

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN SCIENCES, LLC,
Petitioner,

v.

TECAN GENOMICS, INC.,
Patent Owner.

IPR2025-00028
Patent 10,036,012 B2

Before DEBORAH KATZ, ZHENYU YANG, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

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

I. INTRODUCTION

QIAGEN Sciences, LLC (“Petitioner”) filed a Petition (Paper 2, “Pet.”), seeking *inter partes* review of claims 1–15 and 17–22 of U.S. Patent No. 10,036,012 B2 (Ex. 1001, “the ’012 patent”). Tecan Genomics, Inc. (“Patent Owner”) filed a Preliminary Response. Paper 6 (“Prelim. Resp.”).

We have authority under 35 U.S.C. § 314, which provides that an *inter partes* review may not be instituted “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a).

For the reasons provided below, we determine Petitioner has satisfied the threshold requirement set forth in 35 U.S.C. § 314(a). We decline to deny the Petition on the basis of discretion under § 325(d). We institute *inter partes* review of all challenged claims based on all the grounds raised in the Petition.

A. Related Matters

The parties inform us that Patent Owner asserted the ’012 patent against Petitioner in *Tecan Genomics, Inc. v. QIAGEN Sciences, LLC*, Case No. 1:23-cv-01115 (D. Del.). Pet. 2; Paper 3, 1. In that case, Patent Owner also asserted three other patents. Pet. 2; Paper 3, 1. Petitioner concurrently filed three other petitions, challenging the claims of those patents. Pet. 2–3; Paper 3, 1.

Patent Owner also asserted the ’012 patent and the other patents in *Tecan Genomics, Inc. v. Invitae Corp.*, Case No. 1:23-cv-01114 (D. Del.). According to Patent Owner, Integrated DNA Technologies, Inc. filed several petitions for *inter partes* review, challenging the claims of those asserted patents. Paper 3, 1.

B. The '012 Patent

The '012 patent issued from U.S. Patent Application No. 15/471,785 (“the '785 application”). Ex. 1001, code (21).

The '012 patent “provides methods, compositions and kits for targeted nucleic acid sequence enrichment in a nucleic acid sample and for high efficiency nucleic acid library generation for next generation sequencing (NGS).” *Id.* at Abstract; *see also id.* at 2:34–36 (disclosing “methods for enriching for target nucleic acid sequences of interest in a sample comprising nucleic acids”).

The '012 patent states that, with the rapid development of NGS technologies and platforms, whole genome sequencing became more feasible and less expensive. *Id.* at 1:16–18. It was nonetheless “often more practical and cost-effective to select genomic regions of interest for sequencing and analysis.” *Id.* at 1:23–27.

Target enrichment was commonly used in genomic DNA sequencing to selectively capture genomic regions of interest from a DNA sample before sequencing. *Id.* at 1:28–30. At the time of the '012 patent invention, there were three major categories of target enrichment methods, including PCR-based methods, capture-by-hybridization, i.e., on-array or in-solution hybrid capture methods, and capture-by-circularization, i.e., molecular inversion probe-based methods. *Id.* at 1:42–47. According to the '012 patent, each of these methods has its distinct advantages and disadvantages. *Id.* at 1:43–44.

The '012 patent explains that “[t]here is 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.

Additionally, there is a need for high efficiency nucleic acid library generation.” *Id.* at 2:25–29. The ’012 patent purports to address both of these needs. *Id.* at 2:29–30.

Figure 1 of the ’012 patent, reproduced below, is schematic of a preferred embodiment of the methods for enriching for target sequences of interest. *Id.* at 15:57–59.

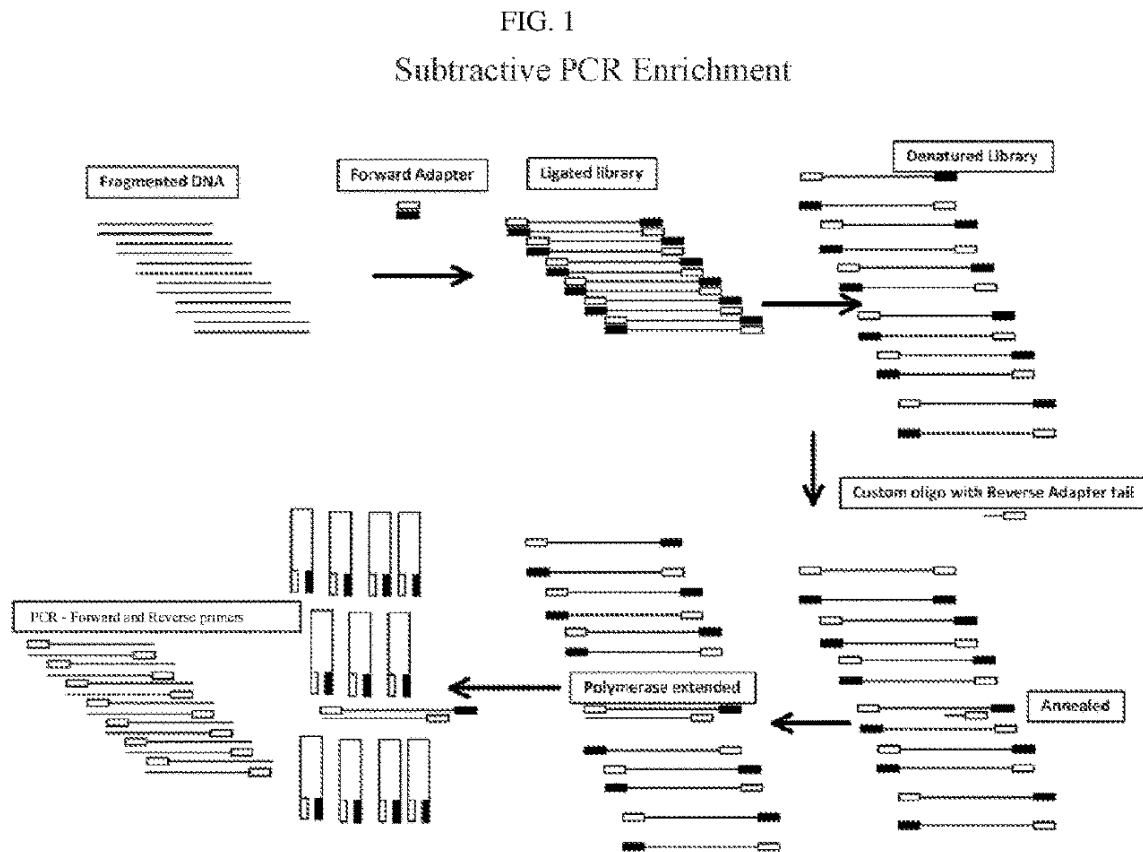


Figure 1 above depicts a method of selective target enrichment using ligation of a single forward adaptor at the ends of the DNA fragments in the DNA library. *Id.* at 5:47–49. The method is discussed in more detail below.

First, the method generates a ligated library of nucleic acid fragments or inserts in which

each fragment or insert of the ligated library comprises a common forward adaptor and a fragment or insert specific

reverse adaptor distinct from the forward adaptor such that subtractive PCR using a primer directed against the common forward adaptor and a primer directed against the reverse adaptor enriches for a nucleic acid fragment or insert comprising a target nucleic acid sequence.

Id. at 15:63–16:5.

Second, the DNA fragments with complementary ends are denatured to generate a denatured library of single stranded DNA fragments with complementary ends. *Id.* at 16:54–57.

Third, “a custom oligonucleotide with a reverse adaptor tail is annealed to the single stranded DNA fragments with complementary ends.”

Id. at 16:61–63.

Fourth, the custom oligonucleotide with a reverse adaptor tail is extended to generate an oligonucleotide extension product with a forward adaptor sequence at one end and a reverse adaptor sequence at the other end.

Id. at 17:37–48.

Finally, subtractive PCR is “performed using a first primer directed against the forward adaptor sequence and a second primer directed toward the reverse adaptor sequence such that 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.” *Id.* at 17:53–60.

C. Illustrative Claim

Independent claim 1 is illustrative of the claimed subject matter and is reproduced below.

1. A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
 - 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;

- 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;
- 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;
- 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;
- 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
- f) sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

Ex. 1001, 35:18–57.

D. Asserted Challenges to Patentability

Petitioner asserts the following challenges to patentability:

Claims Challenged	35 U.S.C. § ¹	Reference
1, 2, 5, 6, 11–15, 17–20, 22	103(a)	Shapero, ² Delseny ³
7–10	103(a)	Shapero, Delseny, Hamady ⁴
3, 4, 21	103(a)	Shapero, Delseny, Jones ⁵

In support of their respective positions, Petitioner relies on the Declaration of Michael L. Metzker, Ph.D. (Ex. 1003), and Patent Owner relies on the Declaration of Carlos D. Bustamante, Ph.D. (Ex. 2028).

II. PRIOR ART DISCLOSURE

A. Jones

Jones was cited by the Examiner during the prosecution of the '785 application. Ex. 1002, 296. Jones is directed to “[m]ethods for genotyping

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. AIA §§ 3(b), 3(c), and 3(n). The '012 patent claims priority to a provisional application filed on January 26, 2012. Ex. 1001, code (60). Petitioner’s challenge assumes this earliest potential priority date (Pet. 7 n.1) and Patent Owner provides no argument to the contrary. Accordingly, we apply the pre-AIA version of §§ 102 and 103.

² Shapero et al., *MARA: a novel approach for highly multiplexed locus-specific SNP genotyping using high-density DNA oligonucleotide arrays*, 32 (e181) NUCLEIC ACIDS RES. 1–9 (2004) (Ex. 1006, “Shapero”).

³ Delseny et al., *High throughput DNA sequencing: The new sequencing revolution*, 179 PLANT SCI. 409–22 (2010) (Ex. 1007, “Delseny”).

⁴ Hamady et al., *Microbial community profiling for human microbiome projects: Tools, techniques, and challenges*, 19 GENOME RES. 1141–52 (2009) (Ex. 1033, “Hamady”).

⁵ U.S. Patent Publication No. 2005/0142577 (Ex. 1011, “Jones”).

polymorphisms using a locus specific primer that is complementary to a region near a selected polymorphism.” Ex. 1011, Abstract.

It teaches

methods for highly multiplexed locus specific amplification of nucleic acids and methods for analysis of the amplified products. In preferred embodiments the amplified targets prepared using Multiplexed Anchored Runoff Amplification (MARA) are analyzed to determine the genotype of SNPs. In some embodiments the invention combines the use of capture probes that comprise a common sequence and a locus-specific region with adaptor-modified sample nucleic acid; the adaptor comprises a second common sequence. The capture probes are extended to produce copies of the sample DNA that contain common priming sequences flanking the target sequence. The copies are amplified with a generic set of primers that recognize the common sequences. The amplified product may be analyzed by hybridization to an array of probes.

Id. ¶ 76.

B. Shapero

Two of the co-authors of Shapero are also co-inventors of Jones. *Compare* Ex. 1006, 1,⁶ *with* Ex. 1011, code (75). Like Jones, Shapero also teaches “a locus-specific DNA target preparation method for highly multiplexed single nucleotide polymorphism (SNP) genotyping called MARA.” Ex. 1006, 1. Figure 1 of Shapero shows the general method and is reproduced below.

⁶ The Petition cites the native page numbers as shown in the Shapero reference, whereas the Preliminary Response cites the page numbers of the Exhibit. Unless otherwise noted, we cite the native page numbers of all Exhibits. For consistency, we request the parties do the same in future filings in this proceeding.

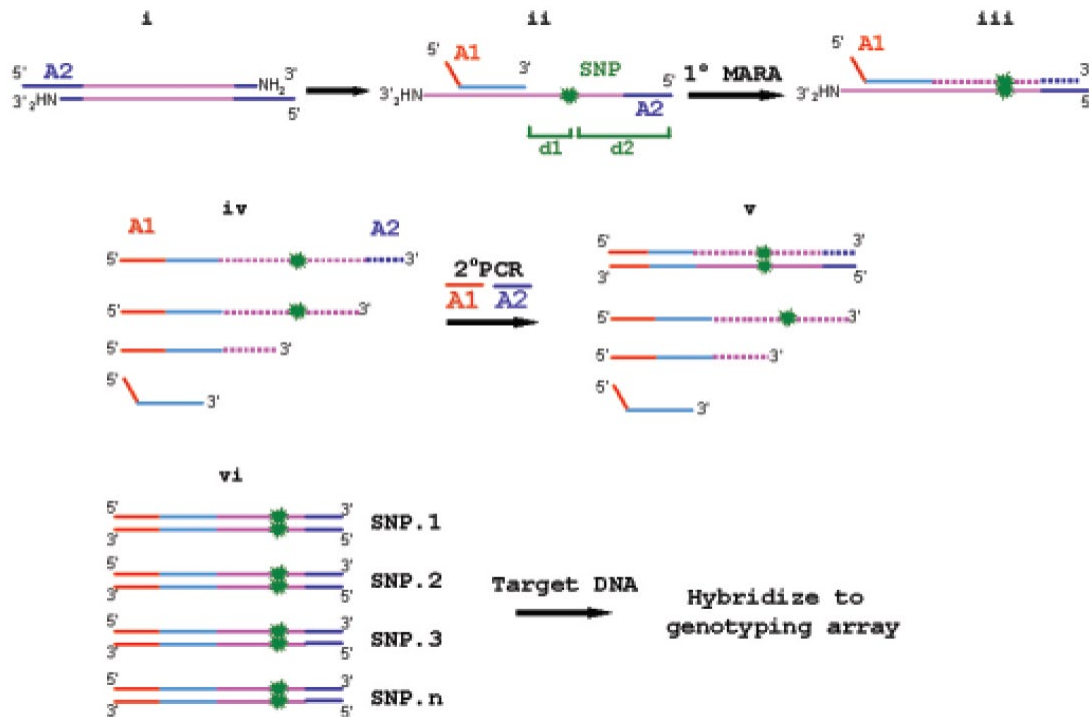


Figure 1 is an overview of the MARA method. *Id.* at 4. Panel (i) shows “[h]uman genomic DNA (pink) is digested to completion with a restriction enzyme and ligated to adapters (blue).” *Id.* In panel (ii), “[a] MARA forward primer (containing common sequence A1) is shown annealing to the bottom strand of DNA upstream of a SNP (green symbol).” *Id.* This primer contains a “common sequence at the 5′ end (designated A1) followed by locus-specific sequence (~25 bases) at the 3′ end.” *Id.* at 3. Panel (iii) shows “[t]he primary MARA reaction involves multiple cycles of primer annealing and extension, which can lead to a full-length extension product (dashed line) that has copied the adapter sequence (A2) from the genomic DNA template.” *Id.* at 4. At the completion of cycling, the reaction may contain, among others, full-length extension products, as shown in panel (iv). *Id.* Panel (v) shows that PCR with primer A2 converts “full-length extension products (which contain an A2 primer annealing site)

into double-strand DNA.” *Id.* “Subsequent cycles of secondary PCR with universal A1 and A2 primers amplify all full-length products derived from the first round locus-specific reaction.” *Id.* MARA target DNA is then prepared for hybridization to genotyping array. *Id.*

In Shapero, the hybridization results “were analyzed by discrimination score (DS) as well as call rate (percentage of successful genotype calls within a DNA sample).” *Id.* Shapero teaches that “if the DS for a SNP from a particular sample is <0.08 , the specificity of the hybridization signal is considered weak.” *Id.* at 4–5. For the 250-plex MARA, Shapero reports “[a] total of 99.4% of the SNPs targeted by locus-specific primers across nine individuals had a mean $DS > 0.08$,” with the targeted SNPs having a mean call rate of 96.2%, whereas “when locus-specific primers were omitted in the primary reaction, 6.6% (of the 258 SNPs) had a mean $DS > 0.08$,” with a mean call rate of 6.3%. *Id.* at 5. Shapero reports similar data for the 750-plex MARA. *Id.* Shapero states that “[t]hese results show that the presence of locus-specific primers allows specific target sequences to be amplified, and in the absence of primers, only small quantities of non-specific products are generated.” *Id.*

C. Delseny

Delseny reviews next-generation sequencing technologies (NGST). Ex. 1007, 408. One class of NGST involves “sequencing by synthesis from amplified molecules distributed in microarrays.” *Id.* Specifically, Delseny describes Illumina technology:

Small DNA fragments are amplified on a solid substrate by “bridge PCR”. The DNA fragments are ligated with 5' and 3' adaptors and denatured, thus resulting in an *in vitro* library of DNA fragments. The fragments are hybridized to a series of forward and reverse primers immobilized on the substrate that

correspond to the adaptors used to prepare the library. During PCR amplification . . . the amplicons resulting from a given fragment . . . form[] a cluster of ~1000 copies of a single fragment. Several million clusters can be accumulated within each of the independent arrays (channels) present in the flow cell, where the sequencing reactions take place. The amplicons are made single-stranded, and a universal sequencing primer is hybridized and extended with modified nucleotides. Each modified nucleotide acts as a terminator: it is labelled with a distinct fluorochrome that is chemically cleavable, so that DNA synthesis is reversibly stopped at each position. An image is recorded at each cycle in four channels so that the nucleotide incorporated in each independent cluster can be determined. Then the cleavable moieties of the incorporated nucleotides are removed, and the cycle is repeated, thus allowing the incorporation of the next nucleotide.

Id. at 410 (internal citations omitted).

D. Hamady

Hamady teaches tools and techniques available to study “human microbiota (the collection of microbes that live on and inside us).” Ex. 1033, 1141. According to Hamady, pyrosequencing “is orders of magnitude cheaper and faster” compared to traditional Sanger-based approaches. *Id.* at 1143. Hamady describes barcoded pyrosequencing using molecular barcoding techniques, in which “[s]equences in each sample are tagged with a unique barcode either by ligation or, for amplicon sequencing, by using a barcoded primer when amplifying each sample by PCR.” *Id.* Hamady explains that “[a]fter sequencing, individual sequences can then be traced back to individual samples using the barcodes they contain.” *Id.* at 1144.

III. DISCRETIONARY DENIAL

Institution of an *inter partes* review is discretionary. *See Cuozzo Speed Techs., LLC v. Lee*, 579 U.S. 261, 273 (2016) (explaining that because 35 U.S.C. § 314 includes no mandate to institute review, “the agency’s

decision to deny a petition is a matter committed to the Patent Office’s discretion”); *see also Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1367 (Fed. Cir. 2016) (stating that under § 314(a), “the PTO is permitted, but never compelled, to institute an IPR proceeding”).

Under 35 U.S.C. § 325(d), in determining whether to institute an *inter partes* review, “the Director may take into account whether, and reject the petition or request because, the same or substantially the same prior art or arguments previously were presented to the Office.” Our § 325(d) analysis employs a two-prong framework: (1) whether the art or arguments presented in the petition are the same or substantially the same as those previously presented to the Office; and (2) if so, whether the petitioner has demonstrated a material error by the Office in its prior consideration of the art or arguments. *Advanced Bionics, LLC v. Med-El Electromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, 8 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

Patent Owner argues that we should exercise our discretion to deny institution under § 325(d). Prelim. Resp. 15–29. According to Patent Owner, “Petitioner relies on art that discloses the same information as what was considered during prosecution and makes the same obviousness arguments raised by the Examiner.” *Id.* at 16. In addition, Patent Owner asserts that “Petitioner fails to demonstrate a material error by the Office.” *Id.* at 22. We are not persuaded by Patent Owner’s arguments.

A. Relevant Prosecution History of the '012 Patent

During prosecution of the '785 application, the Examiner rejected the then-pending claims as obvious over, among other references, the combination of Jones and Tucker.⁷ Ex. 1002, 296.

In response, the applicant submitted a declaration of Dr. Andrew Brooks. *Id.* at 2015–17. Dr. Brooks explained that “the claimed methods involve annealing and extending a target-specific primer to enrich a sequence of interest (rather than, for example, annealing a forward target-specific and reverse target-specific primer pair at a sequence of interest and performing a polymerase chain reaction with the forward target-specific and reverse target-specific primer).” *Id.* at 2015. He stated that he “was skeptical that the claimed methods would provide efficient sequencing data.” *Id.* He further testified that he “observed unexpected results when enriched nucleic acid sequences generated using the claimed methods were sequenced by massively parallel sequencing.” *Id.* at 2016; *see also id.* (“Based on my knowledge and experience in this field, I did not expect and would not have predicted this level of specificity.”).

Relying on Dr. Brooks’ testimony, the applicant argued that “the secondary considerations of skepticism of an expert and unexpected results as described by Declarant outweigh the evidence supporting the *prima facie* case of obviousness.” *Id.* at 2010; *see also id.* (“Declarant’s insights about the specificity of the claimed methods and the generation of unexpected results render the claimed methods nonobvious.”).

⁷ Tucker et al., *Massively parallel sequencing: the next big thing in genetic medicine*, 85 Am. J. HUMAN GEN. 142–54 (2009) (Ex. 1013, “Tucker”).

The Examiner found Dr. Brooks' declaration sufficient to overcome the obviousness rejections and allowed the claims. *Id.* at 2055–56.

B. Analysis

Petitioner asserts that (1) the combination of Shapero and Delseny renders claims 1, 2, 5, 6, 11–15, 17–20, and 22 obvious; (2) the combination of Shapero, Delseny, and Hamady renders claims 7–10 obvious; and (3) the combination of Shapero, Delseny, and Jones renders claims 3, 4, and 21 obvious. Pet. 24–55.

Petitioner represents, and Patent Owner does not dispute, that Delseny and Hamady were not before the Examiner during prosecution of the '785 application. *Id.* at 57. Patent Owner, however, argues that, in the Petition, “Delseny is used for the same reason as Tucker” was used during prosecution. Prelim. Resp. 20 (arguing Delseny “simply discloses sequencing on a massively parallel sequencing platform, just as Tucker does”). After reviewing Patent Owner's analysis, we agree with Patent Owner that Petitioner's reliance on Delseny does not materially differ from the Examiner's reliance on Tucker. *Id.* at 20–21.

Petitioner represents, and Patent Owner does not dispute, that Shapero was not before the Examiner during prosecution of the '785 application. *Id.* at 57. Jones was before the Examiner during prosecution. *See* Ex. 1002, 296. Petitioner, however, points out that, in the Petition, “Jones is only being cited with respect to one ground involving three dependent claims and that ground also involves Shapero and Delseny, which were not before the Examiner.” Pet. 57–58. As such, Petitioner argues, “the inclusion of Jones in one ground does not weigh in favor of denial.” *Id.* at 58. Patent Owner does not challenge this assertion. *See generally* Prelim. Resp.

Petitioner acknowledges that both Shapero and Jones “teach the same MARA technology.” Pet. 57. According to Petitioner, however, Shapero’s experimental results “demonstrate high target specificity achieved by the MARA method, which is absent in Jones. For this reason, Shapero is not cumulative compared to Jones.” *Id.*

Patent Owner disagrees. Patent Owner contends that “Shapero’s data is cumulative of the disclosures of Jones” because it “does not alter the teachings of Jones,” but “merely confirms the conclusions of Jones.” Prelim. Resp. 17. Specifically, Patent Owner asserts that “the data in Shapero does not reflect the use of the MARA method with an NGS platform. Instead, MARA was used with a hybridization array, the same technology claimed in Jones.” *Id.* at 19 (emphasis omitted). According to Patent Owner, NGS and hybridization array technologies use “different techniques and require attention to different factors to achieve reliable, usable data.” *Id.* at 19–20 (citing Ex. 2028 ¶¶ 81–87). Because “Shapero’s data using the hybridization assay does not speak to whether the method would work with NGS,” Petitioner concludes that “[t]he data in Shapero, therefore, is cumulative of the disclosures of Jones.” *Id.* (citing Ex. 2028 ¶¶ 153–163).

On this record, we do not need to resolve this dispute, because even if Shapero is cumulative of the disclosures of Jones, Petitioner has shown that the Office erred in a manner material to the patentability of challenged claims. *See* Pet. 38–43, 58–59; *Advanced Bionics* at 8.

During prosecution, the applicant traversed the obviousness rejection based on Jones and Tucker by relying on evidence of secondary considerations as shown in the Brooks Declaration. Ex. 1002, 2007–12. The

applicant argued that “[t]he secondary [considerations] evidence outweighs evidence supporting the *prima facie* case” of obviousness. *Id.* at 2010.

To accord substantial weight to evidence of secondary considerations, it “must have a nexus to the claims, *i.e.*, there must be a legally and factually sufficient connection between the evidence and the patented invention.” *Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1417 (Fed. Cir. 2022) (internal quotation marks omitted); *see also In re Kao*, 639 F.3d 1057, 1069 (Fed. Cir. 2011) (instructing that “the Board, in considering the evidence of unexpected results, should determine whether there is a nexus between the unexpected [results] and aspects of the claimed invention not already present in the prior art”). Moreover, “when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.” *In re Baxter Travenol Laboratories*, 952 F.2d 388, 392 (Fed. Cir. 1991).

On this record, it is unclear what Dr. Brooks considered to be the closest prior art when he alleged unexpected results. *See* Ex. 1002, 2013–17. We also find no persuasive evidence in either Brooks Declaration or the Examiner’s analysis on the requisite nexus. *See id.*, 2055–56. As a result, we agree with Petitioner that “the Examiner erred in exclusively relying on Dr. Brooks’ declaration” to withdraw the obviousness rejection based on Jones and Tucker. *See* Pet. 58.

C. Conclusion

Because Petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims, we decline to exercise our discretion to deny the Petition under § 325(d).

IV. ANALYSIS

A. Level of Ordinary Skill in the Art

In determining the level of ordinary skill in the art, various factors may be considered, including the “type of problems encountered in the art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *In re GPAC, Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). Furthermore, the prior art itself can reflect the appropriate level of ordinary skill in the art. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001).

Petitioner asserts that:

A person of ordinary skill in the art [“POSA”] as of the earliest priority date of the ’012 patent (January 26, 2012) would have had (i) a Ph.D. in molecular biology, molecular genetics, bioinformatics, biochemistry, or a related field and at least two years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and sequencing experience, including but not limited to high-throughput sequencing technologies or (ii) a Master’s degree in one of the same fields with at least four years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and high-throughput sequencing technologies.

Pet. 13–14 (citing Ex. 1003 ¶ 39).

Patent Owner disagrees with Petitioner’s proposed definition. Prelim. Resp. 11–12. Patent Owner contends that “[b]y 2008, NGS sequencing technologies were performed in laboratories according to published protocols and would have been accessible to experienced laboratory technicians and graduate students.” *Id.* Thus, Patent Owner argues that Petitioner’s proposed definition of the skill level is “higher than ordinary.” *Id.* at 12 (citing Ex. 2028 ¶¶ 88–91). According to Patent Owner, a “POSA would have a Ph.D. in a field related to molecular biology, or a B.S. or M.S.

degree with three-to-five years of experience working in a molecular biology lab.” *Id.*

We find Patent Owner’s proposed definition of the skill level insufficient. As Patent Owner recognizes, the challenged claims relate to sequencing methods using a next-generation sequencing (“NGS”) platform. *See id.* at 8; *see also* Ex. 1001, 35:56–57 (claim 1 reciting “sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform”). Also, as Patent Owner recognizes,

[c]ompared 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 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.

Prelim. Resp. 5 (internal citations omitted). As such, we disagree with Patent Owner that a POSA only need to have education “in a field related to molecular biology” or experience “in a molecular biology lab,” because an artisan having only experience with pre-NGS sequencing methods would not qualify as a POSA.

Instead, for purposes of this Decision, we find a POSA would have had a Ph.D. in molecular biology, molecular genetics, bioinformatics, biochemistry, or a related field. 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. This definition of a POSA is consistent with the skill level reflected in the disclosures of the ’012 patent and prior art. We further note

that our decision to institute review remains the same under either party's proposed definition of the skill level.

B. Claim Construction

In an *inter partes* review, we construe a claim term “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100(b) (2020). Under that standard, the words of a claim “are generally given their ordinary and customary meaning,” which is “the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application.” *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). On this record and for purposes of this Decision, we see no need to construe any claim term expressly.

C. Alleged Obviousness over Shapero and Delseny

Petitioner asserts that the combination of Shapero and Delseny renders claims 1, 2, 5, 6, 11–15, 17–20, and 22 obvious. Pet. 24–51. Based on this record, and for at least the following reasons, we determine Petitioner has established a reasonable likelihood that it would prevail in this assertion.

We focus our analysis on independent claim 1. Petitioner provides detailed analysis to support its argument that the combination of Shapero and Delseny teaches each limitation of claim 1. *Id.* at 24–43. Specifically, Petitioner argues that Shapero teaches the preamble and steps a) through c). *Id.* at 24–31. For step d), Petitioner contends that Shapero teaches the part of “amplifying the one or more oligonucleotide extension products . . . to

enrich for the nucleic acid sequence of interest” (*id.* at 31–32) and Delseny teaches the part of “wherein products of the amplifying comprise a 3’ end with sequence complementary to a sequence on a surface” (*id.* at 32–34). Petitioner asserts that Delseny also teaches steps e) and f). *Id.* at 43.

Patent Owner does not dispute Petitioner’s mapping of claim 1’s limitations to the asserted prior art. *See generally* Prelim. Resp. On this record, we find Petitioner’s analysis persuasive and adopt it as our own. Pet. 24–43. Thus, we find that the combination of Shapero and Delseny teaches each limitation of claim 1.

Petitioner argues that “[a] POSA would have been motivated to combine the enrichment methods of Shapero with the NGS technologies described in Delseny and had a reasonable expectation of success.” Pet. 34–38. Petitioner contends that Delseny recognizes NGS as “a replacement for genotyping described in Shapero.” *Id.* at 36. In addition, according to Petitioner, Shapero, which cites Syvänen,⁸ “teaches that its enrichment methods can be used with the sequencing technologies that existed.” *Id.* at 35 (citing Ex. 1003 ¶ 158). Petitioner asserts that “[a] POSA would have been further motivated to utilize the enrichment methods of Shapero in connection with the NGS technologies described in Delseny given the experimental data in Shapero.” *Id.* Petitioner argues that “[a] POSA also would have had a reasonable expectation of success utilizing Shapero’s enrichment methods with the NGS technologies described in Delseny.” *Id.* at 37.

⁸ Syvänen, *Accessing genetic variation: genotyping single nucleotide polymorphisms*, 2 NATURE REV. GEN. 930–42 (2001) (Ex. 1012, “Syvänen”).

Patent Owner disagrees. Prelim. Resp. 29–51. Patent Owner contends that a POSA would not have had a motivation to combine Shapero’s hybridization array method with Delseny’s NGS because they are different technologies with fundamental differences. *Id.* at 29. According to Patent Owner, Petitioner’s motivation-to-combine arguments are predicated on impermissible hindsight. *Id.* at 29–31. Patent Owner also asserts that a POSA would not have had a reasonable expectation of success in combining Shapero and Delseny to practice the claimed inventions. *Id.* at 43. Patent Owner faults Petitioner for its “overreach as to what can be inferred from [Shapero’s] data about enrichment.” *Id.* at 44. Patent Owner further argues that “the data reported by Shapero demonstrates that MARA suffered from undeterminable deficiencies that could have been fatal to use with NGS.” *Id.* at 46.

On this record and for purposes of institution, we find Petitioner has shown adequately a motivation to combine the Shapero’s enrichment method with Delseny’s NGS technology and a reasonable expectation of success in doing so. We address Patent Owner’s arguments below.

Patent Owner contends that “Delseny teaches away from the claimed methods” because “Delseny cautions against using NGS for the exact genotyping described in Shapero.” Prelim. Resp. 32. According to Patent Owner, “Delseny expresses concerns with the use of NGS for genotyping SNPs due, in part, to errors in base-calling, sequencing read artifacts, and higher false discovery rates.” *Id.* (citing Ex. 1007, 411, 417). Patent Owner emphasizes that “Delseny instead recognizes the pre-NGS Sanger method as the ‘gold standard.’” *Id.* at 33 (citing Ex. 1007, 411). Patent Owner concludes that “Delseny’s concerns and endorsement of pre-NGS Sanger

sequencers would have taught away from using MARA with NGS given the heightened need for read fidelity for the SNP genotyping performed in Shapero.” *Id.* (citing Ex. 2028 ¶¶ 168–171). We are not persuaded by this argument.

It is true that Delseny recognizes the limitations and challenges of NGS. Ex. 1007, 411, 417. But the language in Delseny that Patent Owner identifies does not amount to teaching away, which requires that prior art references “criticize, discredit, or otherwise discourage the solution claimed.” *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). Instead, Delseny notes the limitations of hybridization technology in genotyping. Ex. 1007, 417. According to Delseny, “[t]he ultimate resolution is at the base-pair level and NGSTs now open the possibility to genotype a line by sequencing it.” *Id.* In fact, Delseny specifically teaches that NGS “can substitute for the genotyping microarray strategy because of its higher resolution.” *Id.*

Patent Owner argues that Petitioner’s proposed combination destroys the purpose of Shapero. Prelim. Resp. 41. Patent Owner contends that Shapero’s hybridization array ensures accuracy whereas NGS is less reliable. *Id.* at 41–42 (citing Ex. 2028 ¶¶ 42, 61, 131, 153–163, 170). We are not persuaded by this argument either.

As Patent Owner recognizes, Shapero explains that “[i]n order to leverage the power of SNPs in genetic studies, novel target preparation methods need to be developed that, when combined with methods for allele discrimination, allow rapid and accurate genotypic information at a fraction of the cost of current approaches.” *Id.* at 41 (quoting Ex. 1006, 2) (emphasis removed). Although Patent Owner emphasizes the accuracy aspect of it,

Shapero in fact desires a method that balances accuracy with speed and cost. Ex. 1006, 2. And NGS appears to fit the bill. Indeed, Patent Owner explains that “[a]s 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.” Prelim. Resp. 5 (citing Ex. 2028 ¶ 59).

Patent Owner faults Petitioner for “identif[ying] no prior art references considering the use of a single target-specific primer with NGS.” Prelim. Resp. 49; *see also id.* at 50 (“Petitioner’s silence on prior art solutions that rely on single primer enrichment to solve problems specific to NGS speaks volumes as to why a POSA would not have had a reasonable expectation of success.”). Petitioner’s challenge, however, rests on obviousness, and not anticipation. Thus, the fact that Petitioner does not present a reference that discloses both single primer enrichment method and NGS technology is not fatal to its case. And when it comes to reasonable expectation of success, the test requires neither absolute predictability nor actual success in the prior art. *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985).

Thus, at this stage of the proceeding, we find Delseny’s express teaching that NGS can substitute for microarray in genotyping sufficiently supports Petitioner’s argument that a POSA would have had a reason to modify Shapero’s method, i.e., using hybridization array for SNP genotyping, with Delseny’s NGS technology. This express teaching also lends support to the alleged reasonable expectation of success in combining Shepero’s method methods with Delseny’s NGS technology. *See* Pet. 37–38 (citing Ex. 1003 ¶¶ 164–166).

Patent Owner disagrees with Petitioner on several other arguments related to motivation to combine and reasonable expectation of success. *See* Pet. 34–37; Prelim. Resp. 34–40, 46–47. We do not rely on those arguments in the Petition when rendering this Decision. We nevertheless offer our preliminary observations on those disputes.

Petitioner argues that “a POSA reading Shapero would understand that its enrichment methods generate high on-target specificity and that there is significant enrichment over a situation where no target specific primer is used.” Pet. 37 (citing Ex. 1003 ¶ 163). According to Petitioner, “[t]his experimental data would further motivate a POSA to use the enrichment methods of Shapero with the NGS technologies described in Delseny.” *Id.* Petitioner asserts that Shapero’s experimental data also support its reasonable-expectation-of-success argument. *Id.* at 38.

Patent Owner contends that Shapero’s data is inapplicable because “[t]he experimental data reported by Shapero reflects the use of MARA with hybridization arrays, which function differently than NGS platforms.” Prelim. Resp. 38. Relying on the testimony of its declarant, Patent Owner argues that “[b]ecause of this key difference between hybridization arrays and NGS platforms, a POSA would not have considered data obtained from a hybridization array to be indicative of how any given method might perform with NGS.” *Id.* at 39 (citing Ex. 2028 ¶¶ 80, 153–163, 175–176). Patent Owner further asserts that “a POSA could not have reliably inferred from the reported hybridization data how effective MARA would be with an NGS platform.” *Id.* at 46 (citing Ex. 2028 ¶¶ 153–163).

Patent Owner's challenge of Petitioner's reliance of data reported in Shapero involves fact intensive issues better resolved after the parties fully develop the record during trial.

Petitioner contends that "Shapero teaches that its enrichment methods can be used with the sequencing technologies that existed." Pet. 35 (citing Ex. 1003 ¶ 158). As support, Petitioner points to Shapero's citation of Syvänen. *Id.* at 34. According to Petitioner, Syvänen teaches "DNA-sequencing instruments might also be used as platforms for genotyping SNPs using fluorescently labelled dideoxynucleotides in the minisequencing reactions,' which can be implemented on a 'high-throughput' scale." *Id.* at 35 (quoting Ex. 1012, 937).

Patent Owner counters that Syvänen would not have motivated a POSA to use Shapero's MARA with sequencing technology. Prelim. Resp. 34. According to Patent Owner, Syvänen teaches away from using PCR amplification in claimed methods. *Id.* at 34–36 (citing Ex. 1012, 934–35, 939–40). Patent Owner also contends that Petitioner's reliance on Syvänen is misplaced because "Syvänen is not advocating for DNA sequencing but instead the incorporation of aspects of the DNA sequencing methods." *Id.* at 37 (citing Ex. 1012, 937; Ex. 2028 ¶¶ 127–129, 165–167). On this record, Patent Owner's argument related to Syvänen appears to have merit; it, however, does not outweigh Delseny's express teaching that NGS can substitute for microarray in genotyping.

In sum, based on the current record and for purposes of institution, we find Petitioner has shown sufficiently that the combination of Shapero and Delseny teaches the limitations of claim 1. We also find Petitioner has shown adequately a motivation to combine the Shapero's enrichment

method with Delseny's NGS technology and a reasonable expectation of success in doing so. In other words, Petitioner has established a reasonable likelihood of prevailing on its assertion that the combination of Shapero and Delseny renders claim 1 obvious. We, thus, institute trial to review the challenged claims of the '012 patent.

Petitioner also asserts that the combination of Shapero and Delseny renders claims 2, 5, 6, 11–15, 17–20, and 22 obvious. Pet. 43–51. Patent Owner does not argue these claims separately. *See* Prelim. Resp. 51. In any event, we institute an *inter partes* review as to all challenges raised in the Petition. *See SAS Institute, Inc. v. Iancu*, 138 S. Ct. 1348, 1356 (2018); *see also* 37 C.F.R. § 42.108(a) (“When instituting *inter partes* review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.”).

D. Alleged Obviousness over Shapero, Delseny, and Hamady

Petitioner asserts that claims 7–10 would have been obvious over Shapero, Delseny, and Hamady. Pet. 51–53. Petitioner relies on Hamady for teaching the use of barcodes. *Id.* (citing Ex. 1033, 1143). Patent Owner argues that this challenge fails for the same reasons that Shapero and Delseny fails to render claim 1 obvious. *See* Prelim. Resp. 51–52.

Because we determine that Petitioner has shown a reasonable likelihood to prevail in showing the combination of Shapero and Delseny renders claim 1 obvious, we reject Patent Owner's argument and institute an *inter partes* review as to all challenges raised in the Petition. *See SAS*, 138 S. Ct. at 1356.

E. Alleged Obviousness over Shapero, Delseny, and Jones

Petitioner asserts that claims 3, 4, and 21 would have been obvious over the combination of Shapero, Delseny, and Jones. Pet. 54–55. Petitioner relies on Jones for teaching that the nucleic acids used in the MARA method “may be DNA or RNA.” *Id.* at 54 (citing Ex. 1011 ¶ 43). Patent Owner argues that this challenge fails for the same reasons that Shapero and Delseny fails to render claim 1 obvious. *See* Prelim. Resp. 52.

Because we determine that Petitioner has shown a reasonable likelihood to prevail in showing the combination of Shapero and Delseny renders claim 1 obvious, we reject Patent Owner’s argument and institute an *inter partes* review as to all challenges raised in the Petition. *See SAS*, 138 S. Ct. at 1356.

V. CONCLUSION

Based on the current record, and for the reasons explained above, we find Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. We, therefore, institute an *inter partes* review of all challenged claims on all asserted grounds.

This Decision is not a final determination on the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing could change upon further development of the record during trial. We remind the parties that any argument not raised in a Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed forfeited and/or waived even if asserted in the Preliminary Response. *In re Google Tech. Holdings LLC*, 980 F.3d 858, 862–864 (Fed. Cir. 2020) (holding an argument forfeited when not timely raised before the

Board); *In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), *inter partes* review is hereby instituted on all challenged claims of the '012 patent based on the asserted grounds set forth in the Petition; and

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

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