

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. IPR2024-01506
U.S. Patent No. 11,725,241

PATENT OWNER'S PRELIMINARY RESPONSE

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EXHIBIT LIST

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2014	Wong, K.H, Jin, Y., Moqtaderi, Z., “UNDO: a Bioconductor R package for unsupervised deconvolution of mixed gene expressions in tumor samples,” <i>Current Protocols in Molecular Biology</i> , January 2013
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I. INTRODUCTION

Pursuant to 35 U.S.C. § 323 and 37 C.F.R. § 42.107, Patent Owner Tecan Genomics, Inc. (“Patent Owner” or “Tecan”) submits this Preliminary Response to Integrated DNA Technologies, Inc.’s (“Petitioner” or “IDT”) Petition challenging claims 1-16 (the “challenged claims”) of U.S. Patent 11,725,241 (“the ’241 Patent”). Petitioner has not met its burden of establishing that there is a reasonable likelihood it would prevail with respect to at least one challenged claim, and therefore, the Board should deny the Petition.

Both the Petition’s anticipation and obviousness arguments fail to show that the prior art taught key limitations of the challenged claims. As explained in more detail below, none of the cited prior art discloses or teaches using both an identifier site and at least a portion of the target sequence to identify duplicate reads in a DNA sequencing method. In arguing the opposite, Petitioner glosses over the complexity of the DNA sequencing field and uses impermissible hindsight to conveniently arrive at the challenged claims. The Petition entirely fails to articulate why or how a POSA would have been motivated to combine or modify the cited references, offering only conclusory analyses and relying heavily on expert *ipse dixit* to carry the argument. Thus, Petitioner has failed to show a reasonable likelihood that any challenged claim is either anticipated or rendered obvious, and institution should be denied.

Further, Petitioner relies on prior art references that are substantially similar to art that was considered and relied on by the Examiner. Petitioner has failed to point to any error by the Examiner, making discretionary denial under § 325(d) appropriate here.

II. TECHNOLOGY BACKGROUND

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. EX2009.01. 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” (“Pre-NGS”) technologies. The gold standard of these Pre-NGS technologies was Sanger Sequencing, developed in 1977. *Id.*, .02. Sanger Sequencing was the first method that allowed for a DNA sequence to be determined. In this method, the DNA was amplified in the presence of dye-labeled, chemically modified nucleotides that, when incorporated into the sequence, would prevent further strand elongation. These modified nucleotides would be incorporated at random throughout the duplication process, yielding a variety of smaller fragments, each with a modified nucleotide at its end. *Id.*, .02; *see also* EX2008.01. Each terminal nucleotide could be identified based on the dye-labeled nucleotides. By

correlating the length of the fragments and the identification of the dye-labeled nucleotides, one could determine the nucleotide sequence of the original template DNA strand. *Id.* Although revolutionary, Sanger Sequencing was expensive and ill-suited for large-scale applications. EX2004.01.

B. Next-Generation Technologies

Starting in the early 2000s, the field of genetics was revolutionized by the invention of next-generation sequencing (“NGS”). Compared to traditional, Pre-NGS sequencing methods, NGS sequencing utilized a new design that no longer relied upon disassembling and then piecing together a single original template DNA strand. Instead, NGS sequencing now allowed for hundreds of thousands of original template strands to be sequenced in the same reaction. With NGS, a user could perform massively parallel sequencing, allowing for elements of the genome to be sequenced in a fast, scalable manner. *Id.*, .03. As compared to Sanger Sequencing, NGS was cheaper, more efficient, and capable of assessing both larger genetic samples and larger portions of the human genome in high fidelity. *Id.*, .03.

However, early NGS methods had their drawbacks. NGS was limited to shorter individual sequencing reads than Sanger Sequencing, which greatly increased the difficulty in mapping the sequence reads to a full genome. *Id.* NGS also made it difficult to determine whether reads were duplicate, naturally occurring

repetitive sections of a genome, or mutated sequences of the genome. EX2001.01; *see also* EX2002.01-02.

Targeted enrichment methods became one way to mitigate the issues associated with characterizing a sequence of a genomic area of interest. Rather than amplifying and sequencing the larger, full genome, targeted enrichment was a method of sample preparation in which smaller genomic areas of interest, such as individual genes, were amplified. EX2006.01-02. However, targeted enrichment came with its own set of difficulties. The amplification of the sequence introduced PCR errors. EX2005.05. This made it difficult to determine whether changes in nucleotides across similar sequences were due to mutations, or to PCR error, and confounded the data. There were also errors within the sequencing read, such as signal cross-talk, where signals overlap and do not accurately identify the nucleotide, leading to a sequencing read containing the wrong nucleotide. EX2010.02-03. Lastly, errors occurred during sequencing strand synthesis, leading to sequence strands containing an incorrect insertion or deletion of a nucleotide. EX2007.01-02.

C. 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. EX2015.03-04. 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 are higher that fragments with the same beginning and end sequences would be duplicates. EX1003.0009. 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, used to tag original sequences prior to sample preparation and amplification. EX1033.0099. The presence of the barcode signaled that a fragment was part of an original sequence. *Id.* It also could be used to identify mutations present in the genome

versus mutations introduced via PCR, sequence read, or sequence strand synthesis errors. *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. EX2014.08-09. Shorter barcodes required less space, but reduced the number of unique barcodes available and had limited value for samples that contained many unique fragments. EX2003.041. 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 '241 PATENT

A. Overview

The '241 Patent is directed to a method of detecting, and subsequently removing, duplicate sequencing reads from a sample population. *See, e.g.,* EX1005.0001. The claimed method is beneficial in overcoming issues relating 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. By allowing for greater ability in identifying and removing duplicates, the claimed method provides cleaner sequencing data by allowing unnecessary duplicative data to be filtered out. This is particularly beneficial for sequencing applications where a scientist seeks to understand the amount of starting

material, such as, in relative gene expression studies, where a scientist would need 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

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. Petitioner's definition of a person of ordinary skill in the art ("POSA") requires that "the POSA would have a PhD or equivalent training in one of those fields and several years of work experience (or commensurately less education and more work experience)." Petition, 20; *see also* EX1079.¶184.

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.

Petitioner also proposes that the POSA “would have had specific experience with implementing *and designing library preparation methods* for Illumina, the leading NGS platform in 2013.” Petition, 20. This level of skill inappropriately requires the POSA to be an *inventor* of library preparation methods, which is far above “ordinary skill.” *10x Genomics, Inc. v. Bio-Rad Laboratories, Inc.*, IPR2020-00086, Paper 39, at 11 (PTAB. Apr. 26, 2021) (declining to adopt POSA definition that matched the “actual skill of the inventors” and of “experts in the field,” and was thus “more akin to extraordinary, rather than ordinary skill”); *see also Rohde & Schwarz GmbH & Co., KG v. Tektronix, Inc.*, IPR2018-00645, Paper 7 at 10 (PTAB Oct. 1, 2018) (declining to adopt level of ordinary skill that required “a heightened level of skill” and denying institution). More realistically, the POSA would have had experience with DNA sequencing methods and a working knowledge of how these sequencing methods functioned.

Petitioner’s unduly high POSA standard is central to its arguments. Petitioner relies on the artificially-high knowledge of the POSA throughout the Petition to fill in certain gaps and draw inferences to arrive at the challenged claims that no true POSA would consider. The Board should, therefore, give little weight to arguments that are based on Petitioner’s heightened level of skill. *See Rohde & Schwarz GmbH & Co. KG*, IPR2018-00645, Paper 7 at 10.

Even assuming that Petitioner's definition of a POSA is appropriate, however, the Petition does not show a reasonable likelihood to prevail, as explained further below.

C. Prosecution History

The '241 Patent was granted without rejections. In the notice of allowance, the Examiner explained that the closest identified prior art, Doan, did not teach the claims of the '241 Patent. EX1020.10431. In allowing the '241 patent, the Examiner distinguished the claimed invention from Doan. The Examiner explained that Doan "does not teach or suggest using a combination of target sequence and identifier sequence for duplicate removal." *Id.*, .10434.

D. Claim Construction

For purposes of this Preliminary Response, Patent Owner does not believe any term of the '241 patent needs to be construed beyond its plain and ordinary meaning. Patent Owner reserves the right to identify terms for construction and propose constructions in this proceeding should it be instituted.

IV. THE PETITION FAILS TO ESTABLISH A REASONABLE LIKELIHOOD OF SUCCESS ON AT LEAST ONE CLAIM

A. Grounds 1 and 2: Petitioner Has Not Shown That Any Challenged Claim Is Anticipated By, or Obvious Over, Kivioja

Petitioner argues that Kivioja either anticipates or renders the challenged claims obvious. At the very least, in raising the obviousness arguments, Petitioner acknowledges that the disclosures of Kivioja do not squarely align with the

challenged claims. As explained in more detail below, Petitioner cannot show that Kivioja discloses or teaches all elements of the challenged claims, and therefore has failed to meet its burden regarding Grounds 1 and 2.

Petitioner cannot point to a disclosure in Kivioja that discloses a method of “detecting duplicate sequencing reads” by “identifying sequence reads with identical identifier and target sequences as duplicates” as required by the challenged claims. EX1005.024. The Petition does not point to any other prior art that cures the deficiencies of Kivioja or explain how a POSA would have modified Kivioja to fill these gaps. Petitioner has thus failed to show with a reasonable likelihood that any challenged claim is invalid under Grounds 1 or 2.

1. The Petition Fails to Establish that Kivioja Discloses Identifying Duplicate Sequencing Reads Based on the Identifier Site and the Target Sequence

Claim 1 of the '241 Patent requires “identifying sequence reads with identical identifier and target sequences as duplicates.” EX1005.24. Petitioner argues that Kivioja teaches this limitation of Claim 1 because Kivioja discloses that “the mapped reads with the same gene, position, and label were collected to one UMI and the number of such reads was recorded as the copy number of that UMI.” Petition, 27 (citing EX1012.0005). Petitioner’s characterization of Kivioja, however, ignores 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.

Petitioner admits 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. Petition, 27. Petitioner instead relies on Kivioja's use of 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. Petitioner argues that because Kivioja discloses mapping a sequence to a position on the genome, that a POSA practicing the method of Kivioja would "necessarily use[] the fragment sequence." Petition, 35. There is, however, no disclosure in Kivioja regarding this process. Instead, Kivioja describes only looking to the "gene, position, and label" (i.e., the proposed chromosomal location of the original genomic sequence, the proposed mapped location of the target sequence in the reference genome, and the UMI) of mapped reads when collecting sequencing reads. EX1012.0005. Kivioja does not disclose, and Petitioner does not explain, when or how the gene sequence is used in Kivioja's method.

Additionally, 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. The Petition does not provide any explanation regarding why a POSA would have understood that Kivioja’s use of the gene position would meet the claims, given the different data used in these analyses.

2. Petitioner Has Not Shown a POSA Would Have Been Motivated to Modify Kivioja

Even assuming that the prior art disclosed all limitations of the challenged claims, Petitioner does not provide any explanation of how a POSA (not a person of *extraordinary* skill) would modify the method of Kivioja to allow for identification of duplicates based on both the identifier site 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. Therefore, Petitioner’s obviousness argument cannot cure the deficiencies of Kivioja.

As described above, Kivioja does not require the use of any portion of the target sequence to identify duplicates. *See supra* Section IV.A.1. Petitioner entirely omits any explanation of how or why a POSA would modify the method of Kivioja

to look instead at the combination of the identifier site and a portion of the target sequence (as opposed to the reference genome) to identify mutations. As a result, Petitioner has not shown a reasonable likelihood that any challenged claim is anticipated by or obvious in light of Kivioja.

3. The Petition Has Failed to Establish that Any Dependent Claim is Likely Invalid

Claim 1 is the only independent claim in the '241 Patent, from which all other challenged claims depend. As explained above, the Petition fails to show that the prior art anticipates or renders claim 1 obvious because the prior art lacks disclosure of required elements of the claims. Therefore, the Petition similarly cannot establish any of the dependent claims are obvious.

B. Grounds 3 and 4: Petitioner Has Not Shown That Any Challenged Claim Is Anticipated By, or Obvious Over, Bielas

Petitioner argues that Bielas either anticipates or renders obvious the challenged claims. At the very least, in raising the obviousness arguments, Petitioner acknowledges that the disclosures of Bielas do not squarely align with the challenged claims. As explained in more detail below, Petitioner cannot show that Bielas discloses or teaches all elements of the challenged claims, and therefore has failed to meet its burden regarding Grounds 3 and 4.

Like Kivioja, Bielas does not disclose a method of “identifying sequence reads with identical identifier and target sequences as duplicates,” as required by the

challenged claims. EX1005.24. The Petition does not point to any other prior art that cures the deficiencies of Bielas or explain how a POSA would have modified Bielas to fill these gaps. Petitioner has thus failed to establish a reasonable likelihood that any challenged claim is invalid under Grounds 3 or 4.

1. The Petition Fails to Establish that Bielas Discloses Identifying a Duplicate Sequencing Read Based on the Identifier Site and Target Sequence

Petitioner argues that Bielas discloses identifying duplicate sequence reads as claimed because it “teaches differentiating between true mutations and artifact mutations” and because it discloses “computationally deconvolut[ing].” Petition, 55 (internal quotations omitted). But Petitioner fails to present any support for its position that Bielas’s process of “deconvoluting” is a process for identifying duplicates. As described below, “deconvoluting” is a broad term with a variety of applications. Neither Bielas nor Petitioner provides an explanation regarding what the “deconvoluting” in Bielas entails. Assuming that the “deconvoluting” step includes identifying duplicates, despite a lack of evidence of that in the record, Bielas does not disclose the use of both the identifier site and any part of a nucleic acid fragment as a part of this step.

Without any citation to Bielas, and with only expert testimony for support, Petitioner asserts (wrongly) that Bielas teaches a POSA to “identify duplicate sequencing reads as those comprising an identical Cypher/identifier site and

fragment sequence as other reads.” Petition, 58. Nowhere does Bielas disclose the use of both a Cypher and a portion of the nucleic acid fragment sequence to identify duplicates. Rather, Bielas relies on the two Cyphers to match complementary pairs, and explicitly teaches that it is “[t]he unique cypher tags” that are used to “computationally deconvolute the sequencing data,” not both the cypher and a portion of the nucleic acid fragment. EX1013.0027.

Petitioner further incorrectly alleges that Figure 3B describes a process of de-duplication based on “the Cypher and the fragment sequence.” Petition, 53-54. Petitioner, however, disregards the explicit teachings of Bielas, which describes Figure 3B (shown below) as diagramming a process whereby “[a]ll sequencing reads *having identical cypher pairs*, along with their reverse complements were grouped into families.” EX1013.0031 (emphasis added). Bielas makes clear that it is the “identical cypher pairs,” not the use of the cypher *and* a portion of the target sequence, that allows for grouping the sequencing data.

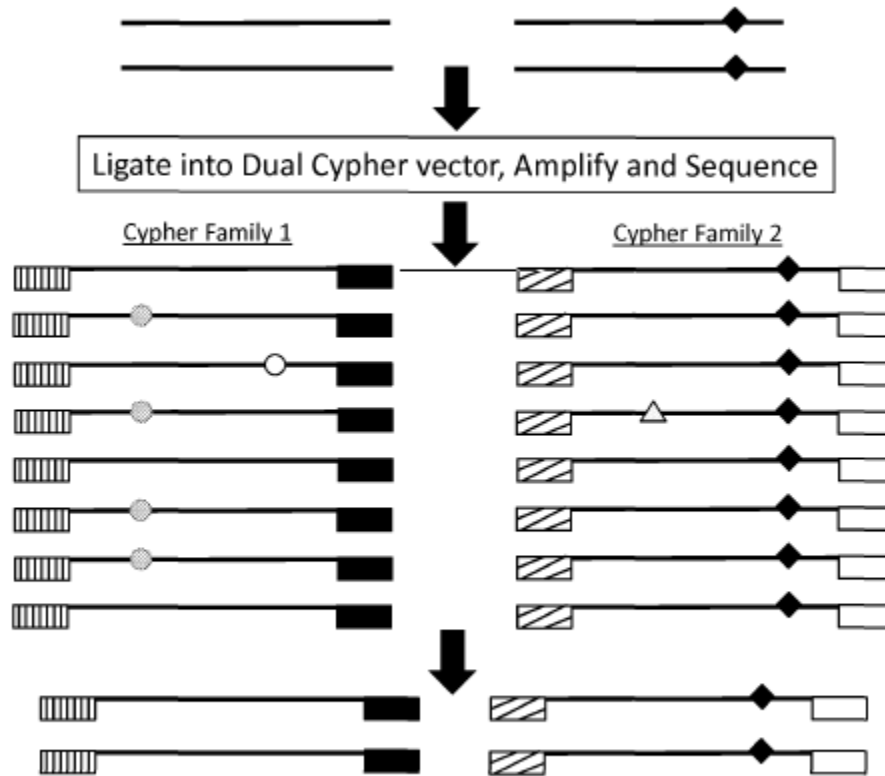


Fig. 3B

EX1013.43.

Rather than identifying duplicates, Bielas is concerned with solving the issue of random errors that arise during sequencing. EX1013.0003. (“The present disclosure relates to compositions and methods for accurately detecting mutations using sequencing....”). Because Bielas is directed to distinguishing between sequencing errors and mutations within the nucleic acid fragments, the Bielas method does not teach a POSA to look to the nucleic acid fragments to match duplicates, since the nucleic acid fragments would contain the very errors and mutations that a POSA seeks to differentiate.

Instead, Bielas teaches a POSA a method of matching sense fragments (i.e., fragments that match the coding strand) and antisense fragments (i.e., fragments that are complementary to the sense strand) in a sample. *See, e.g.*, EX1013.0001. (“The present disclosure provides compositions and methods for accurately detecting mutations by uniquely tagging double stranded nucleic acid molecules with dual cyphers such that sequence data obtained from a sense strand can be linked to sequence data obtained from an anti-sense strand...”). From this, a POSA would not have understood the “deconvolut[ion]” described in Bielas to mean identification (and subsequent removal) of sequencing reads with duplicate identifier sites and nucleic acid fragments. Indeed, it is not clear from Bielas what occurs in that step. The term “deconvolution” is a broad term in the sequencing field, and used in a variety of applications. *See, e.g.*, EX2012.01 (identifying the genus of origin of individual genes in a shotgun sequencing application); EX2011.01 (identifying cell-specific gene expression changes from a mixed gene dataset); EX2013.01 (same). Therefore, Bielas’s use of cypher pairs to “deconvolute” sequencing reads would not have taught a POSA to identify duplicates using a combination of an identifier sequence and at least a portion of the target sequence, as claimed.

2. The Petition Has Failed to Establish that Any Dependent Claim Is Likely Invalid

Claim 1 is the only independent claim in the ’241 Patent, from which all other challenged claims depend. As explained above, the Petition fails to show that the

prior art renders claim 1 anticipated because the prior art lacks disclosure of required elements of the claims. Therefore, the Petition similarly cannot establish any of the dependent claims are anticipated.

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

The Petition does not present any arguments that claim 1 is obvious over Bielas. Ground 2 only addresses the obviousness of dependent claims 4, 5, 11, 12, 15, and 16, all of which depend from claim 1. As explained above, Bielas does not disclose identifying duplicate sequencing reads based on the identifier site and the target sequence, as required in all challenged claims. First, Bielas does not describe a process of identifying duplicates. *See supra* Section IV.B.1. Second, even assuming *arguendo* that Bielas does disclose the identification of duplicate sequences, Bielas does not require the use of any portion of the target sequence to identify duplicates. Examples 1 and 3 require first the use of a Cypher to identify duplicates, and only once duplicates have been identified does Bielas disclose the use of the target sequence to identify *mutations*, not duplicates.

Petitioners do not rely on any other references for this element, and do 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.

Because Petitioners cannot show that Bielas renders claim 1 obvious, Petitioners cannot establish that any of the dependent claims are obvious.

V. THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION

The Board may deny petitions where the same or substantially the same art or arguments were previously considered by the patent office during prosecution. 35 U.S.C. § 325(d); *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (PTAB Feb. 13, 2020). Here, the Examiner considered prior art during prosecution that is substantially the same as the art cited in the Petition, and Petitioner has not identified any material error by the Examiner. The Board, therefore, should exercise its discretion to deny institution under Section 325(d).

A. Discretionary Denial Under § 325(d) Is Appropriate Because the Examiner Considered Substantially the Same Prior Art

The *Becton Dickinson/Advanced Bionics* factors support denying institution because the prior art cited in the Petition is substantially the same as Doan addressed during prosecution. The *Becton Dickinson/Advanced Bionics* factors weigh against institution when the petitioner's asserted references are materially indistinguishable from those previously before the Examiner. *See 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). Here, there are no “material differences” between the references considered by the Examiner and the prior art asserted in the Petition.

In the notice of allowance of the claims of the '241 patent, the Examiner specifically noted that the claimed subject matter was not disclosed in the prior art reference Doan. Doan is directed to a method for detecting genetic variants that utilizes an adapter-integrated unique molecular identifier with amplification, then separates overlapping reads based on the identifier alone or in combination with a sample index. EX2003.06-07, .10, .134.

1. The Examiner Considered Substantially the Same Prior Art as Kivioja

Petitioner alleges that Kivioja teaches “identifying duplicates sequencing reads as reads with the identical identifier sites (the ‘label’) and target sequences (the ‘gene’ and ‘position’).” Petition, 35. The references cited during prosecution disclose sequencing methods with substantially the same elements.

In the notice of allowance, the Examiner cited U.S. 2022/0145380 (referred to as “Doan”), stating that Doan “does not teach or suggest using a combination of target sequence and identifier sequence for duplicate removal.” EX1020.10434. 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 includes disclosure

of the use of a unique molecular identifier attached to a target sequence, amplification of the target sequence and unique molecular identifier, then segregation of 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. EX2003.06-07, .10, .134. Doan then teaches removal of duplicates based on the unique molecular identifier: “all but one read having the same unique molecular identifiers will be removed from the data set....These duplicated amplifications reactions are not considered independent interrogations of the nucleic acid.” *Id.*, .46. Doan, like Kivioja, uses barcodes (i.e. “identifier sites,” or “labels”) to identify sequence reads and does not teach a POSA to look to both the barcode in conjunction with a portion of the target sequence as explained above in Section IV. *See supra* Section IV.A. Instead, both Doan and Kivioja disclose detecting duplicates based on something other than the identifier site and a portion of the nucleic acid fragment.

Additionally, the '241 Patent issued from a line of continuation applications, each of which was before the same Examiner. Earlier in this family of applications, the Examiner cited McCloskey (EX1022). EX1019.0451-54, .0464-65; EX1018.0799. 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. The Examiner initially rejected the claims over McCloskey, stating that McCloskey taught “sequencing the PCR products containing the adapter sequences, grouping the sequencing reads based on the batch stamp and barcode and detecting and removing duplicate reads” EX1018.0432. (citing EX1022.0006); *see also id.*, .0782. Like Kivioja, McCloskey uses barcodes (i.e. “identifier sites,” or “labels”) to identify sequence reads and does not teach a POSA to look to both the barcode in conjunction with a portion of the target sequence. *Supra* Section IV.A.

Thus, the Examiner considered substantially the same prior art as Kivioja when issuing the notice of allowance for the '241 Patent. *See II-VI, Inc. v. Soto*, IPR2021-01359, Paper 10 at 5-10, 19-20, 24-25, 28-33 (PTAB Feb. 15, 2022) (exercising discretion to deny institution under § 325(d), in part because “[t]he asserted art ... or art cumulative to the asserted art ... was evaluated extensively during prosecution of the parent patent”).

2. The Examiner Considered Substantially the Same Prior Art as Bielas

Petitioner alleges that Bielas teaches a method of attaching cyphers to DNA nucleotide fragments prior to PCR and sequencing and using those cyphers to “de-duplicate” the sequencing data. Petition, 52. As explained above, during prosecution, the Examiner allowed the pending claims and specifically cited Doan.

The Examiner noted that while Doan taught the use of unique identifiers to identify duplicative sequences, it did not teach the use of both identifiers and target sequence to identify duplicates. The Cyphers disclosed in Bielas are substantially similar to the unique molecular identifiers disclosed in Doan, in both function and structure. The Bielas Cyphers, like the Doan unique molecular identifiers, are both used by a POSA to identify duplicate sequence reads. *See supra* Section IV.B. And like the identifiers in Doan, the Bielas Cyphers are contained within an adaptor (comprising an adaptor sequence, index sequence, and nucleic acid priming site) added to the end of the target sequence. *See* EX1013.0005., Figs. 1, 2; EX2003.74, .134.

Additionally, the Cyphers disclosed in Bielas are substantially the same as those in McCloskey in both function and structure. The Bielas Cyphers, like the McCloskey barcodes, are both used by a POSA to identify duplicate sequence reads. And like the McCloskey barcodes, the Bielas Cyphers are contained within an adaptor (comprising an adaptor sequence, index sequence, and nucleic acid priming site), added to the end of the target sequence, and can consist of 7 nucleotides. *See* EX1013.0005, Figs. 1, 2; EX1022.0004.

Thus, the Examiner considered substantially the same prior art as Bielas and allowed the claims.

B. Petitioner Has Failed to Identify Any Material Error by the Examiner

The Examiner did not err in determining that the claims were allowable over this prior art, and Petitioner has not identified any material error in the Examiner's determination. "An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims." *Palo Alto Networks, Inc. v. Centripetal Networks, Inc.*, IPR2021-01520, Paper 23, at 16 (PTAB Mar. 22, 2022) (citing *Advanced Bionics, LLC*, IPR2019-01469, Paper 6, at 8 n.9) (exercising discretion under 325(d) because petitioner failed to demonstrate any error, much less material error, by the examiner). Here, Petitioner alleges merely that the Examiner materially erred because "the prior art, including Kivioja and Bielas" taught "using the fragment and the identifier sequence to deduplicate...." Petition, 74. This is incorrect. As explained above, neither Kivioja nor Bielas teaches the claimed method, including the identification of duplicate sequences based on both the identifier site and at least a portion of the fragment sequence. *Supra* Section IV. Petitioner identifies no other reasons for the Examiner's purported material error.

VI. CONCLUSION

In light of the above, Petitioner has not shown that there is a reasonable likelihood that at least one challenged claim is unpatentable, and the Petition should be denied.

U.S. Patent No. 11,725,241

Dated: January 23, 2025

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Preliminary 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 5232 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.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on January 23, 2025, a copy of the foregoing **Patent Owner's Preliminary 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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