

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 IPR2025-00015
U.S. Patent No. 10,036,012

PATENT OWNER'S PRELIMINARY RESPONSE

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Other Authorities

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EXHIBIT LIST

Ex.	Short Name	Description
2001	Evans 2009	Mark F. Evans, <i>The Polymerase Chain Reaction and Pathology Practice</i> , 15 DIAGN. HISTOPATHOL. 344 (2009)
2002	N/A	<i>The Cost of Sequencing a Human Genome</i> , NAT'L INST. OF HEALTH NAT'L HUMAN GENOME RESEARCH INST., https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost (last visited January 29, 2025)
2003	Goodwin 2016	Sara Goodwin et al., <i>Coming of Age: Ten Years of Next-Generation Sequencing Technologies</i> , 17 NAT. REV. 333 (2016).
2004	Mardis 2017	Elaine R. Mardis, <i>DNA Sequencing Technologies: 2006-2016</i> , 12 NAT. PROTOC., 213 (2017).
2005	Fuller 2009	Carl W. Fuller et al., <i>The Challenges of Sequencing by Synthesis</i> , 27 NAT. BIOTECHNOL. 1013 (2009).
2006	Margulies 2005	Marcel Margulies et al., <i>Genome Sequencing in Open Microfabricated High Density Picoliter Reactors</i> , 437 NATURE 376 (2005).
2007	Luo 2012	Chengwei Luo et al., <i>Direct Comparisons of Illumina vs. Roche 454 Sequencing Technologies on the Same Microbial Community DNA Sample</i> , 7 PLOS ONE 1 (2012).
2008	Hert 2008	Daniel G. Hert et al., <i>Advantages and Limitations of Next-Generation Sequencing Technologies: A Comparison of Electrophoresis and Non-Electrophoresis Methods</i> , 29 ELECTROPHORESIS 4618 (2008).
2009	N/A	<i>Six Years After Acquisition, Roche Quietly Shuts 454</i> , BioIT World (Oct. 16, 2013), https://www.bio-itworld.com/news/2013/10/16/six-years-after-acquisition-roche-quietly-shutters-454 .
2010	Mamanova 2010	Lira Mamanova et al., <i>Target-Enrichment Strategies for Next-Generation Sequencing</i> , 7 NAT. METHODS 111 (2010).

Ex.	Short Name	Description
2011	Treangen 2011	Todd J. Treangen et al., <i>Repetitive DNA and Next-Generation Sequencing: Computational Challenges and Solutions</i> , 29 NAT. REV. GENET. 36 (2012).
2012	Brownie 1997	Jannine Brownie et al., <i>The Elimination of Primer-dimer Accumulation in PCR</i> , 25 NUCLEIC ACIDS RES. Nucleic Acids Research 3235 (1997).
2013	Tewhey 2009	Ryan Tewhey et al., <i>Microdroplet-based PCR Enrichment for Large-scale Targeted Sequencing</i> , 27 NAT. BIOTECHNOL. 1025 (2009).
2014	Link 2012	U.S. Patent Application No. 2012/0309002 (published Dec. 6, 2012).
2015	Franck 1998	Sophia M. Franck et al., <i>Multiplex PCR for Enterotoxigenic, Attaching and Effacing, and Shiga Toxin-Producing Escherichia coli Strains from Calves</i> , 36 J. CLIN. MICROBIOL. 1795 (1998).
2016	AmpliTaq Gold	Applied Biosystems, <i>AmpliTaq Gold, with GeneAmp® 10X PCR Buffer or GeneAmp 10X PCR Buffer II & MgCl₂ Solution or GeneAmp 10X PCR Gold Buffer & MgCl₂ Solution</i> (2000).
2017	Fool 2002	University of Hawaii, <i>The Simple Fool's Guide to PCR</i> (2002).
2018	Ying 2019	Hua Ying et al., <i>The Whole-Genome Sequence of the Coral Acropora Millepora</i> , 1 GENOME BIOL. Genome Biology 1374 (2019).
2019		Office Action Summary, Application No. 13/750,768 (U.S. Patent & Trademark Office July 15, 2015).
2020	Milbury 2009	Coren A. Milbury et al., <i>PCR-Based Methods for the Enrichment of Minority Alleles and Mutations</i> , 55 CLIN. CHEM. 632 (2009).
2021	Bustamante Declaration	Declaration of Carlos D. Bustamante, Ph.D.

I. INTRODUCTION

The Board should deny the Petition for *Inter Partes* Review (“Petition”) of claims 1-3 and 5-22 (“the Challenged Claims”) of Tecan Genomics, Inc.’s (“Tecan”) U.S. Patent No. 10,036,012 (“the ’012 patent”) because Petitioner has failed to establish a reasonable likelihood that at least one claim is invalid.

The crux of the Petition is that the sole independent claim of the ’012 patent is either anticipated (Ground 1) or rendered obvious (Ground 2) by Meyer. The Petition, however, misconstrues the methods of Meyer and fails to establish that Meyer discloses the *enrichment* of a *sequence of interest*. Meyer is directed at improving a method for sequencing large amounts of nucleotides in a single sequencing run using the 454 sequencing platform. Petitioner alleges that Meyer’s method of improving the error rate of the sequencing method—which does not result in an increased proportion of the “sequence of interest” over any other portion of the reaction mixture—qualifies as “enrichment” of that sequence. Petitioner further alleges that the end of an RNA strand with a “broken T” sequence, which is a modification introduced by Meyer to assist with the sequencing, is a “sequence of interest,” without any evidence that the *known* sequence of that “broken T” chain is later studied. Both of these positions defy a logical reading of Meyer and the Challenged Claims, and they should be rejected. Petitioner’s arguments regarding Meyer seek to rewrite the disclosure of Meyer to fit the Challenged Claims.

Petitioner's arguments that the Challenged Claims are obvious in light of Meyer similarly fail. Petitioner devotes a single paragraph in its Petition to arguing why certain elements of claim 1 would have been obvious based on Meyer. But Petitioner offers no explanation as to how or why a person of ordinary skill in the art would modify Meyer to allow for enrichment (i.e., the increased proportion of a desirable portion of the mixture over other portions of the mixture) of a sequence "of interest." Without meeting these deficiencies in the disclosure of Meyer, Petitioner cannot meet its burden of showing the Challenged Claims are obvious.

Because Grounds 3-5 rely on the arguments in Ground 1 or 2, Grounds 3-5 necessarily fail as a result of Petitioner failing to establish that Meyer discloses or teaches all limitations of claim 1. The Board, therefore, should deny institution of *Inter Partes* Review on the merits.

Additionally, the Board should deny institution under § 325(d) because the Examiner considered prior art with substantially the same elements as Petitioner alleges are disclosed in Meyer. Petitioner claims, without support, that the Examiner erred by allowing the claims under an unduly narrow interpretation of the "extension" claim limitation. Not only does Petitioner misrepresent the facts before the Examiner during prosecution, Petitioner's narrow reading of the claims contradicts the disclosure in the specification. Petitioner therefore fails to establish that the Examiner materially erred, making denial under § 325(d) appropriate.

In support of this Preliminary Response, Tecan submits the Declaration of Dr. Carlos D. Bustamante, an expert in biomedical data science, genetics, and molecular biology. EX2021.¶¶ 7-18, Exhibit A. Dr. Bustamante's testimony provides additional context regarding the technology at issue in this proceeding and highlights the differences between the prior art and the Challenged Claims.

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. EX2021.¶¶ 32-40. 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. EX2021.¶ 42. 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. *See* EX2021.¶¶ 43-46. 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.* 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. *See* EX2021.¶45. Although revolutionary, Sanger Sequencing was expensive and ill-suited for large-scale applications. EX2021.¶46.

B. Next-Generation Technologies

Starting in the early 2000s, the field of genetics was revolutionized by the invention of next-generation sequencing (“NGS”). EX2021.¶47. 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. EX2021.¶¶47-48. As compared to Sanger Sequencing, NGS was cheaper, more efficient, and capable of assessing both larger genetic samples and longer portions of the human genome in high fidelity. *Id.*

However, early NGS methods had their drawbacks. NGS was limited to shorter individual sequencing reads than Sanger Sequencing, which greatly increased the difficulty in mapping the sequencing reads to a full genome.

EX2021.¶50. Additionally, NGS platforms exhibited a higher error rate than Sanger Sequencing. *Id.* Among the earliest and the subject of Meyer, the 454 Sequencer, which was released in 2004, suffered from a relatively high error rate, especially when sequencing homopolymer regions (long stretches of the same mononucleotides). EX2021.¶51. Homopolymer regions proved problematic because they could throw off the calibration of the 454 Sequencer. *Id.* The 454 Sequencer also suffered from limited throughputs and relatively high costs due to the reagents and specialized equipment. *Id.* The error patterns in 454 sequencing necessitated the use of specialized algorithms to analyze sequencing data. *Id.* Given the issues, Roche announced its discontinuation in 2013. *Id.* Even before that point, researchers came to rely more and more on other platforms, such as Illumina. *Id.*

C. Targeted Enrichment

Targeted enrichment methods became one way to mitigate some of the issues associated with characterizing a sequence of a genomic area of interest, including platform-specific issues. 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. EX2021.¶¶53-54. By doing so, researchers hoped to reduce the errors and noise caused by sequencing broad swathes of genomic data. As of the priority date, the prior art

methods consisted of PCR-based target enrichment, capture-by-hybridization, and capture-by-circularization. EX2021.¶55; EX1001.0016 (1:39-47).

PCR-based target enrichment methods employed the use of a corresponding pair of unique, sequence-specific primers for each target sequence. EX2021.¶56; EX1001.0016 (1:47-50). The need for numerous primer pairs made multiplex PCR impractical due to high levels of non-specific amplification and primer-primer interactions. EX2021.¶56; EX1001.0016 (1:51-53). One attempt at addressing these issues was through microdroplet PCR where each amplification reaction is physically separated into an individual droplet. EX2021.¶59; EX1001.0016 (1:53-58). That method, however, required special instruments, had limited throughput, and required a large number of individual primer pairs when enriching for multiple regions of interest, which made target enrichment expensive. EX2021.¶60; EX1001.0016 (1:58-63).

Hybrid capture methods relied on the selective hybridization of a target genomic region to a custom designed oligonucleotide. EX2021.¶61; EX1001.0016 (1:64-66). The oligonucleotide could be immobilized to a surface or contain a ligand that could be immobilized (such as biotin). EX2021.¶61; EX1001.0016 (1:64-2:4). These methods, however, required complex pools of long, expensive oligonucleotides and long periods of hybridization for efficient capture, as well as the use of expensive instruments. EX2021.¶62; EX1001.0016 (2:4-10). One

additional problem was that due to low levels of efficiency, these methods required large quantities of input nucleic acid. *Id.*

Circularization capture (also referred to as molecular inversion probe or MIP) methods relied on numerous single-stranded linear oligonucleotide probes with a common linker flanked by target-specific sequences. EX2021.¶63; EX1001.0016 (2:11-16). Once the probe annealed to a target sequence, the gap region was filled by polymerization and ligation, resulting in a circularized probe. *Id.* These probes were then amplified using primers specific to the common linker region. EX2021.¶63; EX1001.0016 (2:16-18). These methods, however, exhibited high variability in sequence coverage across target regions and required a large number of target-specific oligonucleotides, driving up costs. EX2021.¶64; EX1001.0016 (2:18-24).

In this backdrop, there was “a need for improved methods for selective target enrichment that allow for low-cost, high throughput capture of genomic regions of interest without specialized instrumentation.” EX1001.0016 (2:25-28). There was “also a need for high efficiency nucleic acid library generation.” *Id.* (2:28-29). The claimed methods of the '012 patent fulfilled these needs.

III. THE '012 PATENT

A. Overview

The '012 patent is directed to methods for sequencing an enriched nucleic acid sequence of interest where a single oligonucleotide is used to select for a target sequence of interest and a common pair of primers is used to selectively amplify the target sequence of interest, thus enriching for that sequence. EX1001.0033. The '012 patent discloses methods that “can be used for the selective enrichment of a plurality of defined target sequences from complex [nucleic acids] with a set of common primers and adaptors, thus circumventing the need for multiplex PCR and multiple primer pairs.” EX1001.0018. The claimed methods, therefore, improve on the then-existing methods by allowing for the selection of a sequence of interest using a single primer as opposed to two target-specific primers. The claimed methods also allow for enrichment through amplification and sequencing of the sequence of interest with a non-target specific set of primers, avoiding the time and expense associated with generating multiple target-specific primers. The claimed

methods improve upon the prior art sequencing methods by creating “a simple, low cost, high throughput system for target enrichment and library preparation.” *Id.*

B. Independent Claim 1

The sole independent claim of the '012 patent, claim 1, is reproduced below.

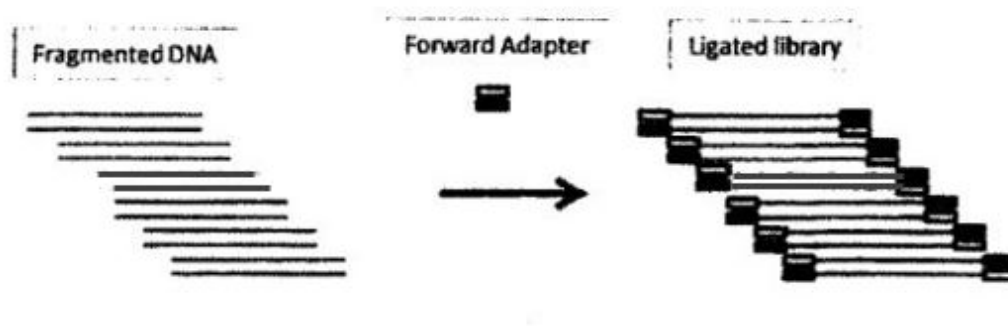
Claim Element	Claim Language
1[pre]	A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
1[a]	obtaining a nucleic acid fragment ligated to a partial duplex adaptor, wherein the nucleic acid fragment comprises a nucleic acid sequence of interest, wherein the partial duplex adaptor comprises a first adaptor sequence, and wherein the partial duplex adaptor comprises a first strand and a second strand, wherein the first strand is longer than the second strand;
1[b]	annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragment ligated to the partial duplex adaptor, wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;

Claim Element	Claim Language
1[c]	extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment ligated to the partial duplex adaptor with a polymerase, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;
1[d]	amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface;
1[e]	annealing a strand of the products of the amplifying to the sequence on the surface using the 3' end with sequence complementary to the sequence on the surface; and
1[f]	sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

The claimed invention is directed at targeting, enriching, and sequencing sequences of interest in samples that also contain sequences that are not of interest.

The Petition attempts to illustrate the method through a series of demonstrative figures prepared by Petitioner. *See* Petition, 18-22. These figures, however, are misleading because they isolate the nucleic acid fragment containing the sequence of interest from the very beginning of the method, grossly oversimplifying the claimed invention and stripping out necessary context. Additionally, Petitioner erroneously conflates the “nucleic acid fragment” with the “sequence of interest.”

Instead, Figure 1 of the '012 patent is an accurate illustration of a preferred embodiment of claim 1. EX1001.0012, 23. Figure 1 “depicts a method for isolating or enriching for a nucleic acid fragment or insert comprising a target nucleic acid sequence from a library or plurality of nucleic acid fragments.” *Id.*, .0023 (15:59-62). Once the DNA is fragmented, “a single forward adaptor is ligated to the DNA fragments.” *Id.* (16:26-27).

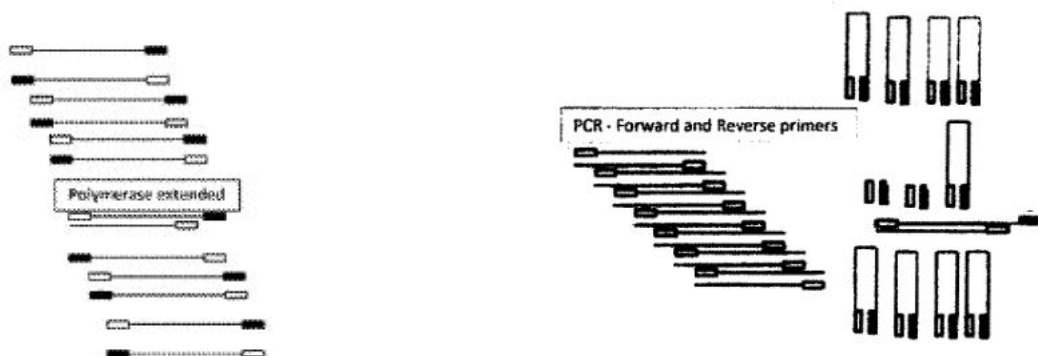


Id., .0012. The forward adaptor “can contain a strand (the ligation strand) that ligates with the free 5’ phosphate on a 5’ end of the DNA fragments and a strand that does not ligate (non-ligation strand) to a 3’ end of the DNA fragments.” *Id.*, .0023 (16:39-

43). After ligation, “the DNA fragments with complementary ends are denatured to generate a denatured library comprising single stranded DNA fragments with complementary ends.” *Id.* (16:54-57).



Id., .0012. Then, “a custom oligonucleotide with a reverse adaptor tail is annealed to the single stranded DNA fragments with complementary ends.” *Id.*, .0023-24 (16:61-63). From there, “the custom oligonucleotide with a reverse adaptor tail is extended using any method known in the art.” *Id.*, .0024 (17:39-41). This extension step occurs through the use of a polymerase.



Id., .0012. The '012 patent discloses that the “primers of the invention are generally oligonucleotides that are employed in an extension reaction by a polymerase along a polynucleotide template, such as in PCR, SPIA, and cDNA synthesis, for example.” *Id.*, .0026 (21:43-53).

“Extension of the custom oligonucleotide with a reverse adaptor tail generates an oligonucleotide extension product with forward adaptor sequence at one end and reverse adaptor sequence at the other end.” *Id.*, .0024 (17:44-47). As part of the method, a pair of primers corresponding to the forward and reverse adaptor sequences is used to selectively amplify the oligonucleotide extension product, enriching for the sequence of interest. *Id.* (17:52-60).

Additionally, the claimed invention provides for the sequencing of the enriched sequence of interest on a massively parallel sequencing platform. *Id.*, .0028-29. The claimed invention does this by incorporating into the tail end of the oligonucleotide a sequence that is complementary to a surface. *Id.* After amplification, the amplified products are bound to the surface and sequenced using an NGS platform. *Id.*

C. Relevant Prosecution History

The '012 patent issued from U.S. Patent Application No. 15/471,785 (“the '785 application”), which was filed on March 28, 2017. EX1001.0001. The '785

application ultimately claims priority to Provisional Application No. 61/591,241, which was filed on January 26, 2012. EX1001.0001.

During prosecution, the Examiner issued several rejections of the proposed claims in light of U.S. Patent Publication No. 2003/0232348 (“Jones 2003”), U.S. Patent Publication No. 2005/0142577 (“Jones 2005”), and Tucker (“Massively parallel sequencing: the next big thing in genetic medicine”). *See* EX1016.0190. For example, the Examiner argued that “Jones [2005] teaches a method for enriching a nucleic acid sequence of interest in a sample comprising nucleic acids” and that Tucker “describes methods of obtaining sequence information about a region of interest in nucleic acid, and specifically describes a number of massively parallel sequencing methods.” *See id.*, .0190-94. According to the Examiner, it “would have been *prima facie* obvious for one of ordinary skill in the art at the time of the invention to analyze the amplification products generated by the method of Jones using one of the massively parallel sequencing methods described in Tucker.” *See id.*

In connection with its response to the Examiner’s rejections, the Applicant submitted the Declaration of Dr. Andrew Brooks (“the Brooks Declaration”), a well-respected researcher in the field who was the Chief Operating Officer of the Rutgers University Cell and DNA Repository, Director of the Rutgers Bionomics Research & Technology Center, and an associate professor of genetics at the time. *See*

EX1016.0300-01. In addition to raising other points, Dr. Brooks explained that a POSA would not have had a reasonable expectation of success in performing the claimed method in 2012. *See id.*, .0302-03. Dr. Brooks explained that he “observed unexpected results when enriched nucleic acid sequences generated using the claimed methods were sequenced by massively parallel sequencing” and that the “results were surprising” given the high level of specificity. *Id.*, .0303. The claims were subsequently allowed. *See* EX1016.0607.

D. 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 the priority date of the '012 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, 25.

Petitioner's definition goes beyond the level of *ordinary* skill in the art. The sequencing methods described in the '012 patent do not require a Ph.D. to understand and perform. In fact, in many laboratory environments, lab technicians and graduate students perform these sequencing methods. EX2021.¶¶65-68. The level of education for a POSA, therefore, is more appropriately a Ph.D. in a field

related to molecular biology, or a B.S. or M.S. degree with three to five years of experience working in a molecular biology lab. *Id.*

Petitioner also proposes that the POSA “would have had specific experience with implementing *and designing library preparation methods* for 454 and Illumina, the leading NGS platforms in 2012.” Petition, 25 (emphasis added). 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”). More realistically, the POSA would have had experience with DNA sequencing methods and a working knowledge of how these sequencing methods functioned. EX2021.¶¶65-68.

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. *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1368 (Fed. Cir. 2004) (“[T]he Board is entitled to weigh the declarations and conclude that the lack of factual corroboration warrants discounting

the opinions expressed in the declarations.”); *Xerox Corp., 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.”); *see also* 37 C.F.R. § 42.65(a) (“Expert testimony that does not disclose the underlying facts or data on which the opinion is based is entitled to little or no weight.”).

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

E. Claim Construction

1. “sequence of interest”

For purposes of this preliminary response, Tecan responds to Petitioner’s invalidity arguments assuming Petitioner’s proposed construction of the term “sequence of interest” – “a polynucleotide sequence of interest, for which enrichment is desired.” *See* Petition, 26. As discussed in detail below, Tecan does not agree with Petitioner’s application of the “for which enrichment is desired” portion of the proposed construction. Petitioner seems to disregard the meaning of “enrichment” in its proposed construction in arguing that Meyer discloses a method

in which the enrichment of a sequence is a goal. Further, Petitioner ignores that this term requires that the sequence be “of interest.”

2. “barcode”

The term “barcode” only appears in claims 7-10 of the ’012 patent. Because the Petition fails to show that claim 1 of the ’012 patent is anticipated by or obvious over Meyer, the Board need not construe this term.

IV. PETITIONER HAS NOT DEMONSTRATED A REASONABLE LIKELIHOOD THAT IT WILL PREVAIL ON ANY CHALLENGED CLAIM

A. Ground 1: Petitioner Fails to Establish that Meyer Anticipates the Challenged Claims

In its strained attempt to map Meyer to the claim limitations, Petitioner contorts Meyer to be a method of enriching nucleic acid fragments, which it is not, and oversimplifies the claimed inventions of the ’012 patent. This misrepresentation of both the claimed inventions and Meyer’s methods taints the entirety of the Petition. As explained further below, Meyer is not a method designed to facilitate enriching for a sequence of interest without the need for target-specific primer pairs.

1. Meyer is a Method for Sequencing an Entire Transcriptome

Unlike the methods of the Challenged Claims, Meyer discloses a method for sequencing an entire coral transcriptome¹ in a single 454 sequencing run. EX1006.0012, *see also* EX2021.¶¶82-84. Published in 2009, Meyer states that it sought to “facilitate genomics studies in corals and other non-model systems” by “describ[ing] methods for transcriptome sequencing using 454, as well as strategies for assembling a useful catalog of genes from the output.” EX1006.0001. To test these methods, Meyer sequences “the transcriptome of planulae larvae from the coral *Acropora millepora*” and *de novo* assembles the transcriptome sequence. *Id.* Meyer concludes that the “methods described here for deep sequencing of the transcriptome should be widely applicable to generate catalogs of genes and genetic markers in emerging model organisms.” *Id.*

Meyer describes two protocols: (1) the method disclosed in Figure 1 that was used to prepare and sequence the coral larvae described throughout the paper (“the general method”); and (2) a modified method disclosed in additional file 4, which Meyer explains “includes minor modifications that we have recently developed to reduce the number of manipulations required, improve reproducibility, and to further

¹ The term “transcriptome” refers to the full range of mRNA expressed by an organism. EX2021.¶ 37.

reduce adaptor concatenation” (“the modified method”). EX1006.0014, *see also* EX2021.¶¶88-89, 97-98.

One of the issues that Meyer sought to overcome was known as the “homopolymer problem.” EX1006.0009, *see also* EX2021.¶85. Homopolymers are large stretches of the same repeating nucleotide. EX2021.¶51. As Meyer explains, “[b]ecause 454 sequencing does not efficiently process homopolymer regions greater than 8 bp in length, the poly-A tails at the 3’ ends of intact transcripts present a problem, and would be expected to result in under-representation of the 3’ ends of transcripts.” EX1006.0009. To resolve this issue, Meyer “simply interrupt[s] the poly-T region with a single C.” *Id.*, .0009. Meyer refers to this sequence as the broken chain T-primer sequence or the broken-T adaptor. The broken chain T-primer sequence is present in both methods. EX2021.¶¶87-88, 98-99.

Meyer's general method is illustrated below:

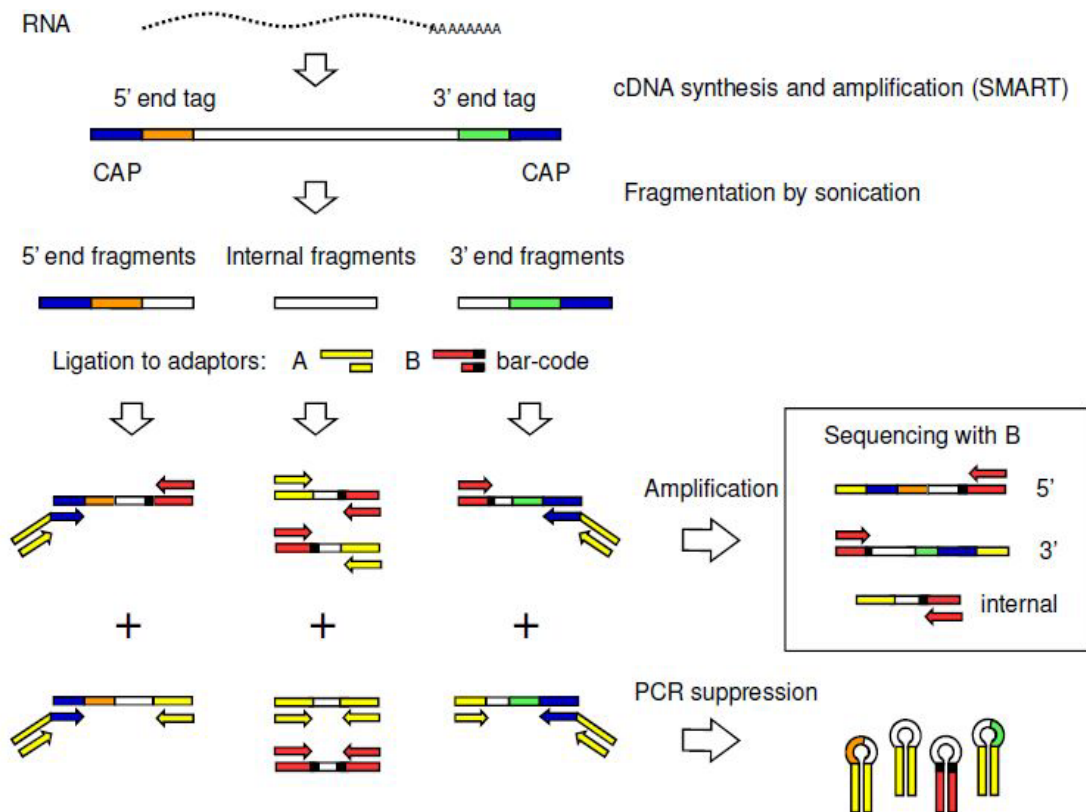


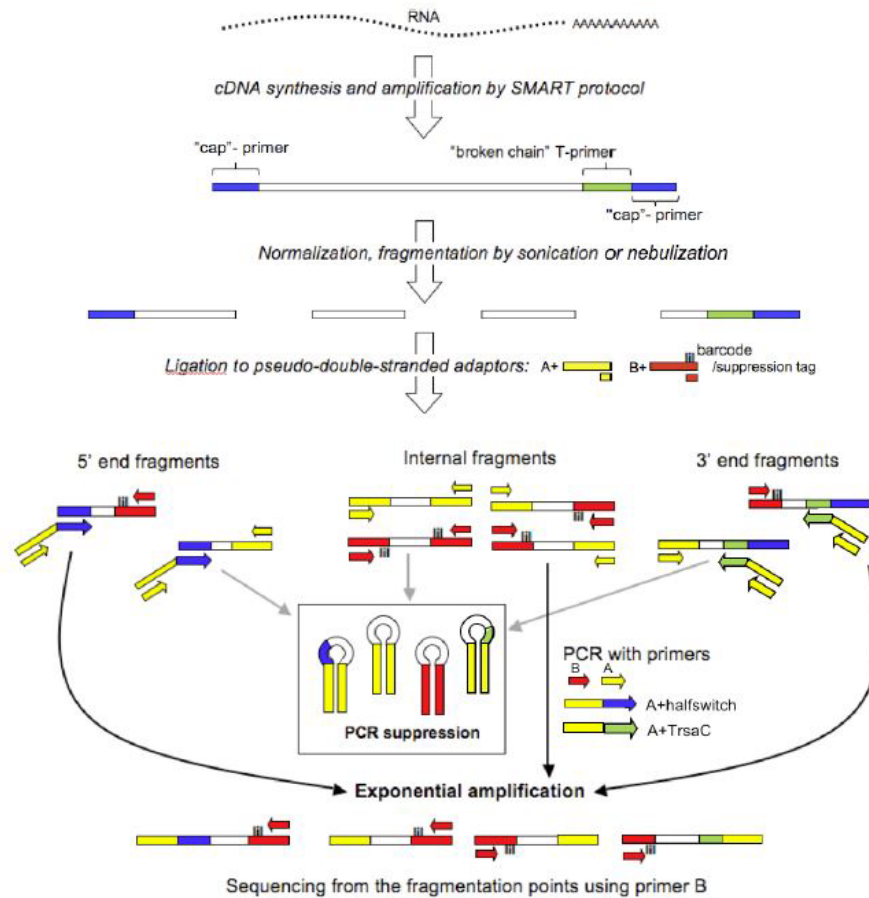
Figure 1
Diagram of cDNA synthesis and 454 library preparation procedures. Three fragment types are produced by sonication: 5', internal, and 3'. Ligation with the partially double-stranded adaptors A and B produces, for each fragment type, certain adaptor configurations that will be amplified (above the '+'), and others that will be suppressed (below the '+') during the subsequent amplification. The procedure preferentially amplifies constructs that are appropriate for 454 sequencing (shown inside box).

Id., .0003. In the general method, Meyer begins by reverse transcribing the coral mRNA through a standard protocol available at the time (SMART protocol). *Id.*; *see also id.*, .0012-13; EX2021.¶¶88-96. During this process, Meyer caps the ends of the nucleic acid strand (shown in blue). EX1006.0003; EX2021.¶¶88-96. From there, Meyer fragments the capped strand, resulting in two end fragments and a number of internal fragments. *Id.* Meyer ligates one of two adaptors (shown in

yellow and red) to the uncapped ends of the fragments. *Id.* For the end fragments, Meyer uses a primer with one end complementary to the cap sequences and another containing the primer A sequence. *Id.* This primer anneals to the cap sequence of the fragment and is extended to generate extension products. *Id.* Meyer generates extension products for all fragments (illustrated by the red, yellow, and blue arrows). *Id.*

Some extension products will be flanked by the same primer sequence. *Id.* The ends of those products will interact with each other, blocking amplification (what Meyer refers to as PCR suppression). *Id.* For extension products flanked by different primer sequences, amplification proceeds. *Id.* As illustrated by Figure 1, PCR suppression occurs randomly across the entire set of fragments, including the 3' end fragment. *Id.* Extension products representing the entire strand are amplified with the same set of standard primers. *Id.* The untargeted, unbiased use of the same primers for amplification results in roughly the same relative population of different fragments after amplification as with fragmentation, which is important for Meyer given that Meyer seeks to sequence the entire transcriptome. EX2021.¶96.

Meyer also discloses a “modified method,” which is illustrated in additional file 4, and notes that the modifications “improve reproducibility and further reduce the occurrence of adaptor concatenation.” EX1006.0019. The modified method is reproduced below:



Id., .0020. This method is the method relied on by Petitioner for its anticipation arguments. Meyer discloses that the same general scheme for reverse transcription, fragmentation, and ligation is followed for both methods (illustrated in the first three steps in the above diagram). *Id.*; EX2021.¶¶97-103. Meyer discloses one notable difference in the protocol scheme: rather than using primers complementary to the cap primer for both end fragments, Meyer uses a primer complementary to the broken chain T-primer sequence for the 3' end fragment—

the same broken chain T-primer sequence that is used in both methods. *Id* Meyer explains that the broken chain T-primer sequence is used to “improve reproducibility and further reduce the occurrence of adaptor concatenation.”

EX1006.0019. Concatenation, as used by Meyer, refers to primer dimer binding, where the adaptors ligate to each other rather than the transcript fragments.

EX2021.¶¶58, 86. The primer dimer complexes contribute to sequencing noise, leading to an increase in read artifacts. *See id*.

While Meyer discloses four types of fragments entering exponential amplification, the relative proportion of end fragments to internal fragments remains the same: one 5' end fragment, eight internal fragments, and one 3' end fragment for every transcript. EX1006.0020; EX2021.¶¶91, 97-103. Meyer's modifications do not impact the number and type of fragments in the reaction mixture. *Id*. Meyer does not report any sequencing read data obtained by using the modified method. *Id*.

2. Meyer Does Not Disclose All Elements of Claim 1

Reading Meyer in the proper context, Petitioner cannot show that Meyer discloses key elements of the Challenged Claims, including “amplifying . . . to enrich” and a “sequence of interest.” A claim is anticipated only “if a single prior art reference discloses each and every limitation of the claimed invention, either expressly or inherently.” *Galderma Lab'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 Fed.

App’x 838, 842 (Fed. Cir. 2020). As such, Meyer fails to anticipate claim 1 of the ’012 patent given its lack of key disclosures that cannot be salvaged through Petitioner’s hindsight-driven revisions of the reference.

a) *“amplifying the one or more oligonucleotide extension products . . . to enrich for the nucleic acid sequence of interest”*

Petitioner argues that Meyer discloses enriching a sequence of interest because Meyer “overcame the issue of underrepresentation of those regions in the final sequencing data normally attributable to 454 sequencing error.” Petition, 45-46. But Petitioner’s position incorrectly conflates reducing read artifacts by improving the sequencing method with enrichment of a component within the sample.

Meyer recognizes that a systemic issue with 454 pyrosequencing is that it does “not efficiently process homopolymer regions greater than 8 bp in length.” EX1006.0009, *see also* EX2021.¶85. This poses a challenge in sequencing an entire transcriptome because of how the transcriptome ends with a polyA tail that is longer than 8 bp in length. *Id.* According to Meyer, the polyA tail would “result in underrepresentation of the 3’ ends of transcripts” within the sequencing reads. EX1006.0009. Meyer resolves this sequencing issue “by simply interrupting the poly-T region with a single C,” thus creating a “broken chain” T-primer. *Id.* As Meyer explains “[t]he purpose of the ‘broken chain’ T-primer is to **reduce read**

artifacts during 454 pyrosequencing.” *Id.*, .0019 (emphasis added). At no point does Meyer disclose that the broken chain T-primer could be used to selectively enrich for the 3' end fragments within the sample over other portions of the transcriptome. EX2021.¶¶124-35.

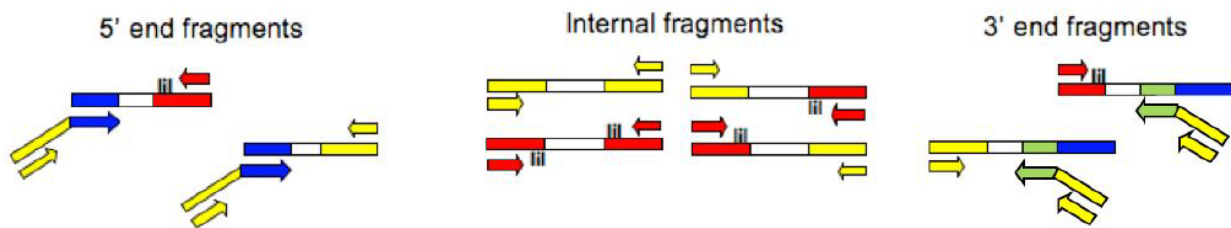
Even assuming that Petitioner's interpretation of “enrichment” is correct, Petitioner misrepresents the data presented in Meyer regarding the alleged improvement over prior 454 sequencing methods. There are two major flaws in Petitioner's reasoning. Petition, 46. First, the “enrichment” to which Petitioner points is not enrichment within a sample, but simply an alleged improvement of the error rate in a sequencing method. Second, even accepting Petitioner's interpretation of “enrichment,” Petitioner distorts the data presented in Meyer.

(1) Meyer Does Not Disclose Enrichment

Meyer never discloses increasing the percentage of the sequence of interest as compared to any other component of the sample. As the '012 patent explains, the purpose of enrichment is to increase efficiency of nucleotide sequencing by focusing on the sequences that are being studied. EX1001.0001. The method described in the '012 patent uses a single, target-specific primer, in combination with a set of common primers, to amplify only the targeted nucleotide sequence(s) within the sample. This results in a sample that is enriched for the targeted nucleotide sequence(s).

Meyer, however, is directed toward improving the error rate of sequencing reads. EX2021.¶¶124-30. Meyer's method does not target amplification of any sequence over other sequences in the sample. See EX2021.¶¶109-123. The explicit purpose of Meyer is to sequence the *entire* transcriptome, and not any targeted portion of it. EX2021.¶¶124-35. Even focusing on the 3' end fragment on which Petitioner relies, there is no evidence that the modified method amplifies that fragment over any other fragment in the sample. EX2021.¶¶119-123.

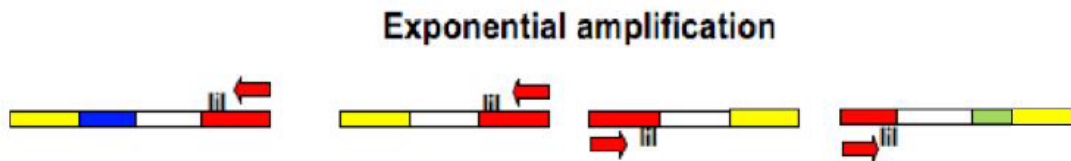
Prior to extension, Meyer discloses the presence of four different sets of nucleic acid fragments. EX1006.0020; EX2021.¶¶98-102, 119-22.



EX1006.0020. One set comprises 5' end fragments, which are flanked at the 5' end by a cap primer (blue) and at the 3' end by one of two adaptors (containing either primer A (yellow) or primer B (red) sequences). EX1006.0020; EX2021.¶¶98-102, 119-22. Two sets comprise internal fragments, which are flanked by one of the two same adaptors. *Id.* The final set comprises 3' end fragments, which are flanked by one of the two same adaptors at the 5' end and a cap primer at the 3' end, and that contain the broken chain T-primer sequence (green). *Id.* While this depiction may

make it appear that there are an equal number of end fragments to internal fragments for amplification, a POSA would have understood from Meyer's estimates that for every one 3' end fragment, there are roughly eight internal fragments and one 5' end fragment. *See* EX1006.0009; EX2021.¶¶91, 98-102, 119-22.

Even after PCR suppression, Meyer also discloses that at least one type of nucleic acid fragment from each set is exponentially amplified, i.e. four different types of nucleic acid fragments. EX1006.0020; EX2021.¶¶98-102, 119-22.



EX1006.0020. Again, the protocol depiction minimizes the number of internal fragments that are exponentially amplified; however, as understood by Meyer's own estimates, every one 3' end fragment undergoes exponential amplification at the same time as eight internal fragments and one 5' end fragment. *See* EX1006.0009; EX2021.¶¶91, 98-102, 119-22. As such, the relative population of the different fragments remains roughly the same from fragmentation through exponential amplification. EX2021.¶¶91, 98-102, 119-22.

Thus, in Meyer, *all non-PCR-suppressed fragments are amplified without any biasing* towards the exponential amplification of one fragment over another. EX2021.¶122. This is plainly not enrichment.

Petitioner argues that Meyer discloses enrichment because the method of Meyer decreases the error rate among the 3' end fragments—*as compared to prior 454 sequencing methods*. Petition, 46 (“The Meyer authors report that their ... method overcame the issue of underrepresentation of those regions in the final sequencing data normally attributable to the 454 sequencing error.”). The “homopolymer problem” that Meyer was trying to fix is an issue caused by the 454 sequencer—not a problem concerning the relative population of 3' end fragments in the amplified products. *See* EX1006.0009, 19-20, *see also* EX2021.¶¶51, 85. At best, Meyer may show improvement regarding the accuracy of sequencing the 3' end fragments between different 454 sequencing methods, but it does not show any sample in which a particular portion of the sequence has been enriched.

(2) Petitioner Mischaracterizes the Data

Even accepting Petitioner’s interpretation of “enrich,” such that the improvement in sequencing accuracy is enrichment, Petitioner mischaracterizes the data presented in Meyer. Petitioner relies on the “modified method” for its anticipation arguments, but the data on which Petitioner relies was generated using the general method. *See* EX2021.¶129. Petitioner does not point to any data regarding alleged “enrichment” seen in the modified method.

Petitioner relies on the raw read data disclosed by Meyer to claim that “the Meyer method enriched for these fragments compared to other nucleic acids in the

original sample.” Petition, 53. As an initial matter, the data reported by Meyer reflects a perceived decrease in sequencing artifacts caused by the 454 platform—it does not reflect the contents of the reaction mixture. EX2021.¶¶123-30. Petitioner’s reliance is further misplaced for at least two reasons: (1) the raw read data did not concern the modified method disclosed in additional file 4; and (2) the raw read data examined the reduction in read artifacts by comparing the proportion of sequencing reads containing the broken chain T-primer sequence to a back-of-the-envelope estimate. EX2021.¶¶128-35. As such, the raw read data does not and cannot evidence enrichment.

First, Petitioner incorrectly claims that Meyer reported the raw read data obtained from “using a primer to specifically target” the broken chain T-primer sequence. *See* Petition, 45-46. Meyer reports raw reads from using the method disclosed in Figure 1 of the publication, which used primers specific to the cap primers at both the 5’ and 3’ end fragments. EX1006.0002-03, 19; EX2021.¶113. Meyer attributes no specific read data to the protocol disclosed in additional file 4, which Meyer describes as reflecting “minor modifications that we have recently developed.” EX1006.0014, 19; EX2021.¶¶97, 119, 129. As such, there is simply no disclosure in Meyer that shows that the modified method resulted in any enrichment of any target sequence reads.

Second, Petitioner claims that “the Meyer authors confirmed that these fragments were found at a greater prevalence than fragments at other portions of the strand, thus confirming that they were enriched compared to other mRNA fragments.” Petition, 53. Putting aside Petitioner’s misattribution of the read data, neither Petitioner nor their expert witness identifies where in Meyer the authors made this “confirmation.” Nor can they because no such disclosure exists. To evaluate whether the general method reduced sequencing read artifacts, Meyer examined how many raw reads contained a single copy of the “broken-T” adaptor. EX1006.0009; EX2021.¶126. Meyer determined that 98,276 raw reads out of a total 628,649 raw reads (15.6%) contained the “broken-T” adaptor, noting that the outcome was “slightly more than the expectation.” EX1006.0009. That “expectation” was based on an estimate by Meyer: Meyer had assumed that the average transcript size was 2,200 bp and that the average read (or nucleic acid fragment) length would be 232 bp, meaning that roughly 10% of all fragments would be the 3’ end fragment. *Id.*; EX2021.¶¶126-127. Meyer concluded that the “comparison suggests that the 3’ ends of transcripts were well-represented in our dataset, *confirming the effectiveness of this solution for overcoming the homopolymer problem.*” EX1006.0009 (emphasis added).

As Dr. Bustamante explains, Meyer’s estimate is very likely flawed given that Meyer assumed that the average length of the transcripts in the study was 2,200 bp

despite the distribution data reported by Meyer showing that the transcript lengths skewed heavily towards being far less than that. EX2021.¶¶131-34. Had Meyer instead assumed that the average length of the transcripts was 1,450 bp (which is not unreasonable given the reported distribution), Meyer's expectation would have been 16%. *Id.* Given that sensitivity, a POSA would not have inferred any more from the comparison than what Meyer did: the data showed "slightly more than the expectation," as compared to prior sequencing methods. *Id.*

For at least these reasons, Meyer fails to disclose "amplifying the one or more oligonucleotide extension products . . . to enrich for the nucleic acid sequence of interest."

b) *"wherein the nucleic acid fragment comprises a nucleic acid sequence of interest"*

Not only does Meyer not disclose enrichment of any particular sequence, it specifically does not disclose enrichment of a "nucleic acid sequence of interest." There is no polynucleotide sequence disclosed in Meyer that is specifically targeted for enrichment and sequencing over other sequences in the sample. EX2021.¶¶108-23.

Petitioner incorrectly points to the broken chain T-primer sequence of Meyer to meet the "nucleic acid sequence of interest" limitation. Petition, 45. This broken chain T-primer sequence is what Meyer discloses as a modified reverse transcription

of the polyA tail of the transcriptome. EX1006.0009, 19-20. The broken chain T-primer sequence, however, would not have been understood by a POSA to be a “nucleic acid sequence of interest” at least because the sequence of the manufactured primer is not “of interest” and enrichment of the broken chain T-primer sequence is not “desired.” EX2021.¶126, 136-41. As Meyer explains, “[t]he purpose of the ‘broken chain’ T-primer is to reduce read artifacts during 454 pyrosequencing.” EX1006.0019. Meyer discloses no interest in the polyA tail beyond using it as a means for improving the representation of 3’ end fragment reads in the final sequencing data. Meyer discloses that the broken chain T-primer sequence is simply a tool for promoting sequence read fidelity. EX2021.¶¶124-30, 136-41. Even Petitioner’s own expert witness, Dr. Sims, concedes that “the sequence of the polyA tail is *not of interest* and can also cause sequencing errors” and that “it is desirable to minimize the extent to which it is included in the resulting cDNA.” EX1085.¶148 (emphasis added); see EX2021.¶142.

Petitioner’s contention that “the library preparation and sequencing method disclosed in Meyer is specifically designed to enrich for nucleic acid fragments (i.e., specifically amplify relative to other fragments) containing a particular ‘nucleic acid sequence of interest’ i.e., the broken chain T primer sequence” is simply incorrect. Petition, 45. Not only is there no enrichment of particular sequences, the modified library preparation protocol disclosed in Meyer (file 4) reinforces that Meyer did not

desire to enrich for the broken chain T-primer sequence because it is not designed for selective enrichment. EX2021.¶¶119-23, 136-41. Meyer discloses that unbiased amplification occurs for fragments representing the entire transcriptome of the coral and not just the 3' end fragment. *Id.*

The parts of Meyer to which Petitioner points for this limitation are neither enriched nor “of interest” for further analysis. Meyer discloses that the fragments undergoing exponential amplification all share a common set of primer sequences: primer A (yellow) and primer B (red). EX1006.0020, *see also* EX2021.¶¶94-95, 102. This lack of primer biasing—especially where the relative populations remain constant throughout the protocol—exemplifies that Meyer did not desire for the broken chain T-primer to be enriched over other portions of the transcriptome. EX2021.¶¶119-23, 136-41. The non-specific amplification process disclosed in Meyer stands in stark contrast to the targeted enrichment and amplification methods described in the '012 patent.

Additionally, Petitioner claims that the broken chain T-primer sequence is a sequence for which enrichment is desired despite conceding that Meyer is instead interested in the “sequence information from *near* the polyA of the mRNA.” Petition, 45 (emphasis added). This distinction is key. Meyer does not suggest any desire to specifically sequence the broken chain T-primer sequence. Meyer instead sought to sequence the entirety of the larval transcriptome of the *A. millepora* coral

in an effort to study “gene expression, genetic connectivity, and stress physiology.” EX1006.0002, *see also* EX2021.¶¶82-84. Meyer was interested in sequencing every area of the transcriptome *except* for the polyA tail. A POSA would have considered the “sequence of interest” in the context of the full claim language and understood that a sequence for which sequencing is not desired is also a sequence for which enrichment is not desired. EX2021.¶¶142-44. Instead, Meyer describes a very different application and methodology—one that is not used to study a target sequence.

For at least these reasons, Meyer fails to disclose the “nucleic acid fragment” and the “nucleic acid sequence of interest” required in claim 1 of the ’012 patent.

c) Meyer Necessarily Fails to Disclose The Remaining Limitations

The limitations directed to a “sequence of interest,” “nucleic acid fragment,” and “enriched nucleic acid sequence of interest” are not isolated from the rest of the claim limitations. Rather, every claim limitation requires that at least one of the three are present:

- A method for sequencing *an enriched nucleic acid sequence of interest*;

- Obtaining *a nucleic acid fragment* ligated to a partial duplex adaptor, wherein the *nucleic acid fragment comprises a nucleic acid sequence of interest*;
- Annealing one or more oligonucleotides in solution to *the nucleic acid sequence of interest in the nucleic acid fragment*;
- Extending the one or more oligonucleotides annealed to *the nucleic acid sequence of interest in the nucleic acid fragment*;
- Annealing a strand of *the products of the amplifying*² to the sequence on the surface; and
- Sequencing the enriched nucleic acid *sequence of interest* on a massively parallel sequencing platform.

While Petitioner attempts to map Meyer to each claim limitation in isolation, the claimed method is not so disjointed. The limitations must be considered in their entirety. And in doing so, it becomes clear just how off base Meyer is from the claimed invention.

² The “products of amplifying” contain the nucleic acid sequence of interest. *See* EX1001.0033, cl. 1.

3. Meyer Fails to Anticipate the Dependent Claims of the '012 Patent

For the reasons that Meyer fails to anticipate claim 1 of the '012 patent, Meyer fails to anticipate any of the remaining dependent claims. *See RCA Corp. v. Applied Digital Data Sys's, Inc.*, 730 F.2d 1440, 1446 (Fed. Cir. 1984) (“Since claim 3 of the Cole patent is dependent upon claim 2, which is not anticipated, claim 3 cannot be anticipated”). As such, Ground 1 of the Petition fails.

B. Ground 2: Petitioner Fails to Establish that Claims 1, 3, 5-8, 10-14, 16, and 20-22 Would Have Been Obvious Over Meyer

1. The Petition Fails to Show that Claim 1 is Obvious Over Meyer

As explained above, Meyer fails to disclose several key elements required by claim 1 of the '012 patent. Petitioner argues that claim 1 would have been obvious over Meyer, but fails to provide any explanation as to how those claim elements would have been obvious to a POSA. “To satisfy its burden of proving obviousness, a petitioner cannot employ merely conclusory statements. The petitioner must instead articulate specific reasoning, based on evidence of record, to support the legal conclusion of obviousness.” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1380-81 (Fed. Cir. 2016). The Petition does not identify which elements of Meyer would be modified to arrive at claim 1 and does not explain why a POSA would have been motivated to make those modifications. The Petition equally fails to address whether the POSA would have had a reasonable expectation of success in making

such modification. The Petition's silence on these points is fatal. *See Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 70 F. 4th 1331, 1345 (Fed. Cir. 2023) (“An obviousness determination requires finding that a person of ordinary skill in the art would have been motivated to combine or modify the prior art and would have had a reasonable expectation of success in doing so.”) (cleaned up); *Eli Lilly and Co. v. Teva Pharm. Int’l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021) (explaining that there is an “additional requirement that the patent challenger also prove that the skilled artisan would have had a reasonable expectation of successfully achieving the claimed invention.”). Petitioner, therefore, fails to meet their burden of showing that claim 1 is obvious in light of Meyer.

2. Meyer Fails to Render Obvious the Dependent Claims of the '012 Patent

For the reasons that Meyer fails to render obvious claim 1 of the '012 patent, Meyer fails to render obvious any of the remaining dependent claims. *See In re Lemay*, 660 Fed. App'x 919, 927 (Fed. Cir. 2016) (“dependent claims are nonobvious if the independent claims from which they depend are nonobvious”) (cleaned up). As such, Ground 2 of the Petition fails.

C. Ground 3 (Claim 2 is Obvious Over Meyer in View of the Knowledge of the POSA and/or Siebert)

Petitioner argues that Meyer could be adapted to practice dependent claim 2. Petition, 72. As explained above, Meyer fails to anticipate or render obvious claim

1 of the '012 patent. Ground 3 fails to address the deficiencies in Grounds 1 and 2 with respect to the only independent claim of the '012 patent. As such, Ground 3 necessarily fails for at least the same reasons.

D. Ground 4 (Claim 9 is Obvious over Meyer in View of the Knowledge of the POSA and/or Kelly)

Petitioner argues that Meyer could be adapted to practice dependent claim 9. Petition, 72. As explained above, Meyer fails to anticipate or render obvious claim 1 of the '012 patent. Ground 4 fails to address the deficiencies in Grounds 1 and 2 with respect to the only independent claim of the '012 patent. As such, Ground 4 necessarily fails for at least the same reasons.

E. Ground 5 (Claims 15 and 17-19 are Obvious Over Meyer in View of the Knowledge of the POSA and/or Bronner and/or Caruccio)

Petitioner argues that Meyer could be adapted to practice dependent claims 15 and 17-19. Petition, 75. As explained above, Meyer fails to anticipate or render obvious claim 1 of the '012 patent. Ground 5 fails to address the deficiencies in Grounds 1 and 2 with respect to the only independent claim of the '012 patent. As such, Ground 5 necessarily fails for at least the same reasons.

V. 35 U.S.C. § 325(D) SUPPORTS DENIAL OF THE PETITION BECAUSE THE EXAMINER PREVIOUSLY CONSIDERED SUBSTANTIALLY THE SAME ARGUMENTS

In determining whether to institute *Inter Partes* Review, the Board may “reject the petition [where] the same or substantially the same prior art or arguments

previously were presented to the Office.” 35 U.S.C. § 325(d). The Board has articulated several nonexclusive factors that guide its application of § 325(d). *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential). These factors have been consolidated into two questions: (1) whether “the same or substantially the same art [or arguments] previously were presented to the Office”; and if so, (2) whether the “petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims.” *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 8 (P.T.A.B. Feb. 13, 2020) (precedential). The Petition fails under both questions.

1. The same or substantially the same arguments were previously before the Office

With respect to the first question, the arguments raised by Petitioner are substantially the same as the arguments the Examiner considered. Petitioner argues that Meyer discloses each limitation of claim 1 of the '012 patent. The same examiner made the same arguments with respect to two different Jones publications (Jones 2003 and Jones 2005) during the prosecution of the '785 application and its parent application. *See* EX1016.0190-94; EX2019.0006-13. The Examiner issued rejections, arguing that Jones 2003 and Jones 2005 disclosed the same elements that Petitioner claims Meyer discloses: “fragmenting nucleic acids in the sample,

wherein the nucleic acid fragments comprise the sequence of interest,” “ligating a first adaptor to a 5’ end of the nucleic acid fragments,” “annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragments comprising the ligated first adaptor, wherein the oligonucleotides comprise a 3’ portion that is complementary to the nucleic acid sequence of interest and a 5’ portion comprising a second adaptor sequence,” “extending said annealed oligonucleotides using a DNA polymerase to obtain extension products,” “amplifying the extension products using a primer that anneals to the complement of the first adaptor sequence and a primer that anneals to the complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest,” and “sequencing the enriched nucleic acid sequence of interest.” *See id.* With respect to the claim limitations “wherein products of the amplifying comprise a 3’ end with sequence complementary to a sequence on a surface,” “annealing a strand of the products . . . to the sequence on the surface,” and “sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform,” the same examiner made the same arguments that the limitations did not confer patentability,

arguing that the limitations would have been obvious based on Jones 2005 in view of Tucker. *See* EX1016.0190-94.

Therefore, under Petitioner's view of claims and the prior art, the Examiner considered substantially the same arguments during prosecution as are presented in the Petition.

2. Petitioner fails to demonstrate a material error by the Office

The only error to which Petitioner points is its allegation that the "Examiner allowed the claims on the ground that the prior art did not teach the recited extension step." Petition, 81. Petitioner seems to be presenting an argument that the extension step limitation as "limited to methods with a distinct extension step outside of a PCR reaction." Petition, 24. Petitioner, however, does not, and indeed cannot, point to any support for such a narrow construction. The specification provides multiple examples where the extension step is part of a PCR reaction, confirming that the Examiner likely understood that the recited extension step could be performed either as part of a PCR reaction or as a separate step. EX1001.0026 (21:43-46) ("primers of the invention are generally oligonucleotides that are employed in an extension reaction by a polymerase along a polynucleotide template, such as in PCR, SPIA, and cDNA synthesis, for example."); *id.*, .0031 (Example 1, 32:1-5) ("DNA fragments from the test library are selectively amplified with two distinct steps: 1)

gene-specific primer extension; and 2) PCR with universal adaptor sequences.”); *id.* (32:16-20) (“[t]he pool of primer extension probes is combined with the test DNA library [] containing the forward adaptor and the HotStarTaq PCR mastermix,” which contains a “thermally-activated Taq DNA polymerase [commonly used in PCR].”); *id.* (32:20-24) (“This solution is placed in a thermal cycler, heated to 95° C for 15 minutes to activate the polymerase and cooled to 70° C for 5 minutes to allow the 16S primers to anneal to DNA inserts and extend into the forward adaptor site.”).

More importantly, however, Petitioner is wrong in its statement that “[n]one of the portions of the references relied on by the Examiner contemplated the ‘primer extension’ step recited in the claims being part of a PCR reaction (as opposed to a separate primer extension reaction as described in the ’012 and ’108 patent specification).” *See* EX1085.¶137. Petitioner’s expert argues that three specific disclosures of Jones 2003 cited by the Examiner “describe linear extension of a single primer that does not take place as part of a PCR amplification reaction.” *See id.*, .0093. However, two of the disclosures identified by the Examiner, and relied on by Petitioner here, explain just the opposite. Jones 2003 describes that the “capture probes are extended in the presence of polymerase and dNTPs.” EX1039.0019, [94]. Jones 2003 further discloses that extension occurred with “AmpliTaq Gold (Applied Biosystems, Foster City, Calif.),” and describes a reaction using the AmpliTaq Gold polymerase as “generic PCR.” EX1039.0023, [129]-[131].

A POSA would have understood that the AmpliTaq Gold DNA polymerase is a hot-start polymerase commonly used in the field to extend nucleic acid sequences through PCR. EX2021.¶¶79-80. Therefore, a POSA would have understood that Jones 2003 described methods where the extension step would be performed as part of a PCR reaction. *Id.* The Examiner’s discussion of Jones 2003 does not suggest that the Examiner understood Jones 2003 to be limited to an extension step outside of a PCR.

As another example, the Examiner considered Link 2012 and identified it as one of three references that were “pertinent” in a rejection of the parent application. EX2019.0015-16. Link 2012 discloses that that such extension may occur through PCR: “The steps of denaturation, primer annealing and polymerase extension can be repeated many times (i.e., denaturation, annealing and extension constitute one cycle; there can be numerous cycles).” *See* EX2014.0010, [50]-[51]. A POSA would have understood that the cycles referred to in Link 2012 were part of a PCR process. EX2021.¶81. As such, the record does not support Petitioner’s position that “the Examiner appeared to be under the impression that the claims required a separate ‘extension’ step that was not part of a PCR reaction.” EX1085.¶139.

As such, Petitioner fails to demonstrate that “the Examiner materially erred as a result of Tecan’s failure to advise the Examiner that it contends that a PCR step

includes an ‘extension’ step.” The Board should, therefore, deny the petition under § 325(d).

VI. CONCLUSION

For the foregoing reasons, Tecan respectfully requests that the Board deny institution of an *Inter Partes* Review.

Dated: January 29, 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 8,900 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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The undersigned hereby certifies that, on January 29, 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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