

U.S. Patent No. 9,546,399

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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INTEGRATED DNA TECHNOLOGIES, INC.,  
Petitioner,

v.

TECAN GENOMICS, INC.,  
Patent Owner

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U.S. Patent No. 9,546,399

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Case No. IPR2024-01502

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**PATENT OWNER'S PRELIMINARY RESPONSE**

## TABLE OF CONTENTS

|      |                                                                                                                                                                                |    |
|------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| I.   | INTRODUCTION .....                                                                                                                                                             | 1  |
| II.  | TECHNOLOGY BACKGROUND .....                                                                                                                                                    | 2  |
| A.   | Development of Sequencing Technology .....                                                                                                                                     | 2  |
| B.   | Next-Generation Technologies .....                                                                                                                                             | 3  |
| C.   | Challenges With Existing Methods of NGS .....                                                                                                                                  | 4  |
| III. | THE '399 PATENT.....                                                                                                                                                           | 6  |
| A.   | Overview .....                                                                                                                                                                 | 6  |
| B.   | Level of Ordinary Skill in the Art.....                                                                                                                                        | 7  |
| C.   | Prosecution History .....                                                                                                                                                      | 9  |
| D.   | Claim Construction.....                                                                                                                                                        | 9  |
| IV.  | THE PETITION FAILS TO ESTABLISH A REASONABLE<br>LIKELIHOOD OF SUCCESS ON AT LEAST ONE CLAIM.....                                                                               | 10 |
| A.   | Ground 1: Petitioner Has Not Shown That Any Challenged Claim Is<br>Obvious Over the Combination of Iafrate and Kivioja.....                                                    | 10 |
| 1.   | Iafrate Does Not Disclose All Elements of the Challenged<br>Claims .....                                                                                                       | 10 |
| 2.   | The Petition Fails to Establish that Kivioja Discloses<br>Identifying Duplicate Sequencing Reads Based on the Identifier<br>and at Least a Portion of the Target Sequence..... | 11 |
| 3.   | Petitioner Has Not Established That a POSA Would Have Been<br>Motivated to Combine Iafrate and Kivioja With a Reasonable<br>Expectation of Success .....                       | 13 |
| 4.   | The Petition Fails to Establish that Any Dependent Claim is<br>Likely Invalid.....                                                                                             | 16 |
| B.   | Grounds 2 and 3: Petitioner Has Not Shown That Any Challenged<br>Claim Is Anticipated By, or Obvious Over, Bielas.....                                                         | 16 |
| 1.   | Bielas Does Not Disclose Identifying a Duplicate Sequencing<br>Read Based on the Identifier Site and Nucleic Acid Fragment 17                                                  |    |
| 2.   | Petitioner Has Not Shown a POSA Would Have Been<br>Motivated to Modify Bielas .....                                                                                            | 20 |
| 3.   | The Petition Has Failed to Establish that Any Dependent Claim<br>is Likely Invalid .....                                                                                       | 22 |

|     |                                                                                                                          |    |
|-----|--------------------------------------------------------------------------------------------------------------------------|----|
| V.  | THE BOARD SHOULD EXERCISE ITS DISCRETION TO DENY INSTITUTION.....                                                        | 22 |
| A.  | Discretionary Denial Under § 325(d) Is Appropriate Because the Examiner Considered Substantially the Same Prior Art..... | 22 |
| 1.  | Iafrate Discloses Substantially the Same Information as Samuels and McCloskey .....                                      | 23 |
| 2.  | Kivioja Discloses Substantially the Same Information as McCloskey .....                                                  | 25 |
| 3.  | Bielas Discloses Substantially the Same Information as McCloskey .....                                                   | 26 |
| B.  | Petitioner Has Failed to Identify Any Material Error by the Examiner .....                                               | 27 |
| VI. | CONCLUSION .....                                                                                                         | 28 |

## TABLE OF AUTHORITIES

| Cases                                                                                                                           | Pages  |
|---------------------------------------------------------------------------------------------------------------------------------|--------|
| <i>10x Genomics, Inc. v. Bio-Rad Laboratories, Inc.</i> ,<br>IPR2020-00086, Paper 39 (PTAB Apr. 26, 2021) .....                 | 8      |
| <i>ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.</i> ,<br>694 F.3d 1312 (Fed. Cir. 2012) .....                           | 16, 20 |
| <i>Advanced Bionics, LLC v. MED-EL Elektromedizinische<br/>GeräteGmbH</i> ,<br>IPR2019-01469, Paper 6 (PTAB Feb. 13, 2020)..... | 21, 27 |
| <i>In re Am. Acad. of Sci. Tech Ctr.</i> ,<br>367 F.3d at 1359 (Fed. Cir. 2004) .....                                           | 16, 20 |
| <i>In re Gorman</i> ,<br>933 F.2d 982 (Fed. Cir. 1991) .....                                                                    | 13     |
| <i>In re NuVasive</i> ,<br>842 F.3d 1376 (Fed. Cir. 2016) .....                                                                 | 16     |
| <i>Palo Alto Networks, Inc. v. Centripetal Networks, Inc.</i> ,<br>IPR2021-01520, Paper 23 (PTAB Mar. 22, 2022).....            | 27     |
| <i>Rohde &amp; Schwarz GmbH &amp; Co., KG v. Tektronix, Inc.</i> ,<br>IPR2018-00645, Paper 7 (PTAB Oct. 1, 2018).....           | 8      |
| <i>Xerox Corp., et al., v. Bytemark, Inc.</i> ,<br>IPR2022-00624, Paper 12 (PTAB Feb. 10, 2023).....                            | 16     |
| <i>Xilinx, Inc., et al v. Analog Devices, Inc.</i> ,<br>IPR2021-00294, Paper 9 (PTAB June 10, 2021) .....                       | 22     |

**TABLE OF EXHIBITS**

| <b>IPR Ex.</b> | <b>Description</b>                                                                                                                                                                                                                                                                             |
|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2001           | Alkan, C., Sajjadian, S., and Eichler, E., “Limitations of next-generation genome sequence assembly,” <i>Nature Methods</i> , Vol.8, No.1, January 2011                                                                                                                                        |
| 2002           | Chiasson, M.J.P., Wilson, R.K, Eichler, E.E., “Genetic variation and the <i>de novo</i> assembly of human genomes,” <i>Nature Reviews</i> , Vol. 16, November 2015                                                                                                                             |
| 2003           | U.S. Patent Publication No. 2002/0145380 A1 to Doan, et al.                                                                                                                                                                                                                                    |
| 2004           | Goodwin, S., McPherson, J.D., McCombie, W.R., “Coming of age: ten years of next-generation sequencing technologies,” <i>Nature Reviews</i> , Vol. 17, June 2016                                                                                                                                |
| 2005           | Kanagawa, T., “Bias and Artifacts in Multitemplate Polymerase Chain Reactions (PCR),” <i>Journal of Bioscience and Bioengineering</i> , Vol. 96, No. 4, 2003                                                                                                                                   |
| 2006           | Mamanova, L., Coffey, A.J., Scott, C.E., Kozarewa, I., Turner, E.H., Kumar, A., Howard, E., Shendure, J., and Turner, D.J., “Target-enrichment strategies for next-generation sequencing,” <i>Nature Methods</i> , Vol. 7, No. 2, February 2010                                                |
| 2007           | Nakamura, K., Oshima, T., Morimoto, T., Ikeda, S., Yoshikawa, H., Shiwa, Y., Ishikawa, S., Linak, M.C., Hirai, A., Takahasi, H., Altaf-Ul-Amin, Ogasawara, N., and Kanaya, S., “Sequence-specific error profile of Illumina sequencers,” <i>Nucleic Acids Research</i> , Vol. 39, No. 13, 2011 |
| 2008           | Sanger, F., Nicklen, S., and Coulson, A.R., “DNA sequencing with chain-terminating inhibitors,” <i>Proc. Natl. Acad. Sci . USA</i> , Vol. 74, No. 12, December 1977                                                                                                                            |
| 2009           | Satam, H., Joshi, K., Mangrolia, U., Waghoo, S., Zaidi, G., Rawool, S., Thakare, R.P., Banday, S., Mishra, A.K., Das, G., Malonia, S.L, “Next-Generation Sequencing Technology: Current Trends and Advancements,” <i>Biology</i> Vol. 997, No. 12, 2023                                        |

|      |                                                                                                                                                                                                                                                                                                   |
|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2010 | Whiteford, N., Skelly, T., Curtis, C., Ritchie, M.E., Löhr, A., Zaranek, A.W., Abnizova, I., Brown, C., “Swift: Primary Data Analysis for the Illumina Solexa Sequencing Platform,” <i>Bioinformatics</i> , Vol. 25, No. 16, 2009                                                                 |
| 2011 | Capurro, A., Bodea, L., Schaefer, P., Luthi-Carter, R., and Perreau, V.M., “Computational deconvolution of genome wide expression data from Parkinson’s and Huntington’s disease brain tissues using population-specific expression analysis,” <i>Frontiers in Science</i> , Vol. 8, January 2015 |
| 2012 | Carr, R., Shen-Orr, S.S., Borenstein, E., “Reconstructing the Genomic Content of Microbiome Taxa through Shotgun Metagenomic Deconvolution,” <i>PLOS Computational Biology</i> , Vol. 9, Issue 10, October 2013                                                                                   |
| 2013 | Wang, N., Gong, T., Clarke, R., Chen, L., Shih, L., Zhang, Z., Levine, D.A., Xuan, J., Wang, Yue, “UNDO: a Bioconductor R package for unsupervised deconvolution of mixed gene expressions in tumor samples,” <i>Bioinformatics</i> , Vol. 31, No. 1, 2015                                        |
| 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                                                                                       |
| 2015 | Mardis, E.R., “DNA sequencing technologies: 2006–2016,” <i>Nature Protocols</i> , Vol. 12, No. 12, 2017                                                                                                                                                                                           |

## **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 (“Petition”) challenging claims 1-3, 5-11, and 14-17 (the “challenged claims”) of U.S. Patent No. 9,546,399 (“the ’399 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. The Examiner raised obviousness arguments during prosecution in line with the arguments in the Petition, but Applicants overcame those rejections. 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; *see also* EX2008.01. 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 ends. *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 with 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 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 '399 PATENT**

#### **A. Overview**

The '399 Patent is directed to a method of detecting, and subsequently removing, duplicate sequencing reads from a sample population. EX1033.0001. 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 (*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 '399 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, 23; see also EX1079.¶184. Petitioner's definition goes beyond the level of *ordinary* skill in the art. The sequencing methods described in the '399 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, 23. 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.*, 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**

During prosecution of the '399 Patent, Applicants overcame multiple rejections based on the prior art references McCloskey (EX1022) and Samuels (EX1033). To overcome these rejections, Applicants distinguished the claimed invention by further defining the identification of a duplicate sequence by using both the identifier site *and* at least a portion of the nucleic acid fragment. Applicants further overcame rejections based on McCloskey and Samuels by arguing that the claimed method was superior to that disclosed in the prior art, in part because it allowed for fewer unique adapters. *See, e.g.*, EX1018.0799. Applicants explained that because the claimed method recited the use of both the adapter and a portion of the target sequence to identify duplicates, fewer unique adaptors would be needed. *See, e.g., id.*

### **D. Claim Construction**

For purposes of this Preliminary Response, Patent Owner does not believe any term of the '399 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. Ground 1: Petitioner Has Not Shown That Any Challenged Claim Is Obvious Over the Combination of Iafrate and Kivioja**

Petitioner argues that the combination of Iafrate and Kivioja renders the challenged claims obvious, but neither Kivioja nor Iafrate discloses key limitations in the challenged claims. Petitioner provides no explanation, other than impermissible hindsight and unsupported expert *ipse dixit*, as to why a POSA (not a person of *extraordinary* skill) would have been motivated to combine Iafrate with Kivioja to achieve the claimed subject matter, let alone with a reasonable expectation of success as required. Petitioner has thus failed to show with a reasonable likelihood that any challenged claim is invalid under Ground 1.

##### **1. Iafrate Does Not Disclose All Elements of the Challenged Claims**

As Petitioner admits, Iafrate discloses a sequencing method using an adaptor comprising an indexing primer binding site, an indexing site, and a target sequence primer binding site. Petition, 28. Notably, Petitioner admits that Iafrate does not disclose a key limitation of claim 1: the requirement that the adaptor contains “an identifier site consisting of between 1 and 8 nucleotides.” *Id.*, 27. Iafrate, therefore, fails to provide a POSA with any teaching regarding the use of a unique molecular identifier (“UMI”). Nor does Iafrate provide any teaching regarding the identification and removal, or separation, of duplicate sequencing reads, as further

required by claim 1 and by the challenged dependent claims. *See, e.g.*, EX1003 at cl. 1, preamble (“[a] method for detecting a duplicate sequencing read...”), cl. 1(d) (“identifying a duplicate sequence read...”). Petitioner attempts to fill in the gaps of Iafrate with the disclosures of Kivioja, but Kivioja is similarly lacking.

**2. The Petition Fails to Establish that Kivioja Discloses Identifying Duplicate Sequencing Reads Based on the Identifier and at Least a Portion of the Target Sequence**

Claim 1(d) of the '399 Patent requires “identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads.” Petitioner relies solely on Kivioja for the disclosure of this limitation. Petitioner argues that Kivioja teaches this limitation 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, 35 (citing EX1079.¶248). 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 cannot point to a disclosure in Kivioja that discloses the use of a portion of the target sequence in combination with the identifier site to identify a duplicate sequence read. Petition, 34. 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.” *Id.*, 40. 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. EX1012.005. 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.

**3. Petitioner Has Not Established That a POSA Would Have Been Motivated to Combine Iafrate and Kivioja With a Reasonable Expectation of Success**

Even assuming that the prior art disclosed all limitations of the challenged claims, Petitioner fails to show that a POSA (not a person of *extraordinary* skill) would have been motivated to combine Iafrate and Kivioja to arrive at the challenged claims, let alone with a reasonable expectation of success. Petitioner relies on improper hindsight, conclusory statements, and the *ipse dixit* of an expert witness, to support its allegations that a POSA would have been motivated to combine the prior art to arrive at the challenged claims and to have a reasonable expectation of success in achieving them. *In re Gorman*, 933 F.2d 982, 987 (Fed. Cir. 1991).

Petitioner claims that a POSA would have been motivated to start with the adaptor of Iafrate and modify it according to the disclosures of Kivioja to arrive at the adaptor required in claim 1. Petitioner admits, however, that neither Iafrate nor Kivioja discloses an adaptor that contains all elements of the claimed adaptor. Petition at 27 ("Iafrate teaches a method of NGS library preparation using an adaptor

with all but one of the features recited in claim 1 of the '399 patent.”), 34 (“Kivioja did not specify a separate sample index primer binding site...”). Petitioner glosses over the differences between the Iafrate and Kivioja adaptors, on the one hand, and the claimed adaptors, on the other, by arguing that Kivioja’s target sequence primer binding site serves the purpose of both of the claimed primer binding sites, but Petitioner provides no explanation on why or how a POSA would combine aspects of the Iafrate and Kivioja adaptors. Petition, 31.

The Petition is, in fact, entirely silent on which aspects of the Iafrate method the POSA would use in any improved sequencing method. Petitioner’s explanation of its obviousness arguments focus solely on the disclosures of Kivioja. *See* Petition, 38-43. The only mention of Iafrate in Petitioner’s obviousness argument for claim 1 refers to providing a motivation to use a shorter molecular tag. *Id.*, 41. But, Iafrate does not disclose a molecular tag, so Petitioner cannot rely on Iafrate for the disclosure of that limitation. Nor does Iafrate have any discussion or suggestion to use a shorter molecular tag. As a result, the Petition lacks any evidence that a POSA (or a person of *extra*ordinary skill for that matter) would have been motivated to combine aspects of Iafrate with aspects of Kivioja to arrive at the claimed invention. Instead, the manufactured motivation to combine these two references in the Petition is entirely based on improper hindsight.

Even assuming that the Petition explained how Iafrate and Kivioja could be combined, however, Petitioner also fails to explain why a POSA looking to improve the method of identifying genetic mutations in Iafrate would look to aspects of Kivioja. Iafrate is primarily directed at methods of identifying unknown mutations in cancer genes. EX1011.0013, .0023-25, .0029; EX1079.¶¶225-228. Kivioja, on the other hand, is primarily directed to karyotyping, counting individual DNA molecules of known genomes. EX1012.0001-02. Kivioja discloses the use of molecular tags to estimate the number of fragments without directly observing each one. *Id.*, .0001. Kivioja also discloses an *in silico* experiment to demonstrate that the molecular tag could be used to accurately estimate the number of chromosomes in a sample by counting the number of molecules with the same molecular tag. *Id.*, .0002. Notably, the method disclosed in Kivioja is only usable when working with a known genome. The Petition does not explain why a POSA would choose aspects of the karyotyping method of Kivioja for use in sequencing unknown genetic sequences as disclosed in Iafrate.

Petitioner offers no explanation for why a POSA would look to combine references that disclose different sequencing methods, directed toward different fields of use. Instead, Petitioner offers merely conclusory, unsupported expert testimony. Petition, 36-37 (citing EX1079,¶¶225-49). Expert *ipse dixit* is insufficient to carry Petitioner's burden to establish a motivation to combine Iafrate

and Kivioja. *See, e.g., In re NuVasive*, 842 F.3d 1376, 1384 (Fed. Cir. 2016); *see also ActiveVideo Networks, Inc. v. Verizon Commc'ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012); *In re Am. Acad. Of Sci. Tech Ctr.*, 367 F.3d 1359 at 1370; *Xerox Corp., et al. v. Bytemark, Inc.*, IPR2022-00624, Paper 12 at 5 (PTAB Feb. 10, 2023) (“I determine that the Board was correct in giving little weight to Petitioner’s expert because the expert declaration merely offered conclusory assertions without underlying factual support and repeated, *verbatim*, Petitioner’s conclusory arguments.”).

**4. The Petition Fails to Establish that Any Dependent Claim is Likely Invalid**

Claim 1 is the only independent claim in the '357 Patent, from which all other challenged claims depend. As explained above, the Petition fails to show that the prior art 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 2 and 3: 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 2 and 3.

Like Kivioja, Bielas does not disclose a method of “identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment as another sequencing read in the population of sequencing reads,” as required by the challenged claims. *See* EX1003.0021. 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 2 or 3.

**1. Bielas Does Not Disclose Identifying a Duplicate Sequencing Read Based on the Identifier Site and Nucleic Acid Fragment**

Petitioner argues that Bielas discloses identifying duplicate sequencing reads as claimed because it “teaches differentiating between true mutations and artifact mutations” and because it discloses “computationally deconvolut[ing]” the fragments. Petition, 55 (internal quotations omitted). 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 in Bielas 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 to identify duplicates as 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 the same Cypher/identifier site and fragment sequence as other reads.” Petition, 61. 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 same cypher and fragment sequence.” Petition, 62. 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.

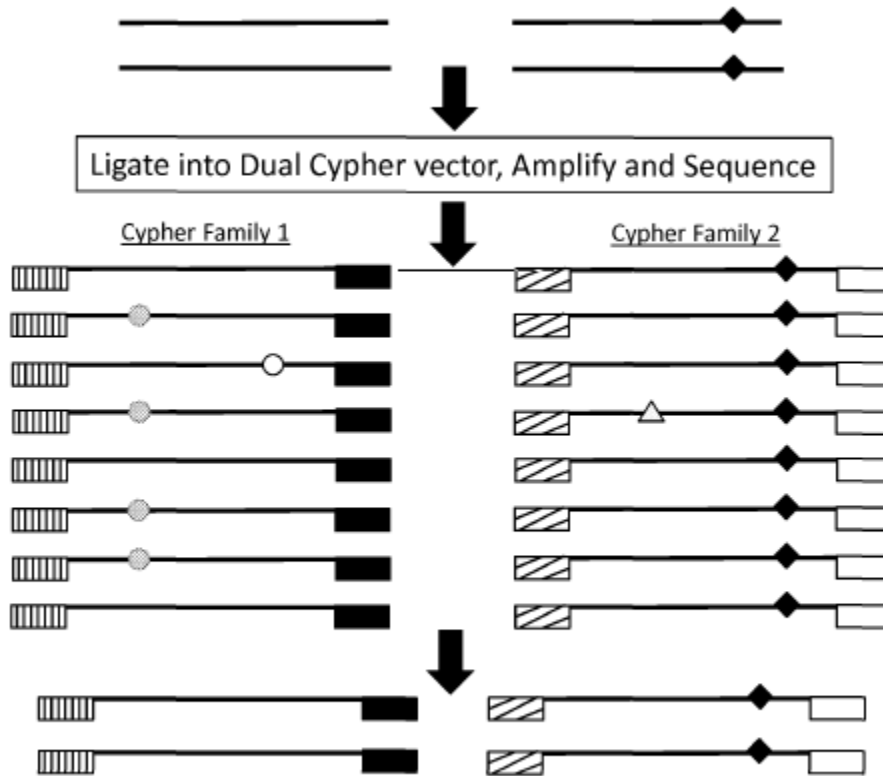


*Fig. 3B*

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 would seek 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. Petitioner Has Not Shown a POSA Would Have Been Motivated to Modify Bielas**

Petitioner also does not provide any explanation of how a POSA (or a person of *extraordinary* skill) would modify the method of Bielas to allow for identification

of duplicates based on both the Cypher and a portion of the target sequence, much less why a POSA would have had a reasonable expectation of success in achieving the claimed method. Petitioner points to two possible modifications of Bielas in its obviousness argument (the components of the adaptors and the length of the identifier site), but does not argue that a POSA would have been motivated to modify any other aspect of Bielas to arrive at the challenged claims. Petition, 67-68. Therefore, Petitioner's obviousness argument cannot cure the deficiencies of Bielas.

As described above, Bielas does not describe a process of identifying duplicates. *See supra* 17-19. 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. *See supra* 20. 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. Petitioner entirely omits any explanation of how or why a POSA would modify the method of Bielas to look instead at the combination of the Cypher and a portion of the target sequence to identify mutations. As a result, Petitioner has not shown a reasonable likelihood that any challenged claim is obvious in light of Bielas.

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

Claim 1 is the only independent claim, from which all other challenged claims depend. As explained above, the Petition fails to show that Bielas renders claim 1 anticipated or obvious, and therefore, the Petition similarly cannot establish any of the dependent claims are anticipated or 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 Samuels (EX1033) and McClosky (EX1022) addressed during prosecution. The *Becton Dickinson/Advanced Bionics* factors weigh against institution when the petitioner's

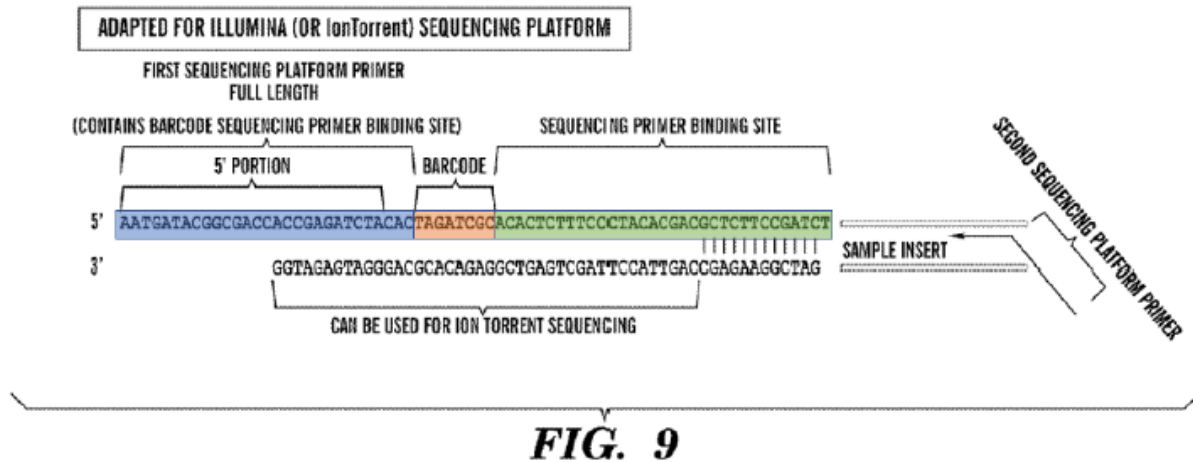
asserted references are materially indistinguishable from those previously before the Examiner. *See Xilinx, Inc., et al v. Analog Devices, Inc.*, IPR2021-00294, Paper 9, at 11 (PTAB June 10, 2021) (exercising discretion to deny institution under 325(d) because petitioner's two asserted references were 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.

During prosecution of the '399 Patent, the Examiner rejected the pending claims over the prior art references Samuels and McCloskey. McCloskey is directed to a method of identifying redundant sequences in a sequencing dataset, and discloses the use of 7-nucleotide-length "barcodes" and "batch-stamps" to do so. EX1022.0004. McCloskey further describes identification of sequence reads based only on reads that share the same "barcode" or "batch-stamp." *Id.*, .0006. Samuels is directed to a method of attaching barcodes to a nucleotide sequence to allow a user to differentiate PCR-caused errors from true single nucleotide polymorphisms. EX1033.0086-87, 94, 97. Samuels further discloses amplifying the barcodes and nucleotide sequence via PCR, and sequencing the amplified products. *Id.*

**1. Iafrate Discloses Substantially the Same Information as Samuels and McCloskey**

Petitioner alleges that Iafrate teaches an adaptor including an index primer binding site, an indexing site, and a sequence primer binding side, as well as library

preparation and sequencing steps. Petitioner relies in particular on Figure 9 in Iafrate:



EX1011.0011.

Like Figure 9, both Samuels and McCloskey disclose a sequencing method that included similar adaptors. For example, Figure 5 in Samuels describes the use of an adaptor, as well as a barcode, for use with sequencing. EX1033.0006. And Figure 1 in McCloskey discloses an adaptor that includes a “batch-stamp” to specify the DNA source (e.g., patient v. sample), a random “barcode” to distinguish between sequences from different cell or allele copies, a primer-binding site, and a genomic target-binding site. EX1022.0003.

During prosecution the Examiner explicitly rejected the pending claims over McCloskey, in particular due to the disclosures of Figure 1, stating that “McCloskey *et al.* teach a plurality of randomly-barcoded oligonucleotides (=adaptors) containing, from the 3' end, a target-specific sequence, batch-stamp sequence,

random 7 bp barcode (=identifier), another primer binding site and another sequence (Fig. 1).” EX1008.0430. The pending claims were also rejected over Samuels, with the Examiner stating that Samuels disclosed an adaptor comprising an indexing primer binding site, an indexing site, an identifier site, and a target sequence primer binding side. *Id.*, .0431 (citing EX1033.86-90). Petitioner alleges that the adaptors disclosed in Iafrate include an index primer binding site, an indexing site, and a target sequence primer binding site. Petition, 28-29. The adaptors in McCloskey and Samuels therefore include the same elements that Petitioner alleges are disclosed in Iafrate. Thus, the Examiner considered substantially the same prior art as Iafrate.

## **2. Kivioja Discloses Substantially the Same Information as McCloskey**

Petitioner alleges that Kivioja teaches “identifying as duplicates sequencing reads with the same identifier site (the ‘label’) and nucleic acid fragment (the ‘gene’ and ‘position’).” Petition, 41. The references cited during prosecution disclose sequencing methods with substantially the same elements.

During prosecution, 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.

Applicants overcame the Section 103 rejections based on McCloskey by arguing that McCloskey disclosed “a method of identifying redundant sequences, based solely on two or more sequence reads sharing an identical ‘barcode’ and ‘batch-stamp,’” rather than the claimed method which required “identifying a duplicate sequence read as the sequencing *read comprising the same identifier site and nucleic acid fragment....*” *Id.*, .0799 (emphasis in original). Like McCloskey, Kivioja discloses detecting duplicates based on something other than the identifier site and a portion of the nucleic acid fragment, as discussed in Section IV. Thus, the Examiner considered substantially the same prior art as Kivioja and Applicants overcame those rejections.

### **3. Bielas Discloses Substantially the Same Information as McCloskey**

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 rejected the pending claims over McCloskey, stating that the McCloskey reference taught the identification of duplicates via the use of molecular barcodes. *See, e.g.* EX1018.0782. The Cyphers disclosed in Bielas are substantially similar to 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. Applicants overcame the rejection, arguing that “McCloskey *et al.* disclose a method of identifying redundant sequences, based solely on two or more sequence reads sharing an identical ‘barcode’ and ‘batch-stamp’ []. McCloskey *et al.* clearly fails to arrive at the instantly claimed method of ‘identifying a duplicate sequencing read as the sequencing read comprising the same identifier site and nucleic acid fragment ....” EX1018.0799. 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 both “an identifier site of 8 nucleotides [and] de-duplicating using both the identifier and fragment sequence.” Petition, 73. 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* at 24-26. 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. 9,546,399

Dated: January 23, 2025

Respectfully submitted,

By: /Linnea P. Cipriano/

Linnea P. Cipriano (Reg. No. 67,729)

GOODWIN PROCTER LLP

620 Eighth Avenue

New York, NY 10018

lcipriano@goodwinlaw.com

Tel: (212) 813-8800

Fax: (212) 937-2204

*Counsel for Patent Owner Tecan Genomics, Inc.*

**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 6,079 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system use to prepare the Response.

Dated: January 23, 2025

/Linnea P. Cipriano/  
Linnea P. Cipriano (Reg. No. 67,729)  
GOODWIN PROCTER LLP  
620 Eighth Avenue  
New York, NY 10018  
lcipriano@goodwinlaw.com  
Tel: (212) 813-8800  
Fax: (212) 937-2204

## **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:

**Thomas S. Fletcher**

(Reg. No. 72,383)  
tfletcher@wc.com  
IDT-Tecan-IPRs@wc.com  
WILLIAMS & CONNOLLY LLP  
680 Maine Avenue SW  
Washington, DC 20024  
Phone: (202) 434-5497  
Fax: (202) 434-5029

**Jessamyn S. Berniker**

(Reg. No. 72,328)  
jberniker@wc.com  
IDT-Tecan-IPRs@wc.com  
WILLIAMS & CONNOLLY LLP  
680 Maine Avenue SW  
Washington, DC 20024  
Phone: (202) 434-5474  
Fax: (202) 434-5029

**Nicholas G. Vincent**

(Reg. No. 79,788)  
nvincent@wc.com  
IDT-Tecan-IPRs@wc.com  
WILLIAMS & CONNOLLY LLP  
680 Maine Avenue SW  
Washington, DC 20024  
Phone: (202) 434-5470  
Fax: (202) 434-5029

/Linnea P. Cipriano/

Linnea P. Cipriano (Reg. No. 67,729)  
GOODWIN PROCTER LLP  
620 Eighth Avenue  
New York, NY 10018  
lcipriano@goodwinlaw.com

Tel: (212) 813-8800  
Fax: (212) 937-2204