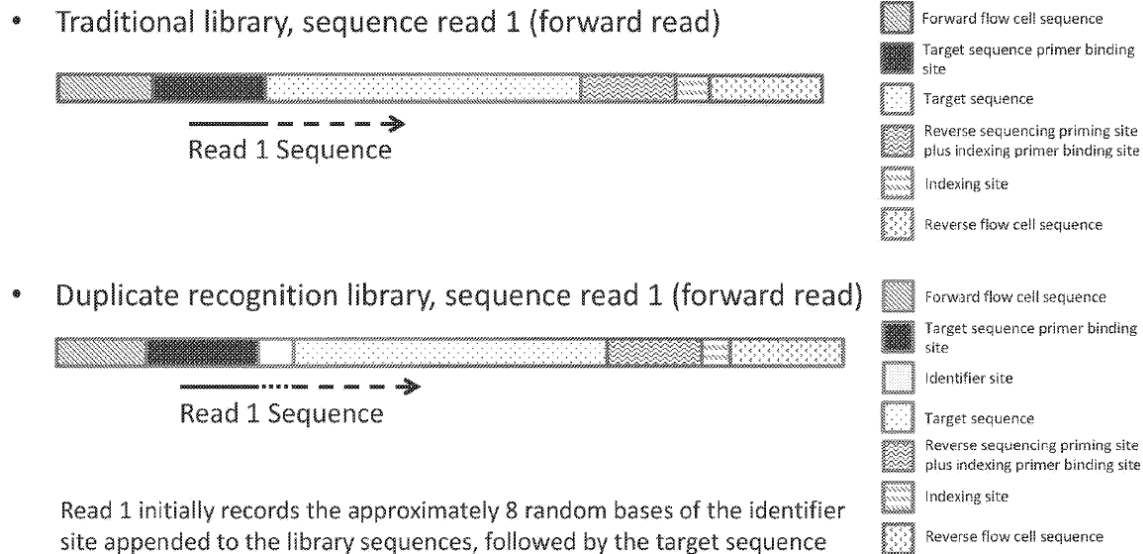


Figure 4

Figure 4 is a block diagram depicting a schematic of “two separate sequence libraries, indicating where the indexing primers and the target primers anneal in a traditional library as compared to a library using an identifier site.” *Id.* at 3:28–31.

2. Illustrative Claim

As noted previously, Petitioner challenges claims 1–16. Pet. 1. Claim 1 is the sole independent claim. Claim 1 is representative of the challenged subject matter and is reproduced below:

1. A method for detecting duplicate sequencing reads, the method comprising:
obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor, wherein each adaptor

comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment;
sequencing the amplicons to generate sequence reads that include identifier and target sequences; and
identifying sequence reads with identical identifier and target sequences as duplicates.

Ex. 1005, 25:33–43.

D. Asserted Challenges to Patentability and Evidence of Record

Petitioner challenges the patentability of claims 1–16 of the '241 patent based on the following reference or combination of references:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–16	102	Kivioja ¹
4, 6, 11, 16	103	Kivioja
1–3, 6–16	102	Bielas ²
4, 5, 11, 12, 15, 16	103	Bielas

Pet.23. In support of its patentability challenge, Petitioner relies on, *inter alia*, the Declaration of Peter A. Sims, Ph.D. (“Dr. Sims”). Ex. 1079.

II. DISCRETIONARY DENIAL UNDER 35 U.S.C. § 325(d)

The Patent Office may deny institution under 35 U.S.C. § 325(d), which provides, in pertinent part, that “[i]n determining whether to institute or order a proceeding under this chapter . . . the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to

¹ Kivioja et al., *Counting absolute numbers of molecules using unique molecular identifiers*, 9 Nature Methods 72 (2011) (Ex. 1012) (“Kivioja”).

² International Patent Application Publication No. WO 2013/123442 A1, published August 22, 2013, filed February 15, 2013, published August 22, 2013 (Ex. 1013) (“Bielas”).

the Office.” The parties dispute whether the Board should discretionarily deny the Petition under 35 U.S.C. § 325(d). Pet. 73–74; Prelim. Resp. 19–24.

Patent Owner asserts that we should discretionarily deny the Petition under § 325(d). Prelim. Resp. 19–24. Specifically, Patent Owner asserts that we should exercise our discretion under 35 U.S.C. § 325(d) to deny the petition because the prior art cited in the Petition is substantially the same as art addressed during the prosecution of the ’241 patent. *Id.* at 19. According to Patent Owner, the *Becton Dickinson/Advanced Bionics* factors weigh against institution because Petitioner’s asserted references are materially indistinguishable from Doan,³ a reference that was before the Examiner previously. *Id.* at 19–20 (citing *Xilinx, Inc. et al v. Analog Devices, Inc.*, IPR2020-01561, Paper 9 at 11 (PTAB June 10, 2021) (exercising discretion to deny institution under § 325(d) because petitioner’s two asserted references were cumulative to those considered during prosecution)). Patent Owner provides arguments below detailing why it believes Kivioja and Bielas, which form the basis of Petitioner’s challenges, are substantially the same as the Doan reference. *Id.* at 20–24 (citing Ex. 2003)

For its part, Petitioner argues that we should not exercise our discretion under § 325(d) because “Kivioja and Bielas were not cited during prosecution, nor were any related or substantially similar references.” Pet. 73. Additionally, Petitioner contend that “to the extent the Examiner allowed the claims on the grounds that the prior art did not teach de-duplication using both the identifier and fragment sequence,” “the Examiner materially erred because the prior art, including Kivioja and Bielas, taught

³ US 2022/0145380 A1, published May 12, 2022 (Ex. 2003) (“Doan”).

using the fragment and the identifier sequence to deduplicate.” *Id.* at 74 (citing Ex. 1079 ¶¶ 654–656).

For the reasons given below, we decline to exercise our discretion to deny.

1. The Legal Standard

In evaluating matters under § 325(d), the Board uses the two-part framework set forth under *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*” or “*AB*”). Under the first prong of that framework, we must determine whether the same or substantially the same art or arguments previously were presented to the Office. If so, we turn to the second prong which focuses on whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims. *Id.* at 8.

a. Advanced Bionics Prong One: whether “the same or substantially the same art or arguments previously were presented to the Office”

In evaluating whether the same or substantially the same prior art or arguments were previously presented to the Office, the Board has identified several non-exclusive factors for consideration. *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, Case IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (Paper 8) (precedential § III.C.5, first para.) (“the *Becton Dickinson* factors”). Specifically, we must weigh the following non-exclusive factors: (a) the similarities and material differences between the asserted art and the prior art involved during examination; (b) the cumulative nature of the asserted art and the prior art evaluated during examination; (c) the extent to which the asserted art was evaluated during examination,

including whether the prior art was the basis for rejection; (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art; (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of prior art or arguments. *Becton Dickinson*, at 17–18. Thus, the *Becton Dickinson* factors are framed as comparing the art or arguments in a petition against what was before an examiner during prosecution.

As Petitioner argues, and Patent Owner does not deny, the prior art at issue in the prosecution are not the same as those raised in the Petition. Pet. 73–74; Prelim. Resp. 19. Nonetheless, Patent Owner asserts that both Kivioja and Bielas are substantially similar to Doan, which was considered by the Examiner during prosecution. Prelim. Resp. 19–23.

Doan is directed to a method of detecting low frequency genetic variants that includes amplifying a target sequence, pooling samples for sequencing, and demultiplexing and alignment of the amplified sequences. Doan teaches attaching a unique molecular identifier to a target sequence, amplifying the target sequence and unique molecular identifier, and then segregating the sequencing reads into “bins” based on the sequence of the unique molecular identifier alone, or the unique molecular identifier in conjunction with the sample index. *See* Ex. 2003, 6–7, 10, 134. Doan also teaches deduplication of sequence reads using the unique molecular identifier. *Id.* at 46.

Patent Owner contends Doan and Kivioja disclose detecting duplicates based on something other than the identifier site and a portion of

the nucleic acid fragment. Prelim. Resp. 21. We are not persuaded because, as explained in more detailed below, Kivioja defines its “unique molecular identifiers (UMIs)” as including the sequence of the label and the 5’ mapped position of the target fragment together. *See* Ex. 1012, 3. At this stage of the proceeding, we currently understand that in order to have a 5’ mapped position, the target fragment must be sequenced, mapped in comparison to a reference sequence, and then included as part of the UMI. *Id.* at 5. This is not the same or substantially the same as the method taught in Doan.

Accordingly, we are not satisfied that Kivioja is the same or substantially the same as Doan. As such, we need not address the remaining the *Becton Dickinson* factors. Due to our determination that the first part of *Advanced Bionics* is not satisfied as to Kivioja, we do not exercise our discretion to deny institution for this reason. Additionally, because Kivioja is not the same or substantially the same as Doan (which is asserted as anticipatory prior art against all the challenged claims), we decline to address Patent Owner’s arguments regarding Bielas.

b. Advanced Bionics Prong Two: whether “the Office erred in a manner material to the patentability of the challenged claims”

Because the Petition does not “present to the Office the same or substantially the same art previously presented to the Office,” we need not consider the second part of the *Advanced Bionics* framework. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 7–8, 10.

2. Conclusion Regarding Discretionary Denial under § 325(d)

The *Advanced Bionics* framework “reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Advanced Bionics*, IPR2019-01469, Paper 6 at 9. Under the present circumstances, we determine that the Office has not considered the

same or substantially the same art or arguments previously, and will not consider same or substantially the same art or arguments in this IPR proceeding. Accordingly, we decline to exercise our discretion to deny institution under § 325(d).

III. PRELIMINARY MATTERS

A. *Claim Construction*

A claim “shall be construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100(b). Under that standard, the “words of a claim ‘are generally given their ordinary and customary meaning.’” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc).

1. “*appended*,” “*identifier site*,” and “*indexing site*”

Petitioner proposes constructions for several terms, including “appended,” “identifier site,” and “indexing site.” Pet. 21–22.

For the term “appended,” Petitioner contends that “[t]he ’241 patent does not place any limitation on how the adaptors are ‘appended’ to the fragments to obtain amplicons” and “[t]he plain and ordinary meaning of ‘appended’ is simply ‘added’ and does not imply any particular restrictions on the means of adding the ‘appended’ adaptor.” *Id.* at 21 (citing Ex. 1079 ¶ 403). Petitioner argues that “[t]he ’241 patent states that ‘[i]n some embodiments, appending the adaptor to the nucleic acid fragments generated by the methods described herein can be achieved using a ligation reaction or a priming reaction’ and “[t]hus, ‘appended’ must encompass attachment by at least ligation and priming reactions, confirming the breadth of the term’s ordinary meaning.” *Id.* at 21–22 (citing Ex. 1005, 9:34–38).

For the term “identifier site,” Petitioner asserts that “[t]he ’241 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.’” Pet. 22 (citing Ex. 1005, 4:45). According to Petitioner, “[a]n ‘identifier site’ ‘can be designed as a set of sequences, or it can be semi-random, or it can be completely random.’” *Id.* (citing Ex. 1005, 4:51–53). Petitioner contends that “[a]n ‘identifier site’ can also ‘be a fixed length, or it can be a variable length.’” *Id.* (citing Ex. 1005, 4:53–54).

With regard to the term “indexing site,” Petitioner argues “[t]he ’241 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.’” Pet. 22 (citing Ex. 1005, 4:37–40).

Patent Owner states that they do “not believe that any term of the ’241 patent needs to be construed beyond its plain and ordinary meaning” but “reserves the right to identify terms for construction and propose constructions in this proceeding should it be instituted.” Prelim. Resp. 9.

Construction is needed only for those terms “that are in controversy, and only to the extent necessary to resolve the controversy.” *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)). Although Petitioner provides us with constructions for “appended,” “identifier site” and “indexing site,” the meaning of these terms are not in controversy at this stage of the proceeding and their constructions will not aid in our analysis. We acknowledge,

however, that the terms “identifier site” and “indexing site” are defined in the ’241 patent. *See* Ex. 1005, 4:37–40, 4:45, 4:51–53.

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

The parties do not request construction of the limitation, “identifying sequence reads with identical identifier and target sequences as duplicates.” Nonetheless, we invite the parties to address the construction of this limitation after institution. *See Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (claims are construed only to the extent necessary to resolve a dispute). Specifically, the parties may wish to address whether the “same identifier and nucleic acid fragment” means that the sequences actually are identical. The ’241 patent states: “A duplicate sequencing read can be a sequencing read with the same identifier site and target sequence as another sequencing read in the population of sequencing reads.” Ex. 1003, 4:10–13. Yet, the claim does not use the exact wording used in the Specification.⁴

The ’241 patent goes on to disclose “apparent duplicates” and “true duplicates” and explain that “apparent duplicates” are derived from sequencing libraries and using conventional measures of duplicate reads i.e., reads were mapped using bowtie and all reads with the same start and end genomic coordinates were counted as duplicates, while “true duplicates” are

⁴ The parties may also comment on whether this limitation in the independent claim at issue in this proceeding has the same meaning as the corresponding limitations in the independent claims at issue in IPR2024-01502 and -1506. *Cf.* Ex. 1003 (claim 1 of U.S. Patent 9,546,399, i.e., “identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment”); Ex. 1004 (claim 1 of U.S. Patent 11,098,357, i.e., “identifying sequence reads with identical identifier and target sequences as duplicates”).

identified when an identifier sequence is introduced through ligation to differentiate between fragments of DNA that randomly have the same start and end mapping coordinates. Ex. 1005, 14:7–17, Fig. 5. The '241 patent references “duplicates” that either “represent unique cDNA molecules derived independently from different RNA molecules” or “PCR duplicates derived from a single RNA molecule.” *Id.* at 1:39–41. According to the '241 patent, “true duplicate” reads have identical identifier sites from the index read of two nucleic acid fragments. *Id.* at 14:22–26, 17:35–38. The '241 patent explains that because “the identifier sequence is not logically present adjacent to naturally occurring sequence, this uniquely identifies the DNA fragment.” *Id.* at 14:42–45. Consistent with this disclosure all but one example in the '241 patent relies solely on the sequence of the identifier to determine the existence of duplicate cDNA molecules in a sample. *Id.* at 16:30–19:23, 20:61–22:11. The only disclosure in the '241 patent that uses both the identifier sequence and a portion of a target sequence is Example 5.

In Example 5 of the '241 patent, mRNA was converted into cDNA fragments. Ex. 1005, 19:29–50. Adaptors with unique sequence identifiers were ligated into cDNA, which was then PCR amplified. *Id.* at 19:51–20:31. The amplified products were purified and sequenced. *Id.* at 20:32–41. The sequence read included a “50 base first read” and a “6 base second read.” *Id.* at 20:41–42. Afterwards, the data was analyzed as follows:

The 6 bases of the index read is used for standard library parsing, separating the data files from the two sample types. The first 50 bases of the target sequence read are compared to each other. Any read that has identical sequence to any other read is identified as a duplicate and removed from the population, thus, only a single copy is retained within the file.

Id. at 20:45–51. The challenged claims reiterate this language found in Example 5 regarding identifying a read that has an “identical sequence” to another read. *See* Ex. 1005, 25:42–43.

Given that errors introduced during PCR or the creation of the cDNA library, as noted by Dr. Simms (*see* Ex. 1079 ¶¶ 113–118, 124, 135, 139; Ex. 1012, 1–4; Ex. 1022, 1–2; Ex. 1025, 1; Ex. 1026, 1, 4), may alter even non-duplicate target sequences, this begs the question of whether the claim term “identical” requires absolute identity between two the sequences. Therefore, the parties are invited to address whether a “duplicate” encompasses a sequence mutation introduced via PCR.

3. “*comprising*”

The parties may address the meaning of the transitional phrase “comprising” and 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 PCR mutations. On this preliminary record, we construe “comprising” as an open-ended transition that is not limited to the listed steps. *See Vivid Techs., Inc.*, 200 F.3d at 811.

B. *Principles of Law Regarding Anticipation*

A prior art reference can only anticipate a claim if it discloses all the claimed limitations “arranged or combined in the same way as in the claim.” *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012) (quoting *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008)). “However, a reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference,

would ‘at once envisage’ the claimed arrangement or combination.”

Kennametal, Inc. v. Ingersoll Cutting Tool Co., 780 F.3d 1376, 1381 (Fed. Cir. 2015) (alteration in original) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)); *see also Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1343 (Fed. Cir. 2016) (distinguishing *Net MoneyIN* when the reference in question explicitly contemplated the combination of the disclosed functionalities). Indeed, anticipation “is not an ‘ipsissimis verbis’ test.” *Akzo N.V. v. United States Int’l Trade Comm’n*, 808 F.2d 1471, 1479 & n.11 (Fed. Cir. 1986)). “An anticipatory reference . . . need not duplicate word for word what is in the claims.” *Standard Havens Prods. v. Gencor Indus.*, 953 F.2d 1360, 1369 (Fed. Cir. 1991).

C. Principles of Law Regarding Obviousness

A claim is unpatentable under 35 U.S.C. § 103 if “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) where in evidence, objective evidence of non-obviousness.⁵ *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). A patent claim “is not proved obvious merely by demonstrating that each of

⁵ At this stage of the proceeding, Patent Owner has not presented objective evidence of non-obviousness.

its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418.

An obviousness determination based on a combination of references requires finding “both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367–68 (Fed. Cir. 2016); *see KSR*, 550 U.S. at 418. Furthermore, an assertion of obviousness “cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR*, 550 U.S. at 418; *In re NuVasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) (a finding of a motivation to combine “must be supported by a ‘reasoned explanation’”).

“In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3)); *see Intelligent Bio-Sys.*, 821 F.3d at 1369. This burden of persuasion never shifts to Patent Owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

We analyze the challenges presented in the Petition in accordance with the above-stated principles.

D. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the “type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are

made; sophistication of the technology; and educational level of active workers in the field.” *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995) (quoting *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962, (Fed. Cir. 1986)). Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner asserts that “[b]ecause the ’241 patent is directed to library preparation and data interpretation methods for NGS, [a person of ordinary skill in the art at the critical time] could have had academic training in any of a variety of fields that used NGS, including chemistry, molecular biology, biochemistry, or medicine.” Pet. 20 (citing Ex. 1079 ¶ 184). According to Petitioner, one of ordinary skill in the art “would have a Ph.D. or equivalent training in one of those fields and several years of work experience (or commensurately less education and more work experience).” *Id.* (citing Ex. 1079 ¶ 184). Petitioner contends that one of ordinary skill in the art “further would have had specific experience with implementing and designing library preparation methods for Illumina, the leading NGS platform in 2013” and “[t]his 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.” *Id.* (citing Ex. 1079 ¶¶ 184–185).

Patent Owner disagrees with Petitioner, asserting that “Petitioner proposes a level of skill in the art that does not accurately reflect the level of ordinary skill in the art as of November 2013, the priority date of the ’241 Patent.” Prelim. Resp. 7. Specifically, Patent Owner argues that “Petitioner’s definition of a person of ordinary skill in the art (‘POSA’)

requires that ‘the POSA would have a Ph.D. or equivalent training in one of those fields and several years of work experience (or commensurately less education and more work experience).’” *Id.* According to Patent Owner:

Petitioner’s definition goes beyond the level of *ordinary* skill in the art. The sequencing methods described in the ’241 patent do not require a Ph.D. plus several years of work experience to understand and perform. In fact, in many laboratory environments, lab technicians and graduate students perform DNA sequencing methods. The level of education for a POSA, therefore, is more appropriately a Ph.D. in a field related to molecular biology, or a B.S. or M.S. degree with three to five years of experience working in a molecular biology lab.

Id.

We do not see a material difference in the parties’ proposed levels of education and work experience. Indeed, although Petitioner asserts that a POSA “would have a PhD or equivalent training,” it allows more work experience to compensate for less education. Pet. 20 (stating that a POSA could have “commensurately less education and more work experience”). We, nevertheless, adopt Patent Owner’s proposal in this aspect because it specifies the years of experience needed.

Patent Owner further disputes Petitioner’s proposal that a POSA would have had experience with “implementing and designing library preparation methods for Illumina, the leading NGS platforms in 2013.” Prelim. Resp. 7–8 (quoting Pet. 20, emphasis added by Patent Owner removed). According to Patent Owner, “[t]his level of skill inappropriately requires the POSA to be an *inventor* of library preparation methods.” *Id.* at 8. We agree with Patent Owner that “experience with implementing and designing library preparation methods for Illumina” is above ordinary skill.

We also agree with Patent Owner’s proposal that “the POSA would have had experience with DNA sequencing methods and a working knowledge of how these sequencing methods functioned.” *Id.* As Patent Owner recognizes, the challenged claims relate to obtaining amplicons with an amplified nucleic acid fragment and an appended adaptor and then sequencing the amplicon to generate sequence reads. *See* Ex. 1005, 25:33–43.

Accordingly, for purposes of this Decision, we find a person of ordinary skill in the art at the critical time would have had a Ph.D. in the field of chemistry, molecular biology, or biochemistry. Alternatively, a person of ordinary skill in the art 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 in the art would have had experience with NGS sequencing methods and a working knowledge of how those methods functioned. This definition of a person of ordinary skill in the art is consistent with the skill level reflected in the disclosures of the ’241 patent and prior art. We further note that neither aspect of the dispute over the skill level affects our decision to institute review.

IV. ANALYSIS

A. Summary of References

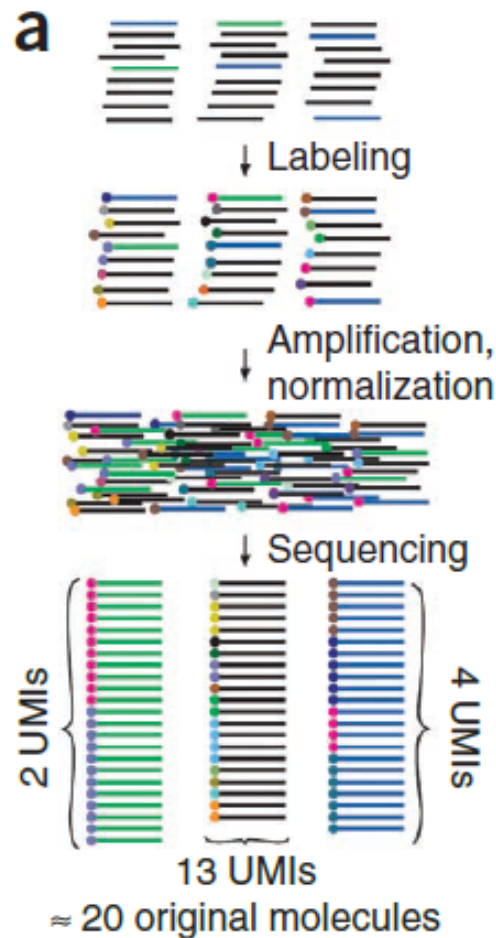
1. Overview of Kivioja (Ex. 1012)

Kivioja is a journal article titled “Counting absolute numbers of molecules using unique molecular identifiers.” Ex. 1012, 1. Kivioja explains that “[c]ounting individual RNA or DNA molecules is difficult because they are hard to copy quantitatively for detection.” *Id.* In view of this, Kivioja describes applying “unique molecular identifiers (UMIs), which make each molecule in a population distinct, to genome-scale human

karyotyping and mRNA sequencing in *Drosophila melanogaster*.” *Id.*
According to Kivioja, “this method can improve accuracy of almost any next-generation sequencing method, including chromatin immunoprecipitation–sequencing, genome assembly, diagnostics and manufacturing-process control and monitoring.” *Id.*

In Kivioja’s method, “each molecule in a population is first made unique,” which “can be accomplished by adding a random DNA sequence label, by fragmenting or by taking an aliquot of a complex mixture that is small enough to contain only distinct molecules.” *Id.* According to Kivioja, “[a]ny combination of these manipulations can be used to generate a library in which each molecule has a distinct identifying sequence.” *Id.* Kivioja designates the resulting unique sequences as “unique molecular identifier (UMIs).” *Id.*

Kivioja's Figure 1(a) is reproduced below.



Kivioja explains that:

Three different DNA species (green, blue and black lines) are labeled with a collection of random labels (colored filled circles). Two green molecules are originally present (top), corresponding to two different UMIs (red, blue) among the sequenced molecules (green; bottom). Information about the original number of molecules (top) is preserved in the number of different UMIs detected by sequencing a sample of the amplified and normalized library (bottom). Even if some UMIs are not observed, the original number of molecules can be estimated using count statistics.

Id. According to Kivioja, “[u]pon deep sequencing, each UMI will be observed multiple times, and the number of original DNA molecules can be

determined simply by counting each UMI only once.” *Id.* Kivioja explains that “[u]nlike read-counting methods that are inherently limited by errors introduced during amplification, the UMI method can be made more accurate by increasing sample size and sequencing depth.” *Id.* at 2.

Kivioja states that a labeling protocol for counting cellular mRNA molecules also was tested. Ex. 1012, 2–3. Specifically, *Drosophila melanogaster* S2 cell RNA was fragmented and converted to cDNA via oligo(dT)-primed reverse transcription and an oligonucleotide with a 10-base-pair random label was incorporated by template switching. *Id.* at 3. Kivioja then “amplified the resulting cDNA fragments directly by PCR and sequenced them.” *Id.* This is depicted in Figure 3(a), which is reproduced below.

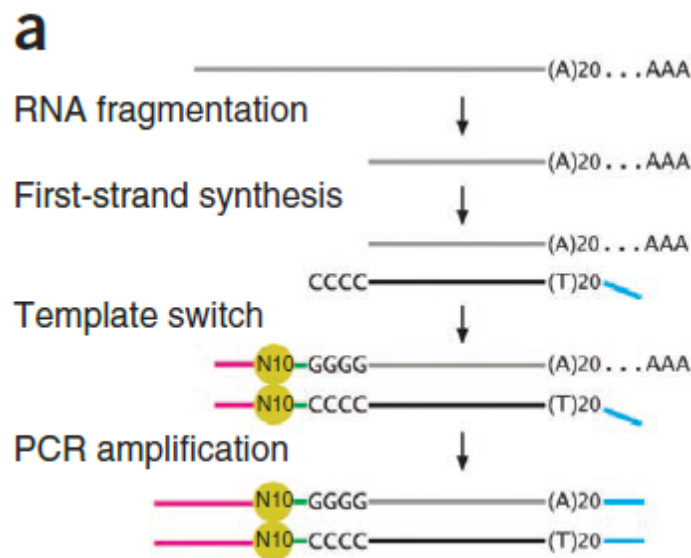


Figure 3(a) is an illustration showing that “mRNA-seq libraries were generated by fragmenting total RNA and reverse-transcribing it to cDNA using an oligo(dT) primer with an Illumina linker (blue) and a 5’ template switch adaptor containing another Illumina linker (magenta), a 10-base-pair random label (N10) and an index sequence (green).” *Id.* at 2. Kivioja states

that the combination of label sequence and the 5' mapped position of the RNA fragment defines the UMI. *Id.* (citing Supplementary Fig. 3). After amplification, the label and index sequences were removed and then sequence read were mapped to reference sequences. *Id.* at 5. Kivioja then explains:

For each gene, the sequence of its longest transcript was used as the reference sequence. Reads were discarded from further analysis if they did not contain the constant sequences expected based on oligonucleotide design, mapped to the wrong strand, had a BWA mapping quality score lower than 20 or a base in the label sequence with an Illumina base call quality score lower than 20.

Id. According to Kivioja, “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.” *Id.*

2. *Bielas (Ex. 1013)*

Bielas is a Patent Cooperation Treaty publication of an international application titled “Compositions and Methods for Accurately Identifying Mutations.” Ex. 1013, code (54). Bielas “relates to compositions and methods for accurately detecting mutations using sequencing and, more particularly, uniquely tagging double stranded nucleic acid molecules such that sequence data obtained for a sense strand can be linked to sequence data obtained from the anti-sense strand when obtained via massively parallel sequencing methods.” *Id.* at 1:15–19.

Bielas explains that the detection of spontaneous mutations and induced mutations that occur randomly throughout a genome can be difficult because such mutations “are rare and may exist in one or only a few copies of DNA.” Ex. 1013, 1:21–24. According to Bielas, however, “a mutation

must be present in as much as 10-25% of a population of molecules to be detected by sequencing.” *Id.* at 1:25–2:3. To address this, Bielas describes

a double-stranded nucleic acid molecule library that includes a plurality of target nucleic acid molecules and a plurality of random cyphers, wherein the nucleic acid library comprises molecules having a formula of X^a - X^b -Y, X^b - X^a -Y, Y- X^a - X^b , Y- X^b - X^a , X^a -Y- X^b , or X^b -Y- X^a (in 5' to 3' order), wherein (a) X^a comprises a first random cypher, (b) Y comprises a target nucleic acid molecule, and (c) X^b comprises a second random cypher. Furthermore, each of the plurality of random cyphers comprise a length ranging from about 5 nucleotides to about 50 nucleotides (or about 5 nucleotides to about 10 nucleotides, or a length of about 6, about 7, about 8, about 9, about 10, about 11, about 12, about 13, about 14, about 15, about 16, about 17, about 18, about 19, or about 20 nucleotides).

Id. at 2:29–3:8.

Bielas describes a first example of dual cypher sequencing of normal and tumor genomic libraries. Ex. 1013, 24:12–14. Bielas states that isolated genomic DNA is fragmented by shearing and “[t]he DNA fragments having overhang ends are repaired (*i.e.*, 20 blunted) using T4 DNA polymerase (having both 3' to 5' exonuclease activity and 5' to 3' polymerase activity) and the 5'-ends of the blunted DNA are phosphorylated with T4 polynucleotide kinase (Quick Blunting Kit I, New England Biolabs), and then purified.” *Id.* at 24:17–22. Furthermore, “[t]he end-repaired DNA fragments are ligated into the *Sma*I site of the library of dual cypher vectors to generate a target genomic library. *Id.* at 24:23–24.

Bielas states that this *Sma*I site is shown in Figure 2, which is reproduced below. Ex. 1013, 24:23–24.

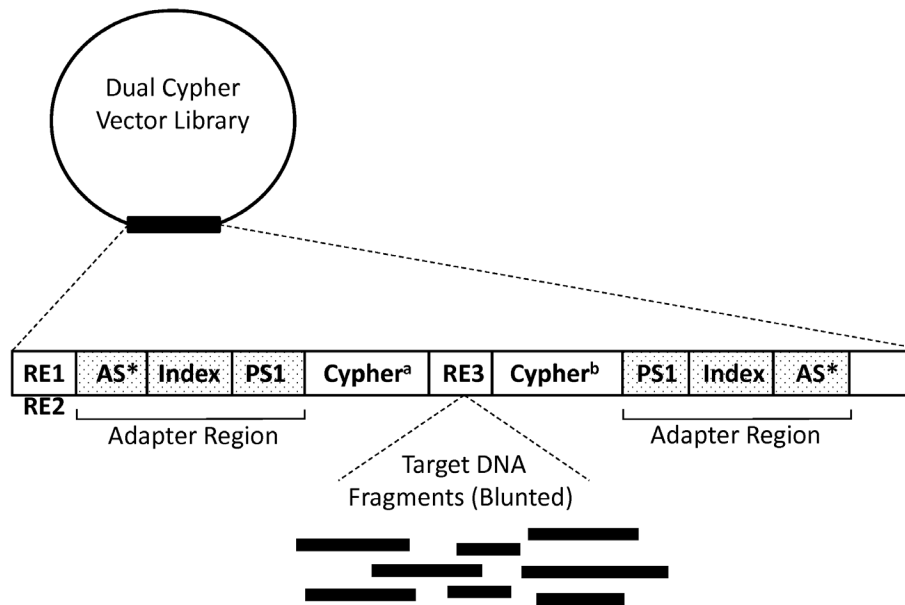


Fig. 2

Figure 2 is a diagram depicting an exemplary vector, “wherein adaptor sequences are included and are useful for, for example, bridge amplification methods before sequencing.” *Id.* at 4:1–3. Bielas explains that “[t]he ligated cypher vector library is purified and the target genomic library fragments are amplified” via a PCR protocol. *Id.* at 24:25–28. Bielas further states:

The amplification is performed using sense strand and anti-sense strand primers that anneal to a sequence located within the adapter region (in certain embodiments, the primer will anneal to a sequence upstream of the AS), and is upstream of the unique cypher and the target genomic insert (and, if present, upstream of an index sequence if multiplex sequencing is desired; *see, e.g., Fig. 2*) for Illumina bridge sequencing.

Id. at 24:28–25:4. Bielas states 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).” *Id.* at 25:7–9.

Bielas describes another example involving the detection of TP53 mutations because a recent study had “determined that TP53 is mutated in 96% of high grade serous ovarian carcinoma (HGSC)” and “the near universality and early occurrence of TP53 mutations in HGSC make TP53 a promising biomarker candidate for early detection and disease monitoring of HGSC.” Ex. 1013, 26:15–21. Bielas states that “[d]ual cypher sequencing of present disclosure was used to detect somatic TP53 mutations that arose during replication in *E. coli*.” *Id.* at 26:21–22. When explaining results, Bielas states:

TP53 Exon 4 DNA from a dual cypher vector library produced in *E. coli* was sequenced with a depth of over a million, and all sequencing reads with identical cypher pairs and their reverse complements were grouped into families to create a consensus sequence. As illustrated in Figure 3B, errors introduced during library preparation (open circle) and during sequencing (gray circle and triangle) were computationally eliminated from the consensus sequence and only mutations present in all reads (black diamonds, Figure 3B) of a cypher family were counted as true mutations (*see* bottom of Figure 3B).

Id. at 29:26–30:2. Figure 3B is reproduced below.

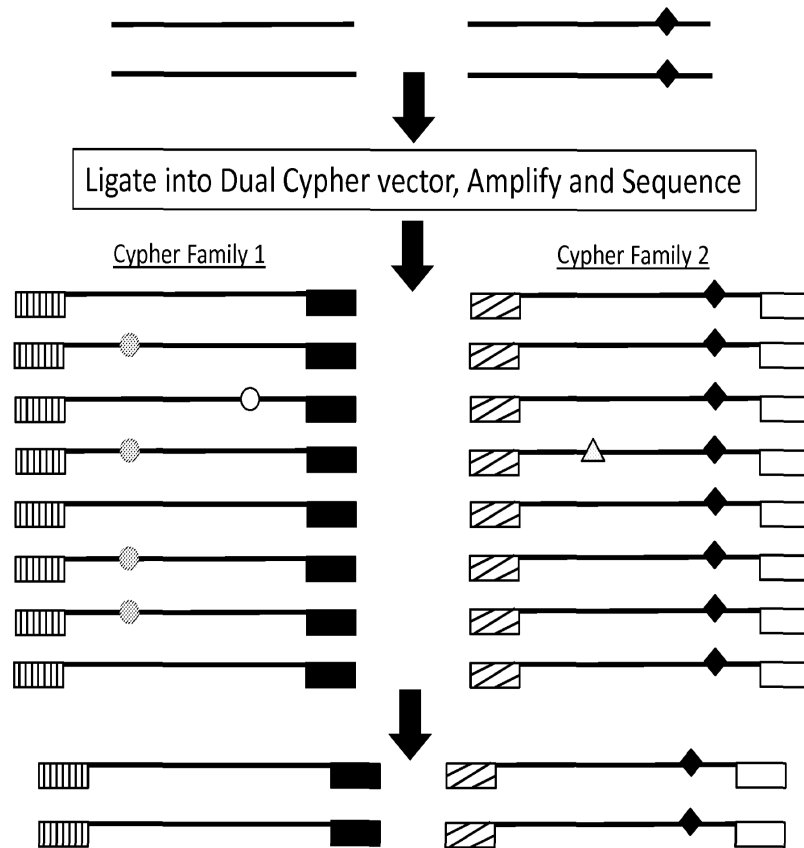


Fig. 3B

Figure 3B is a diagram depicting target sequences flanked by cyphers, separated into cypher families in a cypher library.

B. Claims 1–16 Allegedly Anticipated by Kivioja

Petitioner contends that Kivioja anticipates claims 1–16. Pet. 24–45. Patent Owner disagrees. Prelim. Resp. 9–12. Patent Owner specifically challenges whether Petitioner has shown that Kivioja discloses “identifying sequence reads with identical identifier and target sequences as duplicates,” as claim 1 recites. *Id.*

1. *Analysis of Independent Claim 1*

a. *“A method for detecting duplicate sequencing reads, the method comprising”*

Petitioner contends that to the extent the preamble is limiting and entitled to patentable weight, Kivioja discloses this element in the method of collapsing labeled fragments to a single UMI based on the tag and fragment sequence. Pet. 28 (citing Ex. 1012, 1, 5; Ex. 1079 ¶¶ 236–240). Petitioner acknowledges that Kivioja does not use the word “duplicate,” but argues that Kivioja uses its mRNA sequencing method to detect the number of molecules after different numbers of PCR cycles, that this method necessarily involves the determination of whether particular observed sequences from the Illumina run were original fragments or PCR copies, and that a person of ordinary skill would have recognized that Kivioja teaches a method of detecting and removing duplicates from sequencing information. Pet. 28–29 (citing Ex. 1079 ¶¶ 236–240, 257–260, 395–398).

Patent Owner does not present arguments in the Preliminary Response addressing the specific merits of Petitioner’s contention. *See* Prelim. Resp. 9–13. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

At this stage of the proceeding, we determine that Petitioner has made an adequate showing.⁶ Kivioja discloses that “with the UMI method, one can reproducibly detect the number of molecules after different numbers of PCR cycles without normalization.” *See* Ex. 1012, 2–3. Additionally, we credit the testimony of Dr. Sims, who opines that a person of ordinary skill would have understood that Kivioja teaches a method of detecting and

⁶ We do not need to decide for purpose of institution whether the preamble is limiting.

removing duplicate sequencing reads, i.e., that Kivioja's method of counting unique sequences necessarily identifies duplicate reads. *See* Ex. 1079 ¶ 260.

b. “obtaining amplicons each comprising an amplified fragment of a nucleic acid with an appended adaptor”

Petitioner contends that Kivioja discloses this limitation because Kivioja teaches appending adaptors with random molecular tags (referred to as “labeling”) to nucleic acid fragments and then amplifying those labeled fragments prior to sequencing. Pet. 29 (citing Ex. 1012, 1 Fig. 1(a); Ex. 1079 ¶¶ 399–409). Petitioner then asserts that Kivioja provides an example of obtaining amplicons with both an amplified nucleic acid fragment and an appended adaptor. *Id.* at 30 (citing Ex. 1012, 2, Fig. 3(a)). In this example, Kivioja adds an adaptor to the 5' end of fragmented mRNA using the “template switch” technique. *Id.* at 30–33 (citing Ex. 1202, 2, 4, 14; Ex. 1079 ¶¶ 402–408).

Patent Owner does not present arguments in the Preliminary Response addressing the specific merits of Petitioner's contention. *See* Prelim. Resp. 9–13. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

Having reviewed Kivioja, on this record, we agree with Petitioner that Kivioja discloses this limitation as recited in claim 1. *See* Pet. 29–33. Specifically, we are persuaded that Kivioja's mRNA example demonstrates reverse transcription of mRNA molecules into cDNA, which are then PCR amplified after 5' adaptors are added to the end of the newly transcribed cDNA strand. *See* Ex. 1012, 2, 4, 14, Fig. 3(a). The testimony of Dr. Sims is consistent with the disclosure of Kivioja and supports Petitioner's position. *See* Ex. 1079 ¶¶ 399–409.

c. “wherein each adaptor comprises an identifier site comprising a plurality of nucleotides unique to the amplified fragment”

Petitioner contends that Kivioja discloses this limitation because Kivioja states that the purpose of the molecular tags was to “generate a library in which each molecule ha[d] a distinct identifying sequence.” Pet. 33 (citing Ex. 1012, 1; Ex. 1079 ¶ 411). According to Petitioner, the 5’ adaptor used in Kivioja’s mRNA experiments include a “10-base-pair random label” or “N10” (i.e., an identifier site comprised of 10 nucleotides) that uniquely labels each cDNA fragment generated from the template switch reaction. *Id.* (citing Ex. 1012, 2–3, 14; Ex. 1079 ¶ 412). Petitioner asserts that Kivioja’s mRNA experiment had enough random molecular tags to uniquely label each molecule, so that each adaptor comprised an identifier site with a plurality of nucleotides unique to each amplified fragment. *Id.* (citing Ex. 1012, 5; Ex. 1079 ¶¶ 410–412).

Patent Owner does not present arguments in the Preliminary Response addressing the specific merits of Petitioner’s contention. *See* Prelim. Resp. 9–13. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

Having reviewed Kivioja, on this record, we agree with Petitioner that Kivioja discloses this limitation as recited in claim 1. *See* Pet. 33. Specifically, we are persuaded by Kivioja’s disclosure of the “10-base-pair random label” that is used to identify unique amplicons. *See* Ex. 1012, 1–2, 5, 14. The testimony of Dr. Sims is consistent with the disclosure of Kivioja and supports Petitioner’s position. *See* Ex. 1079 ¶¶ 410–412.

d. “sequencing the amplicons to generate sequence reads that include identifier and target sequences”

Petitioner contends that Kivioja discloses this limitation because Kivioja’s methods are designed for use with “any next generation sequencing method.” Pet. 34 (citing Ex. 1012, 1). According to Petitioner, Kivioja sequences its amplified adaptor-cDNA fragments on an Illumina device. *Id.* (citing Ex. 1012, 4; Ex. 1079 ¶ 247). Petitioner asserts that an ordinarily skilled artisan at the critical time “would have known this generated sequence reads that included the identifier site and target sequence.” *Id.* (citing Ex. 1079 ¶¶ 247, ¶¶ 356–360, ¶¶ 413–415). Petitioner further asserts that an ordinarily skilled artisan would have recognized that Kivioja’s “5’ adaptors” placed the identifier site downstream of the sequencing primer, so that both the identifier and target sequence were sequenced together. *Id.* (citing Ex. 1079 ¶¶ 242, ¶¶ 356–360, ¶¶ 413–415).

Patent Owner does not present arguments in the Preliminary Response addressing the specific merits of Petitioner’s contention. *See* Prelim. Resp. 9–13. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

Having reviewed Kivioja, on this record, we agree with Petitioner that Kivioja discloses this limitation as recited in claim 1. *See* Pet. 34. Specifically, we are persuaded that based on Kivioja’s explicit disclosure and its method of generating amplicons with the N10 label and nucleic acid sequence that Kivioja’s “5’ adaptors” would place the identifier site

downstream of the sequencing primer, so that both the identifier and target sequence would be sequenced together.

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

In discussing the preamble above, we have found that Petitioner has made an adequate showing that Kivioja discloses identifying a duplicate sequencing read. As to “the sequencing read comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads,” Petitioner argues 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. Pet. 34–35 (citing Ex. 1012, 5, Fig. 1(a); Ex. 1079 ¶¶ 274–278, ¶¶ 361–363, ¶¶ 416–419).

Patent Owner argues that Kivioja fails to disclose a process of detecting duplicates based on both an identifier site and at least a portion of the nucleic acid fragment. Prelim. Resp. 10. Patent Owner argues that Kivioja does not disclose the use of a portion of the target sequence in combination with the identifier site to identify a duplicate sequence read. *Id.* at 10–11. Patent Owner argues that Kivioja relies on the “gene” (i.e., a proposed chromosomal location of the original genomic sequence) and its “position” (i.e., the proposed mapped location of the target sequence to the reference genome) rather than any part of the target sequence (i.e., the order of nucleotides within the target sequence) itself. *Id.*

Patent Owner acknowledges that Kivioja describes looking to the “gene, position, and label,” but Patent Owner appears to argue that the Kivioja’s label alone is the UMI (see Prelim. Resp. 11–12 (citing Ex. 1012, 5)), whereas Petitioner appears to understand the UMI to be the combination

of the label and the fragment (*see, e.g.*, Pet. 34–35 (citing Ex. 1012, 1, 5; Ex. 1079 ¶¶ 274–278, ¶¶ 361–363, ¶¶ 416–419)).

On this record, we determine that Petitioner has made an adequate showing that Kivioja uses a combination of the label and fragment as the UMI to determine whether there is duplication. With respect to the mRNA experiments, Kivioja states “[t]he mapped reads with the same gene, position, and label were collected to one UMI.” Ex. 1012, 5.⁷ Therefore, we find that it is a better reading of Kivioja, on this record at the current stage of the proceeding, that Kivioja’s UMI includes the gene, position, and label because it is our understanding that in order to determine a gene fragment’s position, the gene fragment must be sequenced.

Patent Owner also argues:

Kivioja’s process of mapping a sequence to a reference genome and using the position to identify duplicates is not the same as using at least some of the target sequence to identify a duplicate sequence read and would not have taught a POSA to use the target sequence in this process. Petitioner’s argument is essentially that Kivioja uses the identified position in the reference genome as a “surrogate” for the target sequence. But a POSA would not have understood Kivioja’s “surrogate” to be a substitute for the target sequence because the position of a sequence read and the corresponding gene provide different information than the target sequence. Therefore, Kivioja’s use of the gene position would not teach a POSA to use at least a portion of the target sequence for identifying duplicate reads.

Prelim. Resp. 12–13. Patent Owner’s argument appears to be that Kivioja’s method fails to use the target sequence in determining sequence read

⁷ With respect to the DNA experiments, Kivioja states “we used the 5’ genomic position of each mapped read as the UMI.” Ex. 1012, 4. Kivioja also states that “The sequence of the label and the 5’ mapped position of the fragment together define the UMI.” *Id.* at 3.

duplication. All that the claim requires, however, is that the method identifies duplicate sequencing read, where the sequencing read has the same identifier site and nucleic acid as another (i.e., including having identical sequences).

Nevertheless, Patent Owner poses the question of whether Kivioja relies on the sequence of the label and the sequence of the target fragment, when Kivioja states: “The mapped reads with the same gene, position, and label were collected to one UMI.” Ex. 1012, 5. When Kivioja states that reads with the “same . . . label” were “collected to one UMI,” we understand that to mean that the labels have identical sequences. Kivioja also discloses that “two UMIs were merged if they either had identical positions and one mismatch in the label sequences” *Id.* This indicates that not only were identical labels considered to be duplicates, but also labels that had one mismatch, i.e., in order to limit the effect of sequencing errors. *See id.* On this record, because claim 1 contains the transition “comprising,” the claim still is satisfied if the category of identified duplicate reads contains identical labels and also contains more.

We additionally address Patent Owner’s argument that Kivioja uses the position of the target fragment instead of the sequence of the target fragment. Kivioja discloses that “[f]or each gene, the sequence of its longest transcript was used as the reference sequence. Reads were discarded from further analysis if they did not contain the constant sequences expected based on oligonucleotide design, mapped to the wrong strand, [or] had a BWA mapping quality score lower than 20” Ex. 1012, 5; *see also id.* (“Total read count of a gene is the number of accepted reads mapped to its reference sequences.”). On the preliminary record, we understand Kivioja to mean that the mapped position was based on the gene sequence. Ex. 1079

¶ 248, ¶ 276, ¶ 277 (“Mapping reads to the genome necessarily required matching the observed sequence of the nucleic acid fragment to the expected sequence.”), ¶ 278.⁸ On this record, however, we cannot rule out that some additional sequences may be mapped to the same position even if they did not have an identical sequence. *See also id.* ¶ 278 (“Kivioja first mapped the sequence of the nucleic acid fragments to a reference genome and then used ‘the 5’ mapped position of the fragment’ to identify PCR biases, or PCR-introduced error”). Nonetheless, because claim 1 contains the transition “comprising,” the claim is satisfied if the category of identified duplicate reads contains identical nucleic acid fragments and also contains more.

Based on its explicit disclosure, we are satisfied Kivioja relies on the combination of label and nucleic acid fragment to identify duplicates. *See* Ex. 1012, 1 (“We designate the resulting sequences that can be used to uniquely identify copies derived from each molecule unique molecular identifiers (UMIs; Fig. 1).”), 3 (“The sequence of the label and the 5’ mapped position of the fragment together define the UMI.”).

We, therefore, determine that Petitioner has made an adequate showing for “identifying a duplicate sequencing read” at this stage of the proceeding. We will revisit this issue as appropriate on a fully-developed record.

2. *Analysis of Dependent Claims 2–16*

Petitioner provides arguments and evidence regarding dependent claims 2–16. Pet. 35–45. Patent Owner relies on its arguments regarding claim 1 and has not provided separate arguments in regard to these other

⁸ Dr. Sims noted that in Kivioja, after sequencing, reads were mapped to the genome. Ex. 1079 ¶ 277 (citing Ex. 1012, 4).

challenged claims. *See* Prelim. Resp. 13. Nonetheless, the burden remains on Petitioner to demonstrate unpatentability. *See Dynamic Drinkware*, 800 F.3d at 1378.

We have reviewed the Petition’s analysis of the other claimed subject matter not discussed in regards to claim 1 and determine that the analysis is sufficient at this stage. Based on our review of the arguments and evidence submitted for dependent claims 2–16 and the reasons presented previously, we are persuaded for purposes of institution only that Petitioner has shown sufficiently that Kivioja discloses the limitations as recited in dependent claims 2–16.

3. *Summary regarding the Alleged Anticipation Challenge Based on Kivioja*

Based on the current record, Petitioner has established a reasonable likelihood that it will prevail in demonstrating that claims 1–16 are anticipated by Kivioja.

C. *Claims 4, 6, 11, and 16 Allegedly Rendered Obvious by Kivioja*

To the extent claims 4, 6, 11, and 16 are not anticipated by Kivioja, Petitioner argues these claims would have been obvious in view of Kivioja. Pet. 45–49. Patent Owner disagrees. Prelim. Resp. 12–13. Patent Owner specifically challenges whether Petitioner has demonstrated a reason to modify Kivioja to use the combination of the identifier site and a portion of the target sequence (as opposed to the reference genome) to identify mutations. *Id.*

As discussed previously, we are persuaded at this stage of the proceeding that Kivioja uses the combination of the identifier site and a portion of the target sequence (as opposed to the reference genome) to identify duplicate strands of an amplicon. Therefore, given that anticipation

is the epitome of obviousness, we are persuaded that Petitioner has shown sufficiently that Kivioja teaches or at least suggests the limitations as recited in challenged claims 4, 6, 11, and 16.

D. Claims 1–3 and 6–16 Allegedly Anticipated by Bielas

Petitioner contends that Bielas anticipates claims 1–3 and 6–16. Pet. 22–23, 49–67. Patent Owner disagrees. Prelim. Resp. 13–17.

1. Analysis of Independent Claim 1

Petitioner asserts that Bielas discloses all of the limitations of claim 1. Pet. 48–67. Patent Owner argues that Bielas does not disclose identifying a duplicate sequencing read based on an identifier site and nucleic acid fragment. Prelim. Resp. 14. Having found that institution of an *inter partes* review is warranted as to all challenged claims on the challenges asserted in the Petition based on Kivioja, we focus on the one disputed limitation for our analysis of the anticipation challenge based on Bielas, and to provide guidance to the parties for trial.

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

Petitioner contends Bielas discloses that nucleic acid sequence 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. Pet. 58 (citing Ex. 1013, 24–25, 27, 37). Petitioner argues that this process requires Bielas to first identify duplicate sequencing reads as those comprising the same Cypher/identifier site and fragment sequence as other reads. *Id.* (citing Ex. 1079 ¶ 508).

Patent Owner disagrees and argues that neither Bielas nor Petitioner provides an explanation as to what “deconvoluting” in Bielas entails, and

even if deconvoluting identifies duplicates, Bielas does not disclose the use of both the identifier site and any part of a nucleic acid fragment to identify duplicates as part of this step. Prelim. Resp. 14–15.

Bielas states that “[b]arcodes were used to deconvolute the sequencing data.” Ex. 1013, 29:23–24. Bielas also states that “[t]he unique cypher tags are used to computationally deconvolute the sequencing data and map all sequence reads to single molecules.” *Id.* at 25:7–8.

Petitioner argues that Bielas explains, in Example 3, 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.” Pet. 59–60 (citing Ex. 1013, 31–32, 43). Petitioner argues that to perform this comparison, Bielas looks at both the Cypher sequence, to group reads, and the fragment sequence, to ascertain whether a particular sequence contained a mutation. *Id.* at 59 (citing Ex. 1013, 31–32, 43; Ex. 1079 ¶¶ 483–486).

Patent Owner again disagrees, responding that because Bielas is directed to distinguishing between sequencing errors and mutations within the nucleic acid fragments, and the Bielas method does not teach a person of ordinary skill to look to the nucleic acid fragments to match duplicates because the nucleic acid fragments would contain the very errors and mutations that a person of ordinary skill would have sought to differentiate. Prelim. Resp. 19.

We are not persuaded by Patent Owner’s position because it is clear that Bielas uses its cyphers to perform deconvolution. Ex. 1013, 25, 29.

Bielas also differentiates true mutations from mutations created during library preparation. *Id.* at 29–30. We need not reach a determination at this time, however, as to whether Bielas also relies on the target sequence to identify a duplicate because we have determined already to institute an *inter partes* review for the challenged based on Kivioja. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1355 (2018) (noting that the language of 35 U.S.C. § 314(b) “indicates a binary choice—either institute review or don’t”); *see also PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute as requiring “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”). Therefore, whether Bielas’s convolution “identif[ies] a duplicate sequencing read . . . comprising the same identifier site and nucleic acid fragment as another sequencing read” is an issue that the parties may address further at trial.

E. Claims 4, 5, 11, 12, 15, and 16 Allegedly Rendered Obvious by Bielas

Petitioner contends that claims 4 and 5 would have been obvious over Bielas. Pet. 67. In addition, to the extent claims 11, 12, 15, and 16 are not anticipated by Bielas, Petitioner argues these claims would have been obvious in view of Bielas. *Id.* at 67–73. Patent Owner disagrees. Prelim. Resp. 18–19. Patent Owner specifically challenges whether Petitioner has demonstrated a reason to modify Bielas to use the combination of the identifier site and a portion of the target sequence to identify duplicates. *Id.* at 18.

As discussed previously, we do not reach a determination at this time as to whether Bielas also relies on the target sequence to identify a duplicate. But, having found that institution of an *inter partes* review is warranted as to all challenged claims on the challenges asserted in the Petition based on

Kivioja, we proceed with instituting an *inter partes* review as to all challenged claims on the challenges asserted in the Petition based on Bielas. *See SAS*, 138 S. Ct. at 1355.

V. CONCLUSION

Based on the arguments and evidence presented by the parties, we determine that there is a reasonable likelihood Petitioner would prevail with respect to at least one claim challenged in the Petition. Hence, we institute an *inter partes* review of all challenged claims on all challenges included in the Petition.

Any argument not raised in a Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed forfeited and/or waived even if asserted in the Preliminary Response. *In re Google Tech. Holdings LLC*, 980 F.3d 858, 862–864 (Fed. Cir. 2020) (holding an argument forfeited when not timely raised before the Board); *In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–16 in the '241 patent is instituted on all challenges included in the Petition;

FURTHER ORDERED that, according to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial that commences on the entry date of this Decision.

IPR2024-01506
Patent 11,725,241 B2

For PETITIONER:

Thomas Fletcher
Jessamyn Berniker
Nicholas Vincent
WILLIAMS & CONNOLLY LLP
tfletcher@wc.com
jberniker@wc.com
nvincent@wc.com

For PATENT OWNER:

Linnea Cipriano
Scott Weingaertner
GOODWIN PROCTER LLP
lcipriano@goodwinlaw.com
sweingaertner@goodwinlaw.com