

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 IPR2025-00016
U.S. Patent No. 10,876,108

PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

I.	Introduction.....	1
II.	Technology Background.....	3
A.	Development of Sequencing Technology.....	3
B.	Polymerase Chain Reaction (“PCR”).....	3
C.	Next-Generation Technologies.....	4
D.	Targeted Enrichment	6
III.	The ’108 patent.....	9
A.	Overview	9
B.	Independent Claim 1	10
a)	annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest	12
b)	extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest	13
c)	amplifying the one or more oligonucleotide extension products ... thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest	14
d)	sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform	16
C.	Level of Ordinary Skill in the Art	16
D.	Claim Construction.....	16
1.	“sequence of interest”.....	17
2.	“barcode”	17
3.	“enrich”	17
a)	“enriched nucleic acid sequence of interest”	19
b)	“amplifying the one or more oligonucleotide extension products ... thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest”	19
IV.	Petitioner Fails to demonstrate that any claim is unpatentable	22
A.	Ground 1: Meyer Does Not Anticipate the Challenged Claims.....	22

1. Meyer Does Not Disclose Enrichment of a Target Sequence Through Amplification as Required by Claim 1	23
a) Meyer’s Amplification Step Does Not Enrich for the 3’ End Fragments	26
b) A POSA Would Not Infer that the Data Reported in Meyer Demonstrates Enrichment	32
2. Meyer Fails to Anticipate the Dependent Claims of the ’108 Patent.....	41
B. Grounds 2-4: Petitioner Fails to Establish the Challenged Claims are Obvious	41
1. Ground 2: Petitioner Fails to Establish that Claims 8 and 17-18 Would Have Been Obvious Over Meyer.....	41
2. Ground 3 (Claim 2 is Obvious Over Meyer in View of the Knowledge of the POSA and/or Siebert)	43
C. Ground 4 (Claims 11-12 and 19 are Obvious Over Meyer in View of the Knowledge of the POSA and/or Bronner and/or Caruccio)	47
D. Objective Indicia of Nonobviousness	51
1. The Prior Art Taught Away from and Expressed Skepticism for the Claimed Methods.....	51
1. There were long-felt, unmet needs to develop accurate target capture techniques for NGS that were cost-effective and efficient.....	54
2. Industry Praised the Claimed Inventions	57
V. Conclusion	59

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	Page(s)
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Patent Owner Tecan Genomics, Inc. (“Tecan”) submits this Patent Owner’s Response (“POR”) to respond to the Petition (Paper 1) for *inter partes* review (“IPR”) of claims 1-3, 5-12, and 14-19 (“the challenged claims”) of U.S. Patent No. 10,876,108 (“the ’108 patent,” EX1002) filed by Integrated DNA Technologies, Inc. (“Petitioner”), and the Board’s institution decision, Paper 7.

I. INTRODUCTION

The ’108 patent is directed to specific methods for selectively enriching a nucleic acid sequence of interest within a sample using a single target-specific primer. The Petition has failed to prove that any challenged claim is unpatentable because the primary prior art reference on which Petitioner relies—Meyer (EX1006)—fails to disclose critical elements of the challenged claims. Petitioner argues that Meyer, a reference that discloses the amplification and sequencing of an entire transcriptome, anticipates the claimed methods. But the challenged claims require that only nucleic acid fragments with sequences of interest are enriched through amplification. There is no dispute that “to enrich” means “to process so as to add or increase the proportion of a desirable ingredient.” Paper 7, 13. Claim 1 requires that extension products with the sequence of interest are amplified to cause this enrichment. Despite the claim language expressly setting forth this requirement, Petitioner’s analysis entirely omits any discussion as to how the amplification steps

in Meyer cause enrichment. Petitioner's analysis defies the plain language of the claims and, therefore, cannot show that any challenged claim is unpatentable.

Putting the facial deficiencies of the Petition aside, Meyer cannot anticipate the challenged claims because it fails to disclose the claimed enrichment process. As Petitioner admits, the purpose of Meyer was to sequence the entire coral transcriptome, not to focus on any particular sequence of interest. Paper 1, 28. As such, Meyer sought to ensure that all sequences in the sample were adequately represented. Meyer does not disclose the selective amplification (i.e. enrichment) of the 3' end fragments (or any other) over the other fragments in the solution, as confirmed by the first author of Meyer, Dr. Eli Meyer, whose declaration accompanies this Response as EX2287. As Dr. Meyer explains, the amplification of the fragments in Meyer was designed to amplify all fragment types and not to enrich for specific portions of the transcriptome over others. *Id.*, ¶74. In fact, any enrichment of any portion of the transcriptome would have been contrary to the purpose of the study. *Id.*, ¶¶69-70. Dr. Carlos Bustamante, a reputable geneticist and distinguished MacArthur Fellow, confirms that a POSA would not have understood Meyer to disclose a method of enriching for a sequence of interest as claimed. *See* EX2038. Because Meyer does not disclose the claimed enrichment process, the Petition fails.

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. EX2038,¶¶39-47. 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.*,¶74. Sanger Sequencing was the first method that allowed for a DNA sequence to be determined. Although revolutionary, Sanger Sequencing was expensive and ill-suited for large-scale applications. *Id.*,¶78.

B. Polymerase Chain Reaction (“PCR”)

Conceived in 1983, PCR provided researchers with the ability to amplify low amounts of genetic material, which could then be used for further experiments and methods, such as Sanger Sequencing. EX2038,¶57. PCR utilizes enzymes known as polymerases to catalyze the replication of nucleic acids. *Id.* PCR accomplishes this replication through a series of reactions where the complement of a nucleic acid strand is generated. *Id.* Repeated reaction cycles allow for the exponential amplification of the nucleic acid strand. *Id.*,¶¶57-58. While PCR expanded the

capabilities of the field, it was also considered to be error prone. *Id.*, ¶60. Any one of several factors—including primers, polymerases, reaction temperature, and amplification cycles—contributed to the generation of off-target products and other artifacts. *Id.* These errors were exponentially multiplied as more cycles of PCR occurred. *Id.*, ¶61.

Since its advent, researchers have attempted to minimize the errors associated with PCR. For example, numerous methods of PCR were developed as part of “genome walking,” including methods that introduced multiple sets of PCR cycles, additional components (like biotin) that could be used to capture fragments, and specialized adapters and primers that could suppress unwanted PCR amplification. *Id.*, ¶62. In general, each method improved on prior methods but, despite increasing complexity, still suffered from target specificity issues and amplification artifacts. *Id.*, ¶63.

C. Next-Generation Technologies

Starting in the early 2000s, the field of genetics was revolutionized by the invention of next-generation sequencing (“NGS”). EX2038, ¶79. 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.*, ¶80. 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. *Id.* Additionally, NGS platforms exhibited a higher error rate than Sanger Sequencing. *Id.*, ¶88. 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). *Id.*, ¶¶82-83. Homopolymer regions proved problematic because they could throw off the calibration of the 454 Sequencer. *Id.*, ¶88. 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 Illumina sequencers, which dominated the market well before 2012. *Id.*, ¶92.

D. 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. EX2038.¶¶94-95. The '012 patent explains that “target enrichment” was “a commonly employed strategy in genomic DNA sequencing in which *genomic regions of interest are selectively captured* from a DNA sample before sequencing.” EX1001.0016 (1:27-30) (emphasis added). Researchers hoped to use targeted enrichment 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. EX2038.¶96; 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. EX2038.¶97; EX1001.0016 (1:47-50). Pre-NGS experiences had demonstrated the necessity of these primer pairs to ensure adequate target capture. EX2038.¶97. But the need for numerous primer pairs made multiplex PCR impractical due to high levels of non-specific amplification and primer-primer interactions. EX2038.¶98; EX1001.0016

(1:51-53). Given these issues, some researchers began to consider alternative approaches for handling genetic material. Bronner and Caruccio proposed methods of sample preparation that excluded PCR amplification. EX2038, ¶¶331-32. Syvänen proposed developing new methods that excluded PCR amplification and relied on hybridization arrays for target capture. *Id.*, ¶350. One attempt at addressing these issues without disregarding PCR amplification was through microdroplet PCR where each amplification reaction is physically separated into an individual droplet. *Id.*, ¶103; 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. EX2038, ¶104; EX1001.0016 (1:58-63).

Hybrid capture methods relied on the selective hybridization of a target genomic region to a custom designed oligonucleotide. EX2038, ¶107; EX1001.0016 (1:64-66). The oligonucleotide could be immobilized to a surface or contain a ligand that could be immobilized (such as biotin). EX2038, ¶107; 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. EX2038, ¶108; 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. EX2038.¶109; 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. EX2038.¶¶110-11; 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. EX2038.¶¶110-11; EX1001.0016 (2:18-24).

As late as 2011, the art recognized that these three target capture approaches suffered from issues of varying degree with “uniformity, efficiency of coverage and off-target capture.” EX1050.0007. Given these issues, practitioners wondered whether “it may ultimately be more cost-effective to sequence a whole genome” rather than use target capture. EX1050.0007 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 ’108 patent fulfilled these needs.

III. THE '108 PATENT

A. Overview

The '108 patent is directed to methods for sequencing an enriched nucleic acid sequence of interest. EX1002.0033. The '108 patent discloses that the claimed methods “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.” EX1002.0018 (6:14-18). The claimed methods, therefore, improve on the then-existing methods by targeting a sequence of interest using a single primer as opposed to two target-specific primers. The single target-specific primer is used to select for target sequences of interest, and common primer pairs are used to selectively amplify only those sequences containing the target sequence of interest, thus enriching for the target sequence. The claimed methods avoid 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.* (6:27-29).

The '108 patent issued from U.S. Patent Application No. 16/017,340 (“the '340 application”), which was filed on June 25, 2018. EX1002.0001. The '340

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

B. Independent Claim 1

The sole independent claim of the '108 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]	annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in a nucleic acid fragment, wherein the reaction mixture comprises a plurality of nucleic acid fragments, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest comprises a first adaptor sequence, 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;
1[b]	extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment comprising the first adaptor sequence with a polymerase, in the reaction mixture, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end,

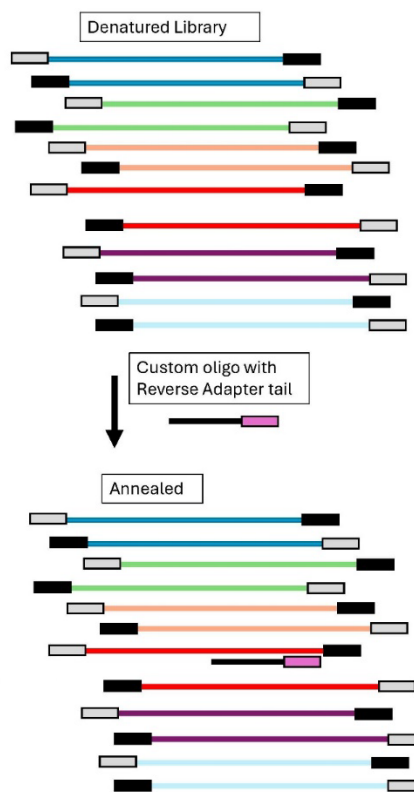
Claim Element	Claim Language
	sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;
1[c]	amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest; and
1[d]	sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

The Petition attempts to illustrate the method through a series of demonstrative figures, but these figures are oversimplified and misleading. *See* Petition, 18-22. Petitioner's figures isolate the nucleic acid fragment containing the sequence of interest from the beginning of the method, stripping out necessary context for how the method works to enrich for the target sequence.

Figure 1 of the '108 patent is an accurate illustration of a preferred embodiment of claim 1.¹ EX1002.0012, 23 (15:59-61). How this figure correlates to the limitations of the claims is outlined below.

a) annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest

After ligation, “the DNA fragments with complementary ends are denatured to generate a denatured library comprising single stranded DNA fragments with complementary ends.” EX1001.0023 (16:54-57);² EX2038.¶123.

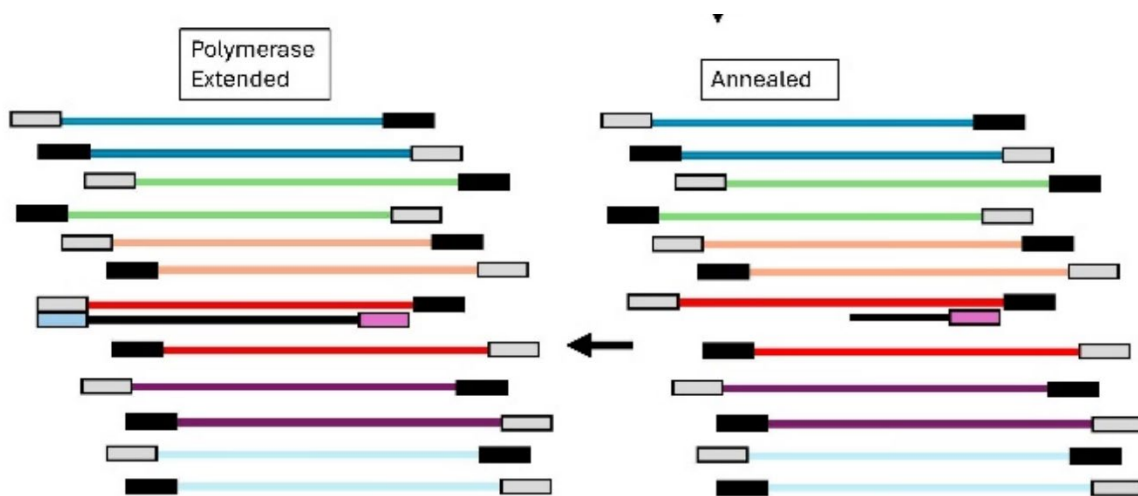


¹ For clarity, Tecan provides a color-coded recreation of Figure 1.

² The '108 patent shares a common specification with EX1001.

Then, “a custom oligonucleotide with a reverse adaptor tail is annealed to the single stranded DNA fragments with complementary ends.” EX1001.0023 (16:61-63). The claimed “one or more oligonucleotides” must comprise (1) a 3’ portion with at least 10 bases complementary to the sequence of interest, and (2) a 5’ tail portion comprising a second adaptor sequence that is not complementary to the sequence of interest. EX2038.¶123.

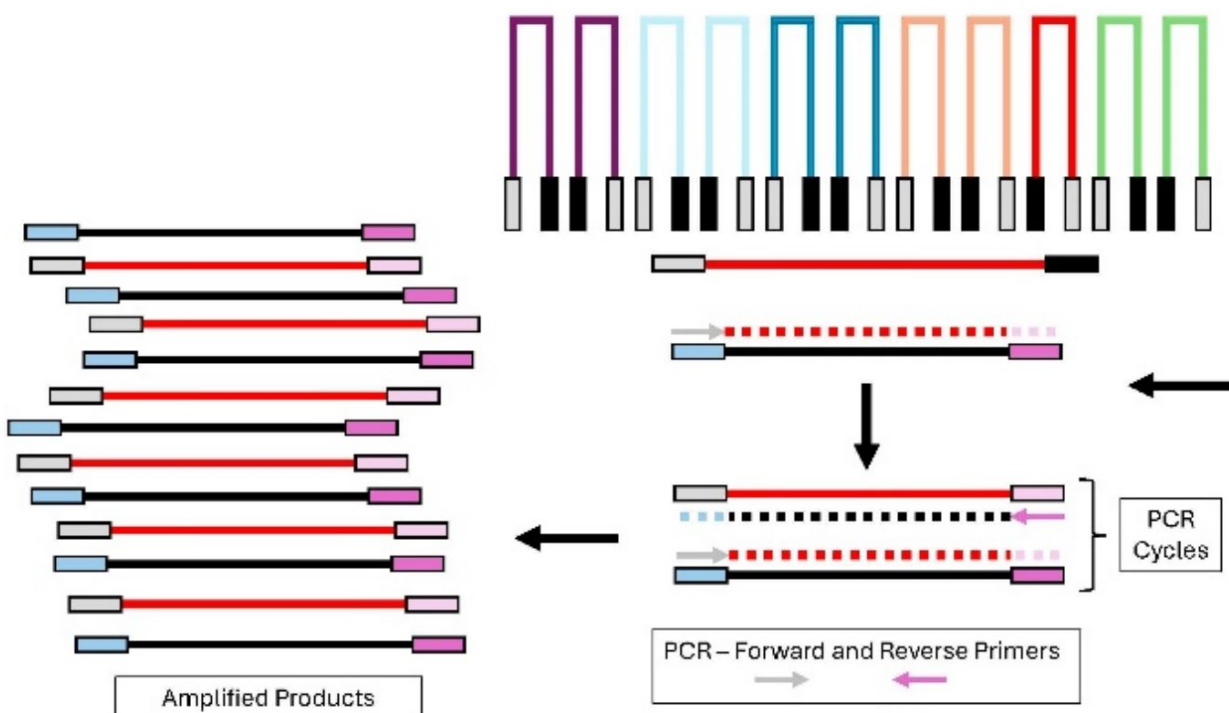
b) extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest



Next, “the custom oligonucleotide with a reverse adaptor tail is extended using any method known in the art.” EX1001.0024 (17:39-41); EX2038.¶124. This extension step occurs through the use of a polymerase. EX1001.0012. In the preferred embodiment, “the custom oligonucleotide with a reverse adaptor tail can only anneal to and be extended on DNA fragments in the denatured library comprising the target sequence of interest for which the custom oligonucleotide with

a reverse adaptor tail is directed.” EX1001.0024 (17:48-52). “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.” EX1001.0024 (17:44-47); EX2038.¶124. The ’108 patent explains that this extension “*allows for selective binding and subsequent enrichment of said nucleic acid fragment*” using the methods described herein.” EX1001.0021 (11:33-39) (emphasis added). That “subsequent enrichment” occurs during the amplification step that follows the extension step. EX2038.¶125.

c) amplifying the one or more oligonucleotide extension products ... thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest



A pair of primers corresponding to the forward (first) and reverse (second) adaptor sequences is used to selectively amplify the oligonucleotide extension product, enriching for the sequence of interest. EX1001.0024 (17:52-60); EX2038.¶125. The '108 patent specifies that “only nucleotide extension products comprising both the first and second adaptor sequence will be amplified and thus enriched.” EX1001.0012 (12:14-17). As Dr. Sims admitted at deposition, this step provides that only the oligonucleotide extension products from step (c) undergo the claimed amplification. EX2037.0012 (186:18-19). Contrary to the narrowed depiction presented in the Petition, the claims require that the sample include fragments in the solution that do not contain the sequence of interest and that those fragments are not amplified. EX2038.¶128; *see* EX2037.0008-09 (172:12-173:17). Without sequences that are not amplified, the sequence of interest could not be enriched—there would be no comparator to measure the enrichment. EX2038.¶128. Only the oligonucleotide extension products of the previous step contain the correct primer binding sites that allow for their amplification. *Id.*,¶129. Through this targeted amplification process, the method enriches for the sequence of interest. The claimed methods require that the resulting amplification products must contain the sequence of interest and a 3' end with sequence complementary to a sequence on a surface.” *Id.*,¶¶125-26.

d) sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform

After the amplified products are annealed to the sequence on the surface, the sample containing the amplified products are sequenced. The patent explains that a “massively parallel sequencing platform” means NGS. *See, e.g.,* EX1001.0019 (26:64-27:2).

C. Level of Ordinary Skill in the Art

The Board adopted the following definition in its Institution Decision:

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

Paper 7, 12. While Patent Owner contends that a POSA may have experience with DNA sequencing methods more broadly than NGS (*see id.*, 10-12), Patent Owner adopts the Board’s definition of a POSA for purposes of this Response.

D. Claim Construction

All terms of the challenged claims are used according to how a POSA would have understood their ordinary meaning. In light of the disputes between the parties and specific requests from the Board, Tecan proposes clarifying constructions of certain claim terms below.

1. “sequence of interest”

The Board construed “sequence of interest” to mean “a polynucleotide sequence of interest, for which enrichment is desired.” *Id.*, 12-13. Patent Owner does not dispute this construction for purposes of its Response.

2. “barcode”

The term “barcode” only appears in claim 8 of the ’108 patent. Because the Petition fails to show that claim 1 of the ’108 patent is anticipated by or obvious over Meyer and therefore also fails to show that any dependent claim is anticipated or obvious, the Board need not construe this term.

3. “enrich”

The ’108 patent is directed to a method for sequencing “an enriched nucleic acid sequence of interest” whereby “one or more oligonucleotide extension products” are amplified “thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest.” *See* EX1002.0033 cl. 1. The Board construed “enrich” to have its plain and ordinary meaning of “to process so as to add or increase the proportion of a desirable ingredient.” Paper 9, 15. Tecan does not dispute the Board’s preliminary definition of the term “enrich” in the abstract. In the context of preparing a sequencing library, Tecan proposes that a nucleic acid sequence of interest is

“enriched” when the proportion of nucleic acid fragments containing the sequence of interest is increased relative to other nucleic acid fragments in the sample.

Petitioner’s papers suggest that there is no dispute regarding the meaning of “enrich” in the context of this patent. Dr. Sims describes the claimed methods as methods “for generating a ‘selectively enriched’ ‘library’ of DNA molecules for sequencing using a ‘Next Generation Sequencing’ (‘NGS’) platform.” EX1085.¶30. According to Dr. Sims, “[t]he library is selectively enriched for a particular ‘sequence of interest,’ such that the sequence of interest appears in the sequencing library at a higher relative proportion than it appeared in the original sample from which the sequencing library was created.” *Id.* This “library” “is comprised of nucleic acids.” EX2037.0003 (150:3). Dr. Sims explained that a nucleic acid fragment is enriched in a sample if after the process, the fragment is “overrepresented relative to others in the original mixture.” *Id.* (151:5-10); *id.*, .0028 (173:12-17) (“an enrichment process results in overrepresentation of certain nucleic acid sequences relative to others in a sample.”).

While there does not appear to be a dispute regarding the meaning of the word “enrich,” Tecan believes additional clarification is necessary for the terms that reference enrichment so as to fully reflect the meaning of enrich as it is used in claim 1 of the ’108 patent.

a) *“enriched nucleic acid sequence of interest”*

The term “enriched nucleic acid sequence of interest” appears in the preamble. While this phrase provides context for the method, it does not add any limiting step to the method that is not otherwise recited in the claim. *Catalina Marketing Int’l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). The enrichment referred to in the preamble refers to the enrichment described during the claimed amplification in limitation 1(c). It is Tecan’s position that the preamble does not need to be separately construed, but to the extent it is limiting, should be given a meaning that is consistent with the enrichment described in limitation 1(c).

b) *“amplifying the one or more oligonucleotide extension products ... thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest”*

The phrase “amplifying the one or more oligonucleotide extension products ... thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest”³ means

³ For ease of reference, Tecan has omitted the language of this limitation that refers to the primers used for the amplification step. It is Tecan’s position that the omitted language does not need construction and does not impact the portion of the claim that is addressed by Tecan’s proposed construction. To be clear, it is Tecan’s position

“increase the proportion of the nucleic acid sequence of interest relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement.” This construction is supported by intrinsic and extrinsic evidence, including testimony from both Petitioner’s expert Dr. Sims and Tecan’s expert Dr. Bustamante.

As an initial matter, the plain language of the claim and this limitation confirms that the amplification step must cause enrichment of the fragment defined in this limitation. A POSA would have understood that “enriching” means to increase the proportion of the sequence of interest present in the solution over other sequences that were not of interest. EX2038.¶¶149-56. A POSA would have understood that based on the specific steps of claim 1, that enrichment would occur as a result of amplification. *Id.*,¶152. Further, a POSA would have also understood based on the language of the claims that the nucleic acid being enriched through amplification would be the extension product defined in the previous step. *Id.*,¶153. The claims define the extension product to include a sequence complementary to the first adapter sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adapter sequence at a second end. *Id.*,¶124. A

that the claim language requires that the amplification be performed using the primers described in the claims.

POSA would have understood that amplification of this extension product via PCR would include amplification of both this sequence and its complement. *Id.*, ¶58. That is, fragments that contain both adapters defined in the claims and the sequence of interest. *Id.*, ¶125.

The patent specification further reinforces that the claimed amplification process must “enrich for the nucleic acid sequence of interest.” The patent explains that the amplification step requires that the amplification occur by “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.” EX1001.0033. The specification explains repeatedly that it is this targeted amplification process of only the oligonucleotide extension products that results in enrichment of these fragments as compared to other fragments in the sample. *See id.*,.0021 (12:14-17) (“[i]n this manner only oligonucleotide extension products comprising both the first and second adaptor sequence will be amplified and thus enriched”); *id.*,.0024 (17:57-60) (“only the oligonucleotide extension product with the forward adaptor sequence at one end and the reverse adaptor sequence at the other end can be amplified and thus enriched”).

Petitioner appears to agree with this interpretation. In arguing that Meyer anticipates the claimed amplification step, Petitioner claims that the “result of [Meyer’s] amplification was to enrich for the 3’ end fragments compared to other

cDNA fragments present in the sample that lacked the requisite adaptors.” Paper 1, 39-40. Petitioner also claims that the amplification step is anticipated because “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.” *Id.*, 50. While Petitioner has failed to prove that either of these statements is accurate, Petitioner’s contentions show that Petitioner understands that the amplification limitation requires that the amplification cause enrichment of the extension products.

Therefore, the Board should adopt Tecan’s proposed construction of this term.

IV. PETITIONER FAILS TO DEMONSTRATE THAT ANY CLAIM IS UNPATENTABLE

A. Ground 1: Meyer Does Not Anticipate the Challenged Claims

Petitioner argues that “Meyer used a method that includes, among other steps, every step claimed in the ’108 patent,” and as such, “anticipates independent claim 1 of the ’108 patent, as well as dependent claims 3, 5-10, and 14-18.” Petition at 28. Petitioner’s representation that Meyer discloses a targeted enrichment method reflects a fundamental misunderstanding of the disclosures of Meyer and the data reported in the reference.

The purpose of Meyer was not to target and enrich for 3’ end fragments over other fragments. EX1006.0001-02; EX2287.¶¶65-72. Rather, Meyer sought to sequence the entirety of a previously unknown genome. EX1006.0001-02;

EX2287.¶¶20-21. From the outset, Meyer notes that NGS “shows great potential for expanding sequence databases of corals and other emerging model organisms” but laments that NGS methods had “not yet been widely applied to emerging model organisms, because of the lack of methods for *de novo* assembly and analysis in the absence of a reference genome sequence.” EX1006.0002. To solve this issue, Meyer discloses procedures that “provide a rapid and cost-effective method for deep transcriptome sequencing in a single 454 sequencing run, improving substantially on previous methods.” *Id.*,.0012. Meyer reports that using this method, a single 454 sequencing run “produced more than 600,000 sequencing reads, allowing the identification of ~11,000 genes and ~30,000 SNPs.” *Id.* As the first author of the paper, Dr. Meyer, confirms, these results served as a proof of concept for sequencing entire nucleic acid samples—not the targeting and sequencing of specific sequences of interest. EX2287.¶¶15-21, 65-77. Ignoring the stated purpose and conclusions of the reference, Petitioner selects isolated disclosures to advance a narrative that does not accurately reflect the disclosure.

1. Meyer Does Not Disclose Enrichment of a Target Sequence Through Amplification as Required by Claim 1

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).

Meyer fails to disclose “amplifying the one or more oligonucleotide extension products . . . to enrich for the nucleic acid sequence of interest.” Petitioner, therefore, cannot carry its burden of proving unpatentability of any claim under Ground 1.

Petitioner vaguely argues that Meyer’s method discloses targeted enrichment but fails to identify what is being enriched (i.e., whether the extension product defined in the claims is being enriched) or which step in Meyer drives the alleged enrichment (i.e., whether the amplification of cDNA fragments causes enrichment as claimed). In its discussion of the preamble, Petitioner claims that the “Meyer method was a method of enrichment in two senses”—enriching for mRNA over other types of RNA, and enriching for the 3’ end fragments over other mRNA. Paper 1, 33. These arguments are a reflection of its expert, Dr. Sims, failing to consider this claim limitation properly—Dr. Sims construed the claim limitations so that enrichment need not occur because of amplification but instead by an earlier step. All these arguments are misplaced.

As Petitioner’s expert Dr. Sims testified at his deposition, it is the SMART protocol used in Meyer that enriches the sample for mRNA over other types of RNA. EX2037.0015 (200:1-8); EX2287.¶¶37, 71. This step occurs before Meyer fragments the nucleic acids and before the fragments are ligated to adaptors—not during the required amplification step. EX2287.¶37. These steps of the Meyer method all occur prior to the first steps of the claimed method. As Dr. Sims

confirmed during deposition, to meet the limitations of the challenged claims, enrichment must occur as part of the *claimed method*, and not prior to the claimed method:

My interpretation is that Claim 1 describes an enrichment process, and so overrepresentation of a nucleic acid sequence of interest at the beginning of the process doesn't satisfy the claim. The process described [in claim 1] enriches. It's possible that other things are going on that also contribute to enrichment, but the process described [in claim 1] is critical for enrichment.

EX2037.0014 (194:9-16). Meyer's enrichment for mRNA using the SMART protocol is, therefore, irrelevant to the analysis of whether Meyer discloses the *claimed* enrichment method. *Id.*,.0014 (194:9-16) (explaining that the claimed enrichment can't occur before the first step of the method).

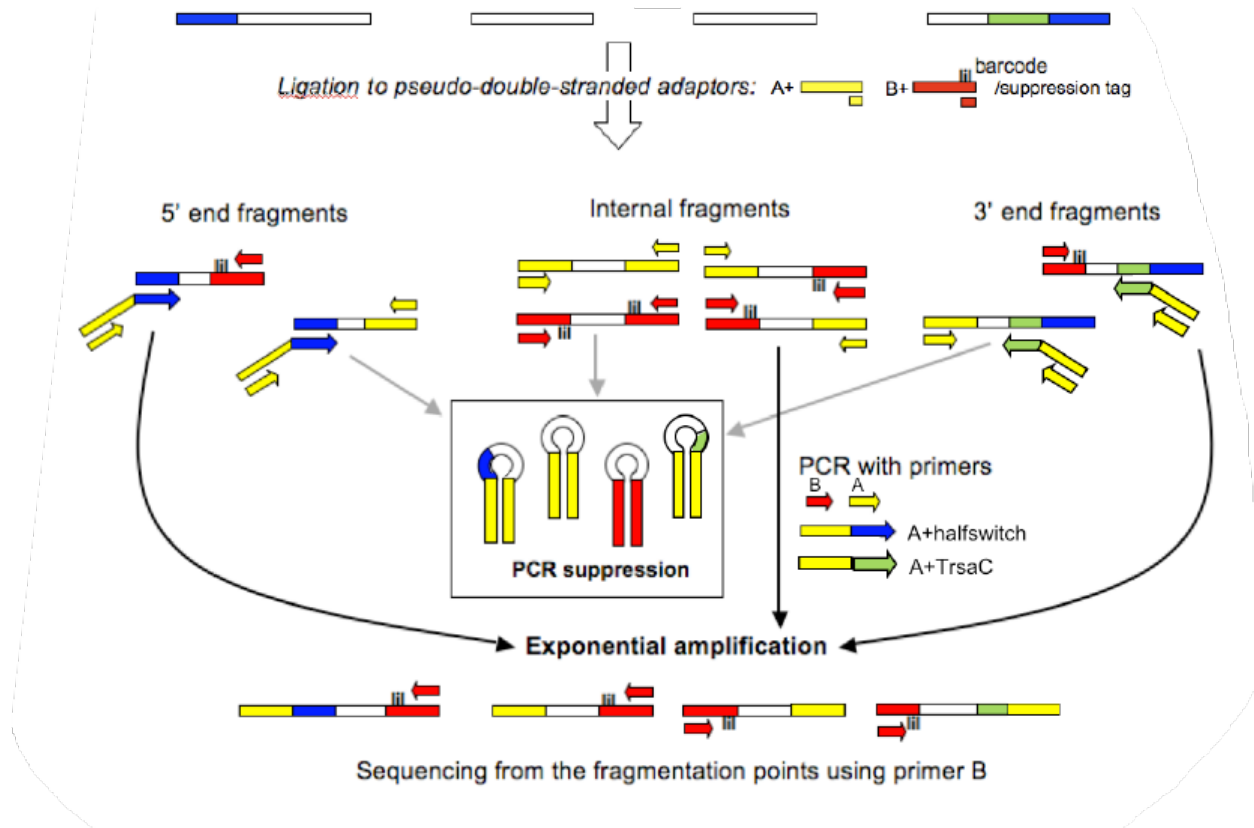
Petitioner's second alleged source of enrichment—enrichment of the 3' end fragments—is also flawed. First, the amplification step in Meyer was not designed to, and does not, enrich for the 3' end fragments. Second, Petitioner relies on Meyer's estimates of the amount of improvement seen with its method, but

Petitioner's inferences are flawed and do not reflect how a POSA would have understood the data.

a) Meyer's Amplification Step Does Not Enrich for the 3' End Fragments

Neither of Meyer's disclosed amplification schemes allow for enrichment of the 3' end fragments.⁴ EX2287.¶¶65-72. Rather, Meyer's methods amplify all fragments with the proper adapter configurations. *Id.*, ¶45. The relevant steps of the Meyer method on which Petitioner relies are reflected in the figure below:

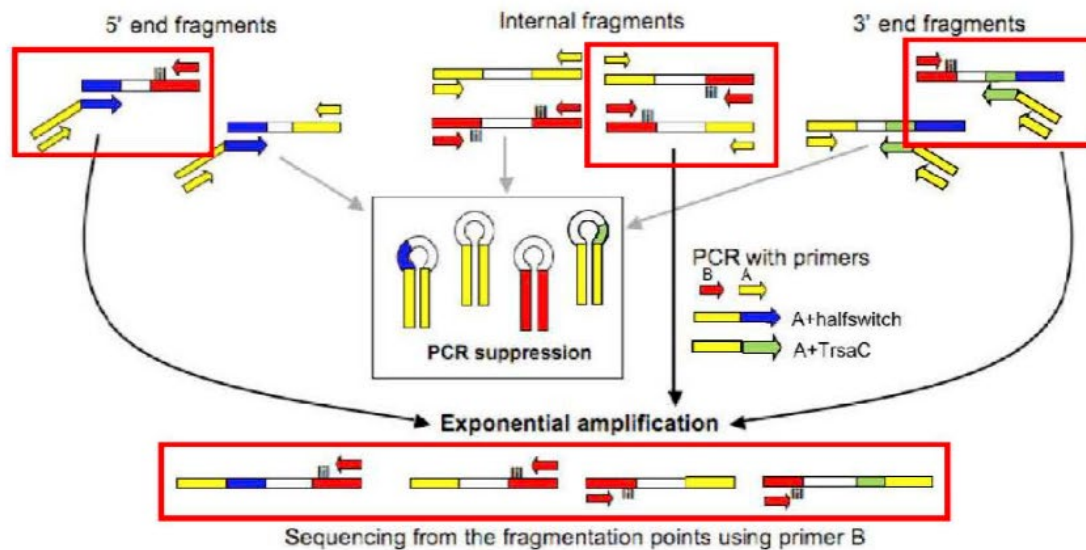
⁴ Petitioner relies entirely on the scheme depicted in Additional File 4 for its anticipation arguments, but Meyer's sequencing experiments followed the scheme in Figure 1. EX2287.¶¶63-64.



EX1006.0020.

Petitioner's arguments track only the amplification of a single type of fragment in the Meyer mixture—the 3' end fragment. In reality, however, after the adapters are added, Meyer depicts *eight* types of fragments: two 5' end fragments that contain either the Primer A or Primer B sequence at one end and the cap primer on the other, four combinations of internal fragments with different sets of flanking primers, and two 3' end fragments that contain either the Primer A or Primer B

sequence at one end and the modified cap primer on the other.⁵ Meyer does not disclose the relative proportions of these fragments. EX2287.¶75.



During the first step of the PCR reaction, Meyer discloses the use of four different primers (below “PCR with primers” in the figure): the 454 universal adapter primers A and B, a primer complementary to the cap primers that introduces the Primer A sequence, and a primer complementary to the broken-T chain that also introduces the Primer A sequence. EX1006.0020. Unlike the annealing step of the ’108 patent where only primers complementary to the sequence of interest anneal,

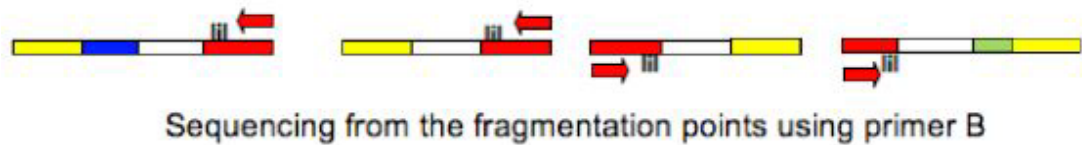
⁵ Petitioner identifies the Primer A and B sequences as the “first adaptor sequence” and “second adaptor sequence” of claim 1. *See* Paper 1, 35-37.

two of Meyer's primers anneal to the complementary sequences on every fragment type. Paper 1, 37 ("Then, these four primers annealed to their respective complementary sequences in the PCR reaction."). Meyer explains that fragments with the same flanking primer sequences will not undergo exponential amplification due to PCR suppression, meaning only half of the 5' end fragments, half of the internal fragments, and half of the 3' end fragments will be exponentially amplified. EX1006.0020.

In the second step of the PCR reaction, Meyer discloses that DNA polymerases extend the primers. While Petitioner focuses just on the primers annealed to the 3' end fragment (*see* Paper 1, 38), the polymerases also extend the primers annealed to the 5' end fragment and the internal fragments. *See* EX2287.¶44. This step creates extension products corresponding to each fragment type in the solution, unlike the extension step of the '108 patent where the only extension products generated are those containing the sequence of interest or its complement. *See supra*, Section III.B.

In the third step of the PCR reaction, Meyer discloses that primers corresponding to the universal 454 adapters exponentially amplify all fragment types. EX1006.0020; *see also* EX2287.¶45, 47-50. While Petitioner again focuses on just the amplification of the 3' end extension products (*see* Paper 1, 38-40), Meyer discloses that all four types of fragments covering the entire transcriptome are

exponentially amplified and subsequently sequenced: the 5' end fragments, the internal fragments, and the 3' end fragments (represented in the simplified figure below).



EX1006.0020. Contrast this with the amplification step of the '108 patent where only fragments containing a sequence of interest are amplified to enrich for that sequence. *See supra*, Section III.B. Petitioner entirely ignores that all fragment types in the Meyer method are amplified, negating the possibility of enrichment of any one particular sequence as compared to the others.

Petitioner seems to introduce yet a third explanation of what is enriched in Meyer, arguing that the “result of that amplification was to enrich for the 3’ end fragments *compared to other cDNA fragments present in the sample that lacked the requisite adaptors.*” *See* Paper 1, 40 (emphasis added). It is unclear whether Petitioner is referring to fragments that lack adaptors altogether or fragments that are subject to PCR suppression due to the binding of two of the same type of adaptor. Either way, Petitioner has not identified any evidence of enrichment of a sequence of interest. First, there is no evidence that fragments lacked adaptors in Meyer’s method. Meyer discloses that the pseudo-double-stranded adaptors were ligated to

the ends of all cDNA fragments that did not contain a cap primer (i.e., all fragment ends except for the 5' and 3' termini of the original cDNA strand). EX1006.0019; EX2287.¶¶40-41. Dr. Sims confirmed at deposition that the goal of this step would be to ligate partial duplex adapters to as many ends as possible. EX2037.0017 (206:7-16). That is—a POSA would have understood that the goal of the ligation step would be to saturate all non-capped fragment ends with adapters. EX2038.¶180. Absent a rare mistake—which Meyer does not disclose—all cDNA fragments will have flanking adapters. Therefore, there is no evidence of enrichment over fragments that do not contain adapters.

Second, PCR suppression—where fragments with two copies of the same adapter sequences are excluded from amplification—does not result in the claimed enrichment of a sequence of interest. In the ligation reaction, adapters attach to fragments at random, that is, without any preference to any particular sequence. EX2038.¶¶180-83; EX2287.¶45. While this results in certain *fragments* being suppressed, PCR suppression in Meyer does not suppress or favor any particular *sequence*. EX2038.¶¶183, 217; EX2287.¶45. The fragments subject to suppression will include sequences spanning the entire nucleic acid sample and would not contribute to enrichment of one sequence over another. EX2038.¶¶183, 215-16, 225-27; EX2287.¶69. Petitioner, therefore, has not identified any aspect of the Meyer amplification step that causes enrichment of a sequence of interest.

b) A POSA Would Not Infer that the Data Reported in Meyer Demonstrates Enrichment

Petitioner argues that “the Meyer authors confirmed that [the 3’ end] 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.” Paper 1, 50. Petitioner’s sole support for this argument is the statement in Meyer: “A single copy of this ‘broken-T’ adaptor was found in 98,276 of the raw reads (16% of the total), slightly more than the expectation (~10%) based on average read length (232 bp) and assuming an average transcript size of 2,200 bp.” EX1006.0009. This estimation, however, fails to support Petitioner’s arguments. First, Petitioner incorrectly conflates the method illustrated in Additional File 4 with the data reported in Meyer, which was obtained through a different method. Second, Meyer used the measurement of the prevalence of the broken-T sequence to confirm that the method resolved the 454 homopolymer problem, not to evidence enrichment of that sequence. Third, a POSA would have understood that Meyer’s assumptions were flawed and could not support any inferences concerning enrichment.

(1) Petitioner Mischaracterizes the Data

Petitioner’s anticipation arguments are entirely based on the method reported in Additional File 4 of the Meyer publication. Petitioner does not point to any steps of the method described in Figure 1 to show anticipation. However, Petitioner’s only

evidence of “enrichment” is based on data derived from performing the method of Figure 1. *See* EX2038.¶247.

Meyer explicitly states that a “cDNA sample was prepared from coral larvae as illustrated in Figure 1, and sequenced using the 454 GS-Flx platform.” EX1006.0002. Meyer reports that “[t]his single sequencing run produced 628,649 reads, with an average sequence length of 232 bases.” *Id.* Meyer uses the same 232 bp average to calculate an expected percentage of reads containing the broken-T chain. *Id.*,.0009. A POSA would have understood that it would be highly unlikely for two sequencing runs, using samples prepared through different methods, to have an identical average sequence length. *See* EX2038.¶¶247, 51.

In Additional File 4, Meyer again confirms that “the version of the protocol shown here includes minor modifications from that used for preparing coral larval cDNA.” EX1006.0019. A POSA would have understood this to confirm that the method illustrated in Additional File 4 was not used to prepare the coral larval samples that were sequenced in Meyer. EX2038.¶247. Dr. Meyer confirms that he did not use the method in Additional File 4 to prepare the samples sequenced in Meyer. EX2287.¶¶63-64. 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; EX2287.¶¶47,

63; EX2038.¶260. Petitioner does not, and indeed cannot, point to any data regarding alleged “enrichment” caused by the method in Additional File 4.

(2) Meyer Used the Data Regarding Prevalence of the Broken-T to Confirm that the 454 Sequencing Issue was Resolved

One of the issues that Meyer’s method sought to resolve was the 454 sequencer’s issues with reading homopolymer sequences. EX2287.¶¶28-31. Meyer discloses that “[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. This underrepresentation is a result of an optical issue with the 454 sequencer—not a deficiency in the sequencing library. EX2038.¶¶88, 248-50; EX2287.¶¶28-31, 73-77. Meyer discloses that the solution to this optical issue was “simply interrupting the poly-T region with a single C” during cDNA synthesis, through modifications of the cap primers used in the SMART protocol. EX1006.0009; EX2038.¶¶240, 249; EX2287.¶31.

The Meyer authors used the data comparing their observed prevalence of broken-T sequences to the estimate of expected prevalence of 3’ ends in the sample to “confirm[] the effectiveness of this solution for *overcoming the homopolymer problem.*” EX1006.0009 (emphasis added). Meyer discloses that the “purpose of the ‘broken chain’ T-primer is to reduce artifacts *during 454 pyrosequencing*, which

may get thrown out of calibration by too strong of a light signal produced from a long mononucleotide stretch (such as polyT or polyA).” EX1006.0019 (emphasis added); EX2287.¶¶28-31.

Petitioner’s reliance on Meyer’s statement about seeing a greater than expected number of reads corresponding to the 3’ end extends beyond the reasonable inferences that a POSA would have drawn from that data. EX2038.¶¶242-73. Meyer’s data demonstrates that the 3’ end fragments were well represented in the sequencing data. EX2287.¶58. There are no other inferences that can reliably be drawn concerning the number of 3’ end fragments in the raw sequencing reads. EX2038.¶¶242-73. There also is no way for a POSA to meaningfully attribute this data to any purported enrichment that resulted from the amplification step in Meyer’s method, especially given the lack of a mechanistic explanation to support an expectation of enrichment during amplification and the lack of controls that would be necessary to assess enrichment. *Id.*, ¶¶251-53; *Dayco Products, Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1368 (Fed. Cir. 2003) (A prior art reference is to be interpreted based on what “one skilled in the art would reasonably understand or infer” from the reference.).

For a POSA to infer that enrichment occurred in any data set, a POSA would need an understanding as to the baseline proportion of the target sequence before the POSA targeted the sequence for selective amplification. EX2038, ¶¶251-53. Meyer

does not disclose the relative populations of the target sequences before the amplification step. *Id.*; EX2287.¶75. The only experimental data reported in Meyer is at the conclusion of the sequencing run. EX2287.¶¶63-64.

A POSA would also have understood that the data regarding the observed and expected number of 3' end fragments was not sufficiently robust to support further conclusions. Specifically, Meyer did not have adequate controls to determine whether the supposed improvement observed was a result of breaking the T chain, increasing internal sequence reads, or adjusting the sonication, all of which can impact the length of the fragments and the sequence read length. EX2038,¶¶251-53. Meyer discloses that both breaking the T chain and increasing the internal sequence reads improved the results, but does not distinguish between the two in any reports of the data. EX1006.0009, 13. With respect to Meyer's use of sonication, Bronner discloses that "standard sonication [] produces a relatively wide range of fragment sizes, so a large proportion of the fragmented DNA is wasted," and "it exposes the sample to a large amount of energy, a lot of which is converted into heat, which can lead to strand dissociation, DNA damage and bias." EX1009.0006. Despite each of these variables likely impacting the sequencing reads, Meyer only reports one set of raw data that reflects all three of these actions. EX1006.0002-09. A POSA reviewing this data would understand that Meyer's method appears to have improved the quality of the sequencing read data but would not be able to attribute

the effects to specific improvements nor attribute any alleged enrichment to any one improvement. EX2038,¶¶251-53.

(3) A POSA Would Have Understood that Meyer's
Data Was Based on Flawed Assumptions

Further complicating the ability to draw inferences from the data reported in Meyer, the alleged 6% increase in 3' end fragments was based on Meyer's rough estimate of the "expected" number of 3' end reads. EX1006.0009. Meyer assumed that the average read length was 232 bp and the average transcript length was 2,200 bp. By dividing the transcript length by the average read length, Meyer estimated that there were approximately 10 fragments per transcript and that roughly 10% of all fragments would be the 3' end fragment. *Id.*; EX2287.¶58; EX2038.¶265. A POSA, however, would have understood that both averages used to form Meyer's estimate were not accurate based on the rest of the data reported in Meyer.

First, a POSA would have understood that the data shows that the average sequence read length was actually longer than 232 bp. As Dr. Bustamante explains, the average size of the sequence reads (232 bp) is not based on a normal distribution (i.e., this data set does not contain an equal number of observations above and below the "average" value). EX2038.¶¶266-68. Instead, the read length is skewed so that the average is actually lower than the central tendency, which is the single value that is considered representative of an entire distribution. *Id.* As a result, a POSA would

have understood that the average read length as reported in Meyer would not be representative of the entire set of read lengths and was instead too low. A POSA would have understood that the appropriate value (e.g., adjusted average, median, or mode) would have been higher, bringing the expected number of 3' end fragments closer to what Meyer actually observed. *Id.*

Second, a POSA would have understood from the average transcript length that the 10% estimate was also inaccurate either because the value used for the average transcript length was wrong or because it was incorrectly used with the average read length. Because Meyer does not disclose how the estimate of the average transcript length was derived, a POSA would have considered all reasonable possibilities in assessing the data. EX2038.¶¶260-273. The record shows three possibilities for the basis of this estimate: (1) the average transcript length in mammals; (2) the reassembled transcript length; or (3) the gel transcript size reported in Meyer. Each of these reinforce the imprecision of Meyer's estimate.

Dr. Meyer believes that the average transcript length was an approximation based on the average transcript length in mammals—not coral. EX2287.¶58. If so, a POSA would have understood that the calculation could not be used to assess enrichment since it was not from the same phylum and different species would have different transcript lengths. EX2038.¶260.

If the estimate of average transcript length is based off the reassembled transcript lengths, a POSA would have recognized that Meyer's estimate is very likely flawed. Meyer assumed that the average length of the transcripts in the study was 2,200 bp, but the distribution data reported by Meyer shows that the transcript lengths skewed heavily towards being far less than that. EX2038.¶¶261-65. As Dr. Bustamante, whose expertise includes biostatistics, explains, had Meyer instead based his assumption about the average transcript length on the data reported in the paper, the estimate would be closer to 1,450 bp. *Id.* Using an average transcript length of 1,450 bp, the expected amount of 3' end fragments would have been 16%—in line with Meyer's reported results. *See id.*

Finally, if the calculation was performed using the gel transcript size reported in Meyer as the average transcript size, as Dr. Sims claims, a POSA would have understood that the proper analysis would be to compare transcript length to fragment length—not transcript length to fragment *read* length. Doing so leads to a conclusion that the expected proportion of 3' end fragments in the population would be approximately 16%, not the 10% Meyer predicted. EX2038.¶¶266-269.

Dr. Sims explains his view that the 2,200 bp was obtained from measuring transcripts immediately after cDNA synthesis. EX1085, ¶ 184; EX1006.0021-23. The gel on which Dr. Sims relies demonstrates the length of the cDNA molecules. EX2038.¶266. To accurately use this data to determine the expected number of

transcript ends, a POSA would understand that the cDNA transcript length would need to be compared to the fragment length, not read length. *Id.* A POSA would understand that sequencing reads at the time tended to be shorter than their corresponding fragments (i.e., the sequencer did not get to the end of every fragment). As a result, using the sequencing *read* length to estimate the number of fragment ends would lead to an estimate of end fragments that is skewed lower than reality. *See* EX2038.¶¶266-269.

A POSA would appreciate that a more accurate comparison would be to use the fragment length that Meyer targeted in their method. Meyer discloses that in their experiments, sonication “produced fragments in the appropriate size range (ca. 300-400 bp).” EX1006.0013. In Additional File 4, Meyer further specified “an average fragment size of 350-400 bp.” *Id.*,0019. Using this range, the proportion of the 3’ end fragments compared to the rest of the sample would be calculated to be from 15.9% (350/2,200) to 18.2% (400/2,200). EX2038.¶¶266-269. This means that approximately 15.9-18.2% of fragments pre-amplification were 3’ end fragments, meaning that the proportion of these fragments *decreased* after amplification (~15.6%). A POSA would understand from these numbers that no enrichment occurred. EX2038.¶270.

In light of the imprecision of Meyer’s estimates, a POSA would not have inferred any more from the comparison than what Meyer did: 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); EX2287.¶¶73-77.

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."

2. Meyer Fails to Anticipate the Dependent Claims of the '108 Patent

For the reasons that Meyer fails to anticipate claim 1 of the '108 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. Grounds 2-4: Petitioner Fails to Establish the Challenged Claims are Obvious

1. Ground 2: Petitioner Fails to Establish that Claims 8 and 17-18 Would Have Been Obvious Over Meyer

Petitioner makes no argument with respect to Meyer rendering obvious claims 1, 3, 5-7, 9-10, and 14-16. Petitioner relies solely on its Ground 1 anticipation arguments for those claims. As such, no obviousness challenge to those claims can be sustained. *See In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1380-81 (Fed.

Cir. 2016). For Ground 2, Petitioner argues that claims 8 and 17-18 would have been obvious over Meyer.

The Petition makes no effort to address whether step 1(d) of claim 1 would have been obvious to a POSA in light of Meyer. For this issue, the Petition fails to make any arguments as to why a POSA would have been motivated to modify Meyer or even whether a POSA would have had a reasonable expectation of success in doing so. Dr. Sims also fails to provide any testimony on this issue. The Petition, therefore, is legally insufficient to support an independent finding of obviousness for any challenged claim. *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.”). Because Petitioner relies entirely on its arguments in Ground 1 for limitation 1(d), Ground 2 fails for the same reasons as Ground 1. Because Petitioner has failed to show that Meyer renders obvious claim 1 of the ’108 patent, Meyer also fails to render obvious any of the remaining dependent claims, including the three challenged in this Ground.

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).

2. 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. Paper 1, 62. Claim 2 requires that the “nucleic acid fragment” of claim 1 comprises genomic DNA. But as explained above, Meyer fails to anticipate or render obvious claim 1 of the '108 patent. *See supra* Section IV.B. Ground 3 fails to address the deficiencies in Grounds 1 and 2 with respect to the only independent claim of the '108 patent. Petitioner relies on Siebert only for the additional element of claim 2 requiring the nucleic acid fragment be genomic DNA. As such, Ground 3 necessarily fails for at least the same reasons as Grounds 1 and 2.

Ground 3 also independently fails because a POSA would not have been motivated to combine Meyer and Siebert to practice the claimed inventions with a reasonable expectation of success. Petitioner argues that a POSA would have been motivated to combine the two references because of “the similar chemistries of cDNA and genomic DNA” and Siebert’s use of “anchored PCR in genomic DNA.” Paper 1, 63. Petitioner’s argument boils down to nothing more than a one-size-fits-all proposition: because researchers were interested in and had used PCR

amplification on genomic DNA, a POSA would have been able to use any sequencing method with genomic DNA. Such a broad justification is insufficient to prove a POSA would have had a motivation to combine and reasonable expectation of success. As discussed in more detail below, Petitioner ignores the specific methods disclosed in these references and ignores that the purposes of Meyer and Siebert are incompatible.

Meyer sought to sequence an entire transcriptome. To do so, Meyer used specific methods to address the homopolymer problem and other sequencing issues caused by sequencing fragments starting at the mRNA's termini. These solutions were specific to sequencing mRNA with the 454 sequencer and relied heavily on the cDNA synthesis process. Siebert sought to “determine the exon-intron boundaries of genes.” *See* EX1007.0002. Siebert calculated the sizes of genomic DNA without the use of sequencing technology. *Id.* Rather than sequence an entire genome or transcriptome, Siebert was interested in mapping specific regions of the genome. A POSA would have understood the broad approaches and sequencing goals of Meyer to be incompatible with the more narrow, targeted approaches and goals of Siebert. EX2038.¶314. Additionally, a POSA starting with Siebert would have no need for solutions addressing the homopolymer tails found only in RNA. *Id.*,¶315.

A POSA would also not have been motivated to use the Meyer method to sequence genomic DNA given that Meyer's solutions for read directionality and

adapter trimming are specific to using cDNA for sequencing. Genomic DNA cannot directly be converted into cDNA (unlike RNA). EX2038.¶313. For a POSA to use the Meyer methods, the POSA would be going out of their way to transcribe genomic DNA into RNA and then convert that to cDNA. *Id.* A POSA would have recognized that this would have been undesirable, especially given that genomic DNA can be sequenced as-is on NGS platforms like 454 and Illumina. *Id.* Additionally, any indirect conversion from genomic DNA to cDNA would then require the POSA to make inferences about the genomic DNA based on the presence of certain sequencing reads. This is because cDNA excludes all non-coding sequences (e.g., introns), which are present in genomic DNA. *Id.*,¶314. A POSA would not be able to use the Meyer methods to sequence these non-coding sequences. *Id.* This is why a POSA seeking to engage in “genome walking” as a means of understanding the boundaries of genomic DNA would not turn to Meyer, which relies heavily on cDNA synthesis.

Relatedly, a POSA starting from Meyer and seeking to modify it to selectively amplify genomic DNA for NGS would not have relied on Siebert. Siebert fails to address any issues specific to sequencing technology and predates NGS. EX1007; EX2038.¶311. Siebert also echoes a concern in the art that would have taught away from a POSA adapting Meyer to practice the claimed inventions with genomic DNA: “both ‘unpredictably primed PCR’ and ‘vectorette PCR’ generated multiple PCR

products even after nested PCR was performed.” EX1007.0001; EX2038.¶316. As Siebert explains, “the presence of multiple PCR products would complicate further characterization without Southern blot hybridization or extensive cloning.” *Id.* A POSA would have understood that to mean that these PCR methods introduced off-target binding and target specificity issues—issues that were especially salient for NGS platforms, which lacked any additional safeguards for promoting target capture. *Id.* Siebert confirmed that conclusion the next year in explaining how genome walking methods suffered from PCR amplification biases. *See id.*,¶317. A POSA would have understood Siebert’s teachings to be in line with other genome walking studies, which cautioned against using a single target-specific primer without additional mechanisms for promoting specificity. *Id.*

Petitioner also argues that “[a]s of the priority date, researchers were scrambling to adapt these decades-old genome-walking techniques for Next Generation Sequencing.” Paper 1, 65. But Petitioner’s expert disagreed. Dr. Sims testified at deposition that a POSA would not have looked to older, pre-NGS methods but would have instead sought to develop new methods that were specifically designed for NGS. EX2037.0003-04 (152:18-153:2). As such, Petitioner fails to demonstrate the requisite motivation to combine.

Petitioner further argues that a POSA would have had a reasonable expectation of success of combining Meyer with Siebert given “the past successful

use of anchored PCR with genomic DNA and/or Siebert.” Paper 1, 65. But Petitioner’s argument fails to address why a POSA would have expected a modified version of Meyer to work with genomic DNA. Siebert teaches that universal primer sequences (e.g., adapter sequences) could be used to prevent amplification of certain fragments. Siebert teaches that prior art PCR methods generated multiple, unintended PCR products after multiple rounds of amplification. EX1007.0001. Coupled with Siebert’s conclusion that the high specificity observed in the reported experiments was due to PCR suppression and not the use of a single, target-specific primer, a POSA would not have expected for a method that uses only one target-specific primer to succeed without some additional modification to improve specificity. EX2038.¶¶318-20. Siebert offers no guidance as to how to design an amplification scheme where the only fragments amplified are the fragments containing both adapter sequences. *Id.* And as described below, the art repeatedly demonstrated to the POSA how unlikely it would be to succeed in using just a single target-specific primer for target capture and selective amplification. As such, Petitioner fails to demonstrate the requisite expectation of success.

C. Ground 4 (Claims 11-12 and 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 11-12 and 19. *Id.*, 66. As explained above, Meyer fails to anticipate or render

obvious claim 1 of the '108 patent. Ground 4 fails to address the deficiencies in Grounds 1 and 2 with respect to the only independent claim of the '108 patent. Petitioner does not claim that Bronner or Caruccio teach the use of a single target-specific primer for enrichment. Paper 1, 66-69. Neither Meyer, Bronner, nor Caruccio teach enrichment through the use of a single target-specific primer and a universal primer pair. EX2038.¶326. As such, Ground 4 necessarily fails for at least the same reasons as Ground 1.

Ground 4 also fails because the prior art combinations do not render obvious the additional limitations of claims 11-12 and 19. Claim 11 using four labeled reversible terminators as part of the sequencing that occurs in the method of claim 1. Claim 19 requires the method of claim 17 where the surface is a flow cell. As Petitioner acknowledges, these methods are specific to Illumina NGS platforms. *Id.*, 66. Claim 11 requires using semiconductor sequencing with the method of claim 1. As Petitioner also acknowledges, this form of sequencing is specific to Ion Torrent NGS platforms. *Id.*, 68. None of the prior art references teach the claimed enrichment process nor using that process with Illumina and Ion Torrent NGS platforms.

Petitioner argues that a POSA would have been motivated to adapt Meyer for use with Illumina because, as Bronner disclosed, “the Illumina SBS sequencing by synthesis approach was the dominant sequencing technology.” Paper 1, 67 (cleaned

up). But Petitioner’s reasoning ignores that Illumina’s dominance in the market by the priority date would have been a reason for a POSA to not look back at Meyer, which was specific to fixing issues with the 454 sequencer. EX2038.¶328. Petitioner argues that a POSA would have been motivated to adapt Meyer for use with Ion Torrent because, as Bronner taught, Ion Torrent also used emulsion PCR to amplify template molecules onto beads and deposited those beads into “millions of wells of a semiconductor chip.” Paper 1, 68 (cleaned up). Those similarities, however, are not related to the specific improvements of Meyer. EX2038.¶329. Petitioner fails to argue how Meyer or Caruccio would have motivated a POSA to adapt Meyer for use with Illumina or Ion Torrent.

In fact, Bronner and Caruccio both teach away from required elements in the claimed methods. Bronner emphasizes multiple ways to reduce—not increase—sample biasing. A POSA would have understood that sample biasing in this case means the increase in the proportion of parts of the sample over others. Bronner teaches that “[e]xcessive PCR cycling should be avoided as it can lead to bias in the library.” EX1009.0015. Bronner also teaches the use of a specific polymerase “to amplify complex fragment libraries with the least amount of bias.” *Id.* Bronner disclaims a library preparation method that employs target-specific primer pairs, stating that “[u]nnecessary PCR amplification steps will exacerbate amplification biases, and so they should be avoided wherever possible.” *Id.*, 0017. Bronner

teaches that while “PCR amplification during library prep allows lower amounts of starting material to be used, [it] introduces bias.” *Id.*,.0019. For this reason, Bronner teaches a “PCR-free library method.” *Id.* That method does not “employ any target-specific primers or an amplification scheme to enrich for target sequences.” EX2038.¶331. As Dr. Bustamante explains, “a POSA considering Bronner’s teachings would not have been motivated to modify Meyer to promote target biasing and enrichment through its PCR amplification scheme.” *Id.*

Caruccio teaches methods that randomly fragment DNA and insert transposon ends onto the ends of the fragments. EX1008.0006. Those ends can then be used to generate oligonucleotide extension products that contain both universal adaptor sequences. *Id.* Because the transposomes can introduce transposon ends at both ends of double-stranded DNA, a POSA would have understood that this process could not be combined with using target-specific primers to incorporate universal primers. EX2038.¶332. A POSA considering Caruccio’s teachings would not have been motivated to modify Meyer to incorporate the universal primer sequences through the use of a partial duplex adapter and a target-specific primer. *Id.* A POSA also would not have been motivated to use transposomes, which insert at random points in DNA, to target specific sequences of interest. *Id.*

Petitioner argues that a POSA would have had a reasonable expectation of success in modifying Meyer for use with Illumina and Ion Torrent in light of

Caruccio. But neither Caruccio, Meyer, nor Bronner show the POSA how to practice the claimed invention given that none of the references teach target enrichment through a single target-specific primer. EX2038.¶333. There is no guidance as to how to modify Meyer’s amplification scheme to selectively target and enrich for specific fragments over others. *Id.* For these additional reasons, Ground 4 fails.

D. Objective Indicia of Nonobviousness

Objective indicia constitute independent evidence of nonobviousness and are often considered to “be the most probative and cogent evidence of nonobviousness.” *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012). Because of how probative this evidence is to the inquiry, objective indicia “must be considered in every case where present.” *Apple Inc. v. Samsun Elecs. Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (*en banc*).

1. The Prior Art Taught Away from and Expressed Skepticism for the Claimed Methods

“A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ... would be led in a direction divergent from the path that was taken by the applicant.” *Millennium Pharmas., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017). Additionally, “[i]f industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness.” *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317 (Fed. Cir. 2016). As Dr. Bustamante explains, a POSA

would have been aware of nearly two decades worth of literature by 2012 that demonstrated concerns with the amplification process on which the claimed methods rely, such as target specificity and off-target binding. EX2038.¶¶62-69, 100-03, 345-52 (compiling prior art disclosures). Additionally, publications concerning how to improve NGS library preparation methods emphasized the need for accurate target specificity. *Id.*

In particular, the prior art taught away from the use of a single target-specific primer for amplification, given concerns about specificity and off-target binding. *Id.* For example, Miura 2005 (EX2047) discloses that conventional PCR amplification “uses a pair of unique primers to selectively amplify the target sequence” and that specificity is achieved “by a synergistic effect between the specificities of the two primers.” EX2047.0001. Miura 2005 also discloses that pre-NGS, there were genome walking methods that departed from this convention by instead using only “a single unique primer in combination with a common primer.” *Id.* Miura 2005 teaches that these pre-NGS methods were understood to “often [be] plagued with non-specific amplification products derived from so-called ‘off-targets.’” *Id.*

Even Siebert recognized these issues as early as 1996—a year after the Siebert prior art reference relied on by Petitioner published. Siebert remarked that many genome walking methods suffered from “a high background of non-specific PCR products,” which often made “it necessary to do a second round of PCR with nested

primers to achieve greater specificity.” EX2038.¶346; EX2043.0002. Siebert explained that using PCR suppression could improve on the technique; however, Siebert also acknowledged that the amplification of some cDNA still yielded high levels of unwanted amplification products. *Id.* In those instances, Siebert recommended the use of additional, more complex methods to filter out background products. *Id.*

Nearly a decade and a half later, Sohn 2011 (EX2050) reiterated that while “many studies have been made to improve the genome walking method,” “it is still in need of improvement.” EX2038.¶349; EX2050.0003. Sohn explained that the “most serious problems of the PCR-based genome walking methods are low amplification efficiency and non-specific amplification.” *Id.* Sohn noted that to “improve this problem, complicated multi-step methods were developed, including secondary PCR, purification of desired PCR products using biotinylated primers, or improvement of PCR cycle conditions.” *Id.* Even then, “satisfactory performance [had] not yet been achieved.” *Id.*

More broadly, the art taught away from and expressed skepticism at various amplification methods. Tsoktouridis 2005 (EX2048) compared various PCR amplification methods and found “no simplicity, low reproducibility, high backgrounds of nonspecific PCR products, insufficient homopolymer tailing, small PCR product amplification, and laborious time-consuming procedures.”

EX2038.¶350. Prior art publications recognized that “the best way to avoid bias during PCR is to avoid library amplification by PCR altogether.” EX2042.0011. Quail 2008 (EX2053) and Kozarewa 2009 (EX2054) taught methods of adapter ligation that bypassed PCR amplification. EX2038.¶¶69, 351. Bronner and Quail taught that “[u]nnecessary PCR amplification steps will exacerbate amplification biases, and so they should be avoided wherever possible” and that it was possible to perform NGS without PCR amplification. EX1009.0018-19. In 2011, Quail reported that “[l]ibraries prepared without PCR amplification performed best.” EX2038.¶351; EX2071.0001. Based on this landscape, a POSA would have understood that the art was skeptical of PCR amplification and that the art taught away from using a single target-specific primer to amplify samples prior to NGS. EX2038.¶352.

1. There were long-felt, unmet needs to develop accurate target capture techniques for NGS that were cost-effective and efficient

“Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.” *WBIP*, 829 F.3d at 1332. In the mid- and late-2000s, practitioners recognized that the technology suffered from “the inability to easily target specific regions of a genome.” EX2038.¶353; EX2062.0003. Scientists acknowledged that new “sequence capture [(target specific)] methodologies [were]

required for time- and cost-effective sequence analysis in high-throughput genomic projects.” EX2038.¶353; EX2064.0001. But any viable method of targeting sequences would require accuracy and efficiency. EX2038.¶353. The art continued to emphasize concerns with off-target specificity. For example, Kelly reported that even with primer pairs, unintentional amplification of unwanted sequences was prevalent, which led to discarding half of the sequencing reads. *Id.*; EX1010.0005.

The targeted library preparation methods at the time relied on complex, specialized instrumentation. EX2038.¶354; EX2062.0002-07; EX2064.0001-02. Practitioners viewed PCR-based methods as “laborious, time-consuming and costly” and where multiplexed, “difficult to check successful amplification per fragment,” increasing the “chance of obtaining artifacts.” EX2038.¶355; EX2051.0003. The lack of target-specific methods not requiring specialized instrumentation resulted in cost-conscious researchers re-using instruments, like hybridization arrays, despite risks of sample contamination. *Id.*, ¶354. Caruccio recognized at the time that “there is greater demand for cost-effective, streamlined library preparation methods.” EX2056.0001. Caruccio’s solution (Nextera) attempted to improve efficiency by sacrificing target specificity—Nextera uses transposition to randomly fragment and tag DNA fragments. *Id.* While that solution was viable for certain applications, it failed to address target capture concerns. EX2038.¶354.

Despite considerable work in the field to address these needs, the solutions developed fell short of resolving the problems. One review of the prior art as of 2011, just before the priority date of the '108 patent, determined that the three categories of targeting methods (PCR, circularization, and hybrid capture) all suffered from varying degrees of “uniformity, efficiency of coverage and off-target capture.” EX1050.0007. Given the problems, Moorthie taught that “it may ultimately be more cost-effective to sequence a whole genome” rather than use target capture. *Id.*

These needs remained unmet until the claimed inventions. One month before the priority date, researchers noted that current target enrichment and sequencing library preparation methods were “laborious, time-consuming, prone to experimental errors and difficult to automate.” EX2052.0002. These researchers complained that the methods had “complex protocols which require large amounts of starting genomic DNA” and that they were “susceptible to coverage biases secondary to amplification and molecular artifacts.” *Id.* The researchers proposed a form of capture by circularization that failed to address the high number of custom oligonucleotides required. EX2038.¶356. Before the claimed methods, the field did not have an efficient solution for targeting portions of the genome for sequencing.

2. Industry Praised the Claimed Inventions

Industry praise “provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected” the claimed invention to succeed. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). As reflected by praise from the industry, the claimed inventions, as embodied in NuGEN and Tecan’s SPET products, addressed the long-felt, unmet needs in the art. As Dr. Bustamante explains, NuGEN and Tecan’s SPET products were designed to perform the claimed methods. EX2038.¶¶335-43 (demonstrating nexus between the claimed inventions and commercial embodiments). Tecan’s Ovation and Allegro products are coextensive with the claimed methods. *Id.* The products also embody the unique SPET covered by the claimed methods. *Id.*

After release of these products, the field praised the convenience and efficiency that the products provided. One study conducted by Italian and Spanish research institutions and funded by the European Union described the claimed technology as “a new, robust, customizable solution for targeted genotyping.” EX2038.¶359; EX2065.0001. It also described the technology as “a customizable solution for targeted sequencing at an affordable price.” EX2065.0002. As explained by Barchi, the claimed technology’s “reliance on single primers, rather than on primer pairs, greatly simplifies panel design, and allows higher levels of

multiplexing than PCR-based genotyping.” *Id.* Barchi concluded that the technology “performed well with DNA samples prepared by different laboratories using different DNA mini-preparation protocols,” that it provided “the ability of multiplexing thousands of samples in a single sequencing run,” and that it “allow[ed] the discovery of thousands of novel SNPs not originally included in the panel.” *Id.*,.0013

These findings are echoed in other industry publications. An editorial in Biocompare’s Future Lab (which is exclusively sponsored by Petitioner) extols a Tecan commercial embodiment of the claimed inventions, explaining that “[u]sing single primers instead of primer pairs greatly simplifies the design of primer panels, and allows higher levels of multiplexing compared to amplicon-based enrichment.” EX2038.¶360; EX2067.0003. In a study performed by Italian and British research institutions, the researchers explained that “[u]nlike other methods, [the claimed] technique allows for the execution of cost-effective genotyping experiments while providing full control on target sites,” which it attributed in part to the “high efficiency enrichment system” and “the scalability to tens of thousands of probes in a single reaction.” EX2038.¶361; EX2068.0006. It reported that the study “results suggest that [the claimed] SPET genotyping is a very effective approach for genotyping a large number of loci,” and “suggest[ed] that it might be a valuable tool for large-scale genotyping studies in virtually all species.” EX2068.0008. Another

study conducted by the famed Jackson Laboratory for Genomic Medicine and Baylor College of Medicine described a commercial embodiment of the claimed inventions as “widely used for genotyping” and an adaptation “as a quantitative, straightforward, and cost-effective method for profiling mouse microbial communities.” EX2038.¶362; EX2069.0002.

In sum, the claimed methods resolve what were long-felt, unmet needs in the art for NGS library preparation methods that were target specific, cost-effective, and efficient. The inventors developed these methods despite the prior art teaching away from and expressing skepticism towards both the use of a single target-specific primer for targeted enrichment and amplification as a library preparation step. These secondary considerations bolster the novelty and nonobviousness of the claimed methods.

V. CONCLUSION

For the foregoing reasons, Tecan respectfully requests that the Board reject Petitioner’s arguments and instead affirm that the claimed methods are novel and nonobvious.

Dated: July 18, 2025

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Response** complies with the type-volume limitation of 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(b)(1). The Response contains 12,272 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system use to prepare the Response.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on October 14, 2025, a copy of the foregoing **Patent Owner's Response** and all supporting documents were served on the counsel of record for Petitioner by delivering a copy via electronic mail to the following addresses:

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