

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 GEORGIANNA W. BRADEN, ZHENYU YANG, and
TIMOTHY G. MAJORS, *Administrative Patent Judges*.

YANG, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Denying Petitioner's Motion to Strike
37 C.F.R. § 42.5

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 instituted trial to review the challenged claims (Paper 7, “DI”).

Thereafter, Patent Owner filed a Response to the Petition (Paper 17, “PO Resp.”), Petitioner filed a Reply to Patent Owner’s Response (Paper 22, “Reply”), and Patent Owner filed a Sur-reply to Petitioner’s Reply (Paper 27, “Sur-reply”). Petitioner filed a Motion to Strike (Paper 31), and Patent Owner filed an Opposition to the Motion (Paper 33). An oral hearing for this proceeding was held on February 11, 2026, and the transcript of that hearing is of record. *See* Paper 45 (“Tr.”).

The Board has jurisdiction under 35 U.S.C. § 6 and issues this Final Written Decision pursuant to 35 U.S.C. § 318 and 37 C.F.R. § 42.73. For the reasons provided below, we find Petitioner has shown, by a preponderance of the evidence, the unpatentability of claims 1–15 and 17–22.

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.

Petitioner concurrently filed IPR2025-00029 against U.S. Patent No. 10,876,108 (“the ’108 patent”), which claims priority to the same provisional patent application as the ’012 patent. Pet. 2; Paper 3, 1.

Patent Owner also asserted the ’012 patent in *Tecan Genomics, Inc. v. Invitae Corp.*, Case No. 1:23-cv-01114 (D. Del.). Patent Owner represents

that Integrated DNA Technologies, Inc. filed IPR2025-00015 and IPR2025-00016, challenging the '012 patent and the '108 patent, respectively. Paper 3, 1.

B. The '012 Patent

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).” Ex. 1001, Abst.; *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. Ex. 1001, 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. Ex. 1001, 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 also a need for high efficiency nucleic acid library generation.” Ex. 1001, 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. Ex. 1001, 15:57–59.

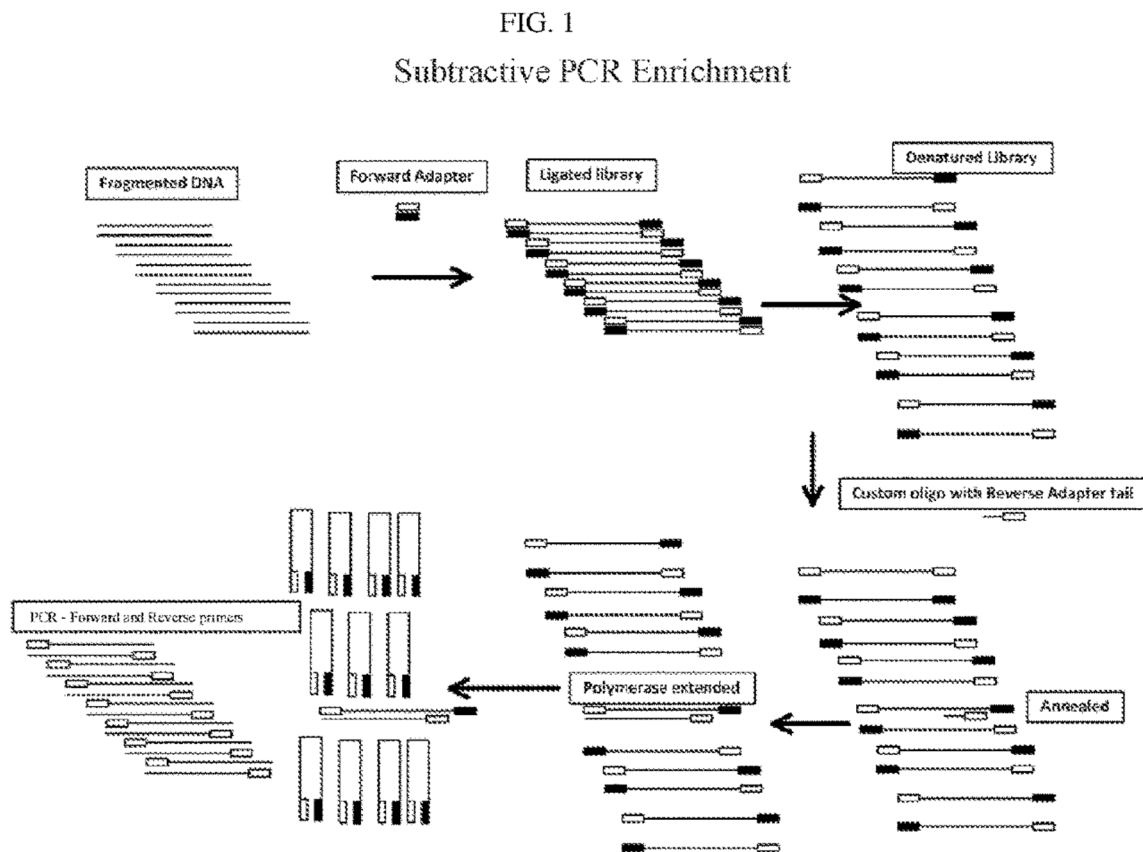


Figure 1 above depicts a method of selective target enrichment using ligation of a single forward adaptor at the ends of the DNA fragments in the DNA library. Ex. 1001, 5:47–49. The method is discussed in more detail below.

First, the method generates a ligated library of nucleic acid fragments or inserts in which “each fragment or insert comprises a common forward

adaptor and a fragment or insert specific reverse adaptor” at its 5’ end that is “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 forward adaptor sequence at one end and 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	References
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 Declarations of Michael L. Metzker, Ph.D. (Exs. 1003, 1121), and Patent Owner relies on the Declaration of Carlos D. Bustamante, Ph.D. (Ex. 2107).

II. ANALYSIS

A. Principles of Law

To prevail in this *inter partes* review, Petitioner “shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence.” 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d).

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”).

A claim is unpatentable for obviousness if “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103 (pre-AIA); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) when in evidence, objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966). The strength of each of the *Graham* factors must be weighed in every case and must be weighed en route to the final obviousness determination. *See, e.g., Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983) (instructing that evidence of objective indicia, when present, must always be considered in determining obviousness).

We analyze the challenges to patentability in accordance with these principles.

B. 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).

In the DI, we addressed Patent Owner’s arguments disputing Petitioner’s proposed definition. DI 17–18 (citing Prelim. Resp. 11–12). We stated that

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.

Id. at 18.

After institution, Patent Owner states that, for purposes of this proceeding, it adopts the Board’s definition of a POSA. PO Resp. 12.

Based on the entirety of the trial record, we maintain our finding of a POSA’s skill level.

C. 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.

D. Prior Art Disclosure

1. Jones

Jones is directed to “[m]ethods for genotyping polymorphisms using a locus specific primer that is complementary to a region near a selected polymorphism.” Ex. 1011, Abst.

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.

2. Shapero

Two of the co-authors of Shapero are also co-inventors of Jones. *Compare* Ex. 1006, 1, *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.

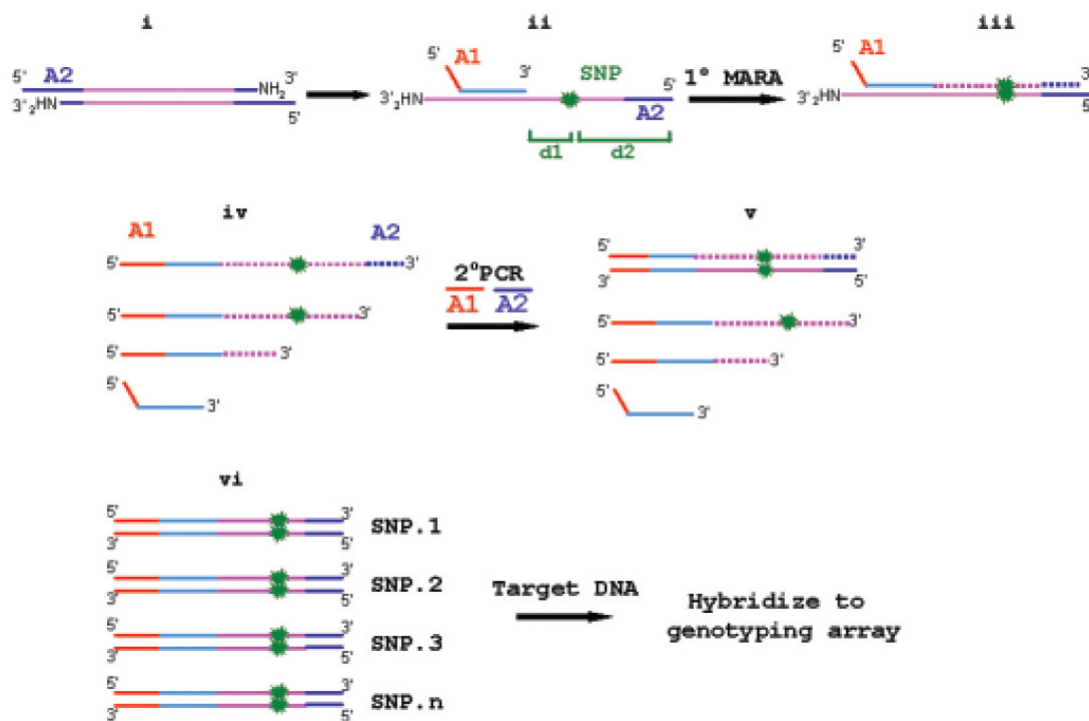


Figure 1 is an overview of the MARA method. *Id.* at 4. Panel (i) shows “[h]uman genomic DNA (pink) is digested to completion with a restriction enzyme and ligated to adapters (blue).” *Id.* In panel (ii), “[a] MARA forward primer (containing common sequence A1) is shown annealing to the bottom strand 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.*

3. 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).

4. 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.

E. 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. After reviewing the entire record developed at trial, and as explained below, we determine Petitioner has shown by a preponderance of the evidence that the challenged claims would have been obvious over the combination of Shapero and Delseny.

1. 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* PO Resp.; *see also* Tr. 97:19–20 (“The enrichment steps of the MARA method, [Patent Owner

does] not dispute that they align with the patent claims.”), 50:14–18 (the same). 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.

This, however, does not end our inquiry. After all, “[a] patent composed of several elements is not proved obvious by merely demonstrating that each of its elements was, independently, known in the prior art.” *KSR*, 550 U.S. at 418. Instead, “it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does.” *Id.*; *see also In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (stating that a party that asserts obviousness of a claim must show that “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so”).

The questions we must answer, then, are whether Petitioner has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had a reason to combine the teachings of Shapero and Delseny, and in doing so, would have had a reasonable expectation of success to arrive at the claimed invention. For the following reasons, we answer both questions in the positive, despite Patent Owner’s contentions to the contrary. We also find that evidence of objective indicia does not outweigh the other *Graham* factors and the evidence of obviousness on this record.

a. Reason to Combine and Reasonable Expectation of Success

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,⁶ “teaches that its enrichment methods can be used with the sequencing technologies that existed.” *Id.* at 35 (citing Ex. 1003 ¶ 158; Ex. 1012, 932, 937). Petitioner asserts that a POSA would have been further motivated to combine the enrichment methods of Shapero with the NGS technologies described in Delseny because “Delseny recognizes that NGS is a replacement for genotyping described in Shapero.” *Id.* at 36. 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.

Patent Owner disagrees. PO Resp. 16–53. Patent Owner contends that a POSA would not have had a motivation to combine MARA with NGS technology. *Id.* at 18. According to Patent Owner, “Shapero reflects the use of the MARA method with microarrays, which function differently than the surfaces used with NGS platforms.” *Id.* at 20. Patent Owner also asserts that “Delseny would not have motivated a POSA to modify Shapero to arrive at the claimed methods.” *Id.* at 31. Patent Owner further argues that Syvänen and other prior art taught away from Petitioner’s proposed combination. *Id.* at 35–45. Patent Owner also asserts that a POSA would not have had a

⁶ Syvänen, *Accessing genetic variation: genotyping single nucleotide polymorphisms*, 2 NATURE REV. GEN. 930–42 (2001) (Ex. 1012, “Syvänen”).

reasonable expectation of success in combining Shapero and Delseny to practice the claimed inventions. *Id.* at 47–53.

On this record, we find Petitioner has met its burden to show a reason to combine Shapero’s enrichment method with Delseny’s NGS technology and a reasonable expectation of success in doing so. We explain our reasoning below.

As an initial matter, we note Patent Owner’s argument that, in the Reply, “Petitioner turns away from Delseny and towards neanderthal sequencing papers like Green and Briggs, and other references like Fradkov, Tucker, and Metzker, even though it did not rely on these references for its obviousness argument.” Sur-reply 18 (citing Reply 2–3, 15, 19). According to Patent Owner, we should give these “new arguments” little weight because “Petitioner is prohibited from relying on ‘an entirely new rationale to explain why one of skill in the art would have been motivated to’ create Petitioner’s combination.” *Id.* (quoting *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369-70 (Fed. Cir. 2016)). Petitioner is prohibited from presenting a new theory of motivation to combine. *Id.* (citing *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369-70 (Fed. Cir. 2016)).

We do not find Petitioner’s reliance on the references identified by Patent Owner improper new arguments. Instead, Petitioner merely addresses Patent Owner’s arguments in the Response. For example, Petitioner cites Green (Ex. 1102) and Briggs (Ex. 1116) to rebut Patent Owner’s argument that “in 2012 a POSA would expect an SPE library to only enrich at the 50% level (POR.67) and that a POSA would understand that enrichment was too low to analyze on an NGS platform. POR.25.” *See* Reply 2–3. Similarly,

Petitioner relies on Tucker (Ex. 1013) to respond to Patent Owner's argument that "POSAs would be steered away from sequencing a Shapero MARA library on an NGS platform because NGS has high error rates and Sanger would have been the preferred modality. POR.33-34." *Id.* at 15. Thus, we accord Petitioner's Reply its proper weight.

We also note that Shapero was published at the end of 2004 (Ex. 1006, 1 (showing the manuscript was "[a]ccepted November 24, 2004")), and the earliest possible priority date of the challenged claims is January 26, 2012 (Ex. 1001, code (60)). In other word, Shapero was published only a little over seven years before the putative priority date, not "decades," as in *Leo Pharma Products, Ltd. v. Rea*, 726 F.3d 1346 (Fed. Cir. 2013). *See* 726 F.3d at 1356. Thus, we reject Patent Owner's argument that, in this case, the "elapsed time between the prior art and the priority date evinces that the claimed invention was not obvious to try." PO Resp. 46 (quoting *Leo Pharma.*, 726 F.3d at 1356 (internal brackets omitted)).

We further note that the inventors of the '012 patent viewed the targeted nucleic acid sequence enrichment and library generation as their invention. Indeed, the Summary of the Invention describes the invention of the '012 patent as "methods for enriching for target nucleic acid sequences of interest in a sample comprising nucleic acids," "methods for generating a library of nucleic acid sequences," and "methods for enriching for target nucleic acid sequences of interest from a library." Ex. 1001, 2:34–36, 3:13–15, 4:12–13, 4:55–57. The '012 patent touts that "the methods of the present invention create a simple, low cost, high throughput system for target enrichment and library preparation." *Id.* at 6:25–27.

The '012 patent explains that “the methods and compositions disclosed herein can be efficiently and cost-effectively utilized for *downstream analyses*, such as next generation sequencing or hybridization platforms, with minimal loss of biological material of interest.” *Id.* at 28:8–12 (emphasis added); *see also id.* at 26:64–27:2 (“The methods, compositions and kits described herein can be useful to generate amplification-ready products for *downstream applications* such as massively parallel sequencing (i.e. next generation sequencing methods), generation of libraries with enriched population of sequence regions of interest, or hybridization platforms.”) (emphasis added).

Thus, the specification of the '012 patent perceives target enrichment as its invention, and massively parallel sequencing, as well as hybridization platforms, as possible downstream applications. Claim 1 is directed to a method for sequencing an enriched nucleic acid sequence of interest, the method comprising steps for enriching the sequence of interest and sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

It is undisputed that Shapero’s MARA encompasses the same enrichment steps recited in claim 1. *See* Tr. 50:14–18, 97:19–20. Patent Owner emphasizes that Shapero’s MARA method was developed using microarrays. PO Resp. 18. Although we agree with Patent Owner on this fact, we reject Patent Owner’s contention that a POSA would not have used MARA with NGS technology because “Petitioner has not identified anything in the prior art that suggests Shapero’s MARA method could be used with NGS.” PO Resp. 31 (citing Ex. 2107 ¶¶ 271–274); *see also id.* at 18 (arguing that Shapero does not suggest MARA “could be used in other

contexts with success”); 34–35 (“Delseny entirely fails to suggest the use of a single target-specific primer for target capture with NGS or any form of target capture with NGS for genotyping.”); 40 (“Petitioner, therefore, points to nothing in Syvänen that would have motivated a POSA to expand the existing methods in Shapero to arrive at the challenged claims.”) 45 (arguing that between 2007, when NGS platforms became commercially available, and January 26, 2012, the priority date of the ’012 patent, “there were *zero* publications disclosing or suggesting the use of Shapero’s MARA method with NGS”).

As we previously explained, Petitioner’s challenge rests on obviousness, and not anticipation. *See* DI 23. Thus, the fact that Petitioner does not present a single reference that discloses both Shapero’s MARA and NGS technology being combined is not fatal to its case. *Id.*

And for an obviousness analysis, we “need not seek out precise teachings directed to the specific subject matter of the challenged claim,” because we “can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” *KSR*, 550 U.S. at 418; *see also id.* at 419 (cautioning that the obviousness analysis cannot be confined “by overemphasis on the importance of published articles and the explicit content of issued patents”). Instead, “any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.” *Id.* at 420.

Shapero teaches using its MARA method with microarray technology to detect SNPs. *See* Ex. 1006, 1 (stating Shapero teaches “a locus-specific DNA target preparation method for highly multiplexed single nucleotide polymorphism (SNP) genotyping”). According to Shapero, there was a need

“for the development of robust, flexible, cost-effective technology platforms for scoring SNP genotypes in large numbers of samples.” *Id.* Citing Syvänen as an example, Shapero explains that “[t]here [we]re a multitude of genotyping methodologies for SNPs that ha[d] been described over the years.” *Id.*

According to Delseny, those genotyping technologies, however, had “limited resolution” and required “much time and human resources.” Ex. 1007, 417. In addition, “many SNPs are missed.” *Id.* Delseny reviews some NGS technologies, which “open the way to using sequencing as a genotyping tool.” *Id.* at 415; *see also id.* at 417 (“The ultimate resolution is at the base-pair level and NGSTs now open the possibility to genotype a line by sequencing it, provided a reference genome is available.”). It is undisputed that, by 2010, “scientists were genotyping using next generation sequencing.” Ex. 1120, 367:18–24.

Thus, both Shapero and Delseny identify a “need or problem known in the field of endeavor,” which provides a reason for combining Shapero’s teaching of the MARA method for target enrichment and Delseny’s teaching of NGS for genotyping. *See KSR*, 550 U.S. at 420; *see also id.* at 417 (“[A] court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.”).

Patent Owner acknowledges Delseny’s teaching that NGS “can substitute for the genotyping microarray strategy because of its higher resolution.” PO Resp. 31 (quoting Ex. 1007, 417). Nonetheless, Patent Owner contends that “Delseny’s discussion of genotyping with NGS is entirely based on the Han publication (EX2117), which describes the sequencing of entire rice genomes with NGS.” *Id.* at 32 (citing Ex. 2107

¶¶ 191–196, 238–243). According to Patent Owner, “[a] POSA reading Delseny in the proper context would have understood Delseny to suggest that NGS could potentially be used for genotyping where the entire genome is sequenced.” *Id.* (citing Ex. 2107 ¶¶ 239–243). We are not persuaded by this argument.

As Petitioner correctly points out, Delseny specifically discusses “Targeted Sequencing.” *See* Reply 15 (citing Ex. 1007 § 4.4; Ex. 1121 ¶¶ 38–39). Delseny teaches that

[b]ecause many genomes contain large amounts of repetitive sequences and transposable elements, selecting relevant portions might be of interest. This selection is particularly important in medicine, in which sequencing the same locus in a large range of patients is an important target. This finding has led to the development of methods to capture the desired sequences.

Ex. 1007, 417. Although Delseny does not explicitly link targeted sequencing with genotyping, it does not require a leap of faith to connect the adjacent disclosures. *See KSR*, 550 U.S. at 421 (“A person of ordinary skill is also a person of ordinary creativity, not an automaton.”). On this, we credit Dr. Metzger’s testimony that, by 2012, there were “no technical hurdles” that would have dissuaded a POSA from analyzing a library enriched by Shapero’s MARA method on an NGS platform. *See* Ex. 1121 ¶ 38.

Patent Owner contends that, because microarrays confer target specificity whereas the NGS platform is unable to filter off target sequences, a POSA would not have decoupled MARA from the downstream application of microarray in Shapero to use it in another downstream application of NGS. PO Resp. 20–24. Patent Owner refers to Shapero for teaching 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 24 (quoting Ex. 1006, 2) (emphasis by Patent Owner). According to Patent Owner, “Shapero’s reference to ‘methods for allele discrimination,’ means ‘[h]igh-density arrays.’” *Id.*

We do not read Shapero so narrowly. Indeed, Shapero makes clear that high-density array is only an example of allelic discrimination. *See* Ex. 1006, 2 (“When coupled with a method for allelic discrimination ***such as*** high-density array hybridization, this method provides access to large numbers of locus-specific SNPs in a single reaction and thus may facilitate the use of SNPs in genome-wide association studies.”) (emphasis added); *see also id.* at 7 (“When MARA is combined with a method for highly parallel allele discrimination, ***such as*** high-density DNA oligonucleotide array hybridization, it affords a level of locus-specific SNP genotyping that is not readily accessible through traditional target preparation methods such as multiplex PCR.”) (emphasis added). Thus, although Shapero reports data using MARA method with microarrays, its conclusion that “MARA may serve as a target preparation method for highly multiplexed locus-specific SNP genotyping” is not limited to microarrays as the only downstream application. *See id.* at 2.

Patent Owner asserts that a POSA would have understood “accuracy would be the primary concern for any modified use of MARA.” PO Resp. 25 (citing Ex. 2107 ¶ 151). In the DI, we pointed to Shapero’s stated desire to “allow rapid and accurate genotypic information at a fraction of the cost of current approaches.” DI 22 (citing Ex. 1006, 2). We stated that “[a]lthough

Patent Owner emphasizes the accuracy aspect of it, Shapero in fact desires a method that balances accuracy with speed and cost. And NGS appears to fit the bill” because “[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.” *Id.* at 22–23 (citing Prelim. Resp. 5).”

In its Response, Patent Owner contends that “[a]t no point does Shapero discuss the balancing of accuracy with speed and cost nor that optimizing a balance between [accuracy and] speed and cost was the goal.” PO Resp. 25 (citing Ex. 2107 ¶ 151). Generally, we “need not seek out precise teachings” in prior art when assessing reasons to combine prior art teachings. *See KSR*, 550 U.S. at 418. More importantly, here, Shapero in fact explicitly teaches “there is still a need for the development of ***robust, flexible, cost-effective*** technology platforms for scoring SNP genotypes in ***large numbers of samples***.” Ex. 1006, 1 (emphases added); *see also id.* at 2 (“In 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.”) (emphases added); *id.* at 8 (“[T]he development of molecular methods, such as MARA for highly multiplexed locus-specific target DNA preparation, has a number of possible ***cost-effective*** applications to harness the genetic power of SNPs.”) (emphasis added). Shapero’s repeated references to speed and cost

demonstrate that while accuracy is an important concern, it is not the only one.⁷

Indeed, Petitioner proffers evidence to show that for certain applications, a POSA would have been content with sequencing results that were only 4–40% on target. Reply 3 (citing Ex. 1102, 712; Ex. 1116, 319; Ex. 1120, 165:22–169:10; Ex. 1121 ¶¶ 7–9).

Patent Owner dismisses Exhibits 1102 and 1116, arguing that they relate to sequencing neanderthal DNA, which “is a niche area of research that poses unique challenges that may lead a researcher to be ‘willing to throw away a large amount of the data.’” Sur-reply 9 (citing Ex. 1120, 71:24–73:25, 161:19–164:3, 178:8–25). We are not persuaded by Patent Owner’s argument. Claim 1 requires enriching for a nucleic acid sequence of interest, which does not exclude ancient DNA, even if its “source material is scarce.” *See* Sur-reply 9. Instead, a high off-target rate may be justified, “depend[ing] on the biological question and the motivation of the investigator.” Ex. 1120, 162:24–163:1.

Moreover, even in 2008, “[g]iven the low cost of sequencing, tight specificity may not be that important. As sequencing prices drop, if half your reads map someplace else, or aren’t directly mappable to your region of interest, maybe you don’t care—you just throw them away.” Ex. 2029, 1103 (internal quotation marks omitted). In sum, numerous prior art teachings support our conclusion that a desire for both accuracy and speed/cost-

⁷ It is worth noting that the ’012 patent similarly identifies, as background knowledge, “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.” Ex. 1001, 2:25–28.

effectiveness would have motivated a POSA to use Shapero's MARA with NGS. *See* DI 22–23.

Petitioner asserts that “the experimental data in Shapero shows a high on-target specificity that a POSA would understand would likely work for NGS applications.” Pet. 38. We do not address this argument because we are persuaded that a POSA would have had a reasonable expectation of success when using Shapero's MARA with NGS in view of Delseny's express teaching that “NGS can be a replacement for array-based genotyping, as used in Shapero.” Pet. 38.

Patent Owner argues that “Delseny discloses the potential use of NGS instead of microarrays for genotyping where the entire genome is sequenced and where a reference genome is available for comparison.” PO Resp. 52. We are not persuaded by this argument. As explained above, Delseny expressly teaches targeted sequencing. Ex. 1007, 417–18 (“This finding has led to the development of methods to capture the desired sequences.”). And for the alleged requirement that a reference genome is available, we agree with Petitioner that “[e]ven if that was true . . . it still falls within the scope of the claims.” *See* Reply 14; *see also id.* at n.4 (“All the examples in the patent call for sequencing the 16s bacterial loci, which had been well characterized by 2012.”) (citing Ex. 1121 ¶ 39).

It is well established that “[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.” *KSR*, 550 U.S. at 416. Here, Shapero teaches using an enrichment method with microarrays for genotyping. It is undisputed that the method of claim 1 uses the same enrichment method as

Shapero's but with a different downstream application: NGS, which was readily used for genotyping at the time of the invention.

Petitioner argues that “[t]hese facts satisfy the requirements for finding obviousness that the Supreme Court identified in *KSR*.” Reply 13–14 (arguing that “at the time of the invention, if there is a known problem for which there are a finite number of predictable solutions, the anticipated success leads to a finding of obviousness”) (citing *KSR*, 550 U.S. at 420–21). Patent Owner disputes Petitioner's assertion. Sur-reply 3. Citing “EX1007.0419-422; EX1012.0934; EX1025.0041-42; EX1038.0114,” Patent Owner argues that “Petitioner's own art demonstrates[] there were hundreds, if not thousands, of potential solutions.” *Id.*

It is unclear to us how the citations support Patent Owner's argument. For example, “EX1007.0419-422” appears to refer to the “References” cited in Delseny. Although Delseny cites 155 references, not all of them correlate to potential solutions, let alone each correlating to a distinct solution. *See* Ex. 1007, 419–22. In fact, all technologies reviewed by Delseny fall under the umbrella of “next-generation sequencing technologies (NGST).” *See id.* at 408. Delseny categorizes the new sequencing technologies into three groups: sequencing by hybridization (such as Affymetrix microarrays), sequencing by synthesis (including Pyrosequencing and Illumina technology), and sequencing single molecules. *Id.* at 408–09. Notably, Delseny does not discuss sequencing by hybridization because it “is a re-sequencing technology that now seems of limited value as compared with the other technologies.” *Id.* at 408.

Similarly, “EX1012.0934” shows Syvänen's Table 2, which lists about two dozen SNP-genotyping methods, categorized into five groups:

hybridization methods (including microarrays), allele-specific PCR, primer extension, also termed “DNA-polymerase-assisted genotyping” (including pyrosequencing and minisequencing), oligonucleotide ligation, and endonuclease cleavage. *See* Ex. 1012, 934. “EX1025.0041-42” shows a figure illustrating Microdroplet PCR, Solid-phase capture, and Solution-phase capture, which was further divided into MIP-based approach and Biotinylated RNA-based approach. Ex. 1025, 41–42. “EX1038.0114” shows a table with four methods: PCR, MIP, On-array hybrid capture, and In-solution hybrid capture. Ex. 1038, 114.

In our opinion, these well-defined genotyping methods represent just a handful, and thus, limited, categories, not as Patent Owner argued, “hundreds, if not thousands, of potential solutions.” *See* Sur-reply 3.

Patent Owner contends that Petitioner’s challenge is “[b]ased solely on impermissible hindsight.” PO Resp. 1. “Any judgment on obviousness,” however, “is in a sense necessarily a reconstruction based upon hindsight reasoning.” *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971). “[B]ut so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant’s disclosure, such a reconstruction is proper.” *Id.*

Here, Petitioner relies on prior art teachings available at the time of the ’012 patent and technical reasoning possessed by the POSA that we find persuasive to account for the components of an obviousness analysis, including mapping of each limitation of claim 1, as well as the reason to combine and reasonable expectation of success. *See* Pet. 24–43; Reply 13–20.

b. Objective Indicia of Non-Obviousness

We next consider evidence of objective indicia. *See Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (“The so-called ‘objective’ criteria must always be considered and given whatever weight is warranted by the evidence presented.”) (internal citation omitted).

Patent Owner argues that (1) the prior art taught away from and expressed skepticism for the claimed methods; (2) there were long-felt, unmet needs; (3) industry praised the claimed invention; (4) Petitioner copied the claimed invention; (5) Petitioner’s prior statements support the non-obviousness of the claimed inventions; and (6) there were unexpected results. PO Resp. 54–69; Sur-reply 24–28. We address these arguments below.

i. Alleged Teaching Away and Skepticism

Patent Owner argues that prior art teaches away from the combination of Shapero and Delseny. PO Resp. 34–47, 54–57. We are not persuaded by this argument.

A reference teaches away “when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.” *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004). “The prior art’s mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed.” *Id.*

a) Teaching Away from Shapero

Patent Owner argues that references that discussed Shapero “taught away from its use with NGS.” PO Resp. 56 (citing Ex. 2107 ¶ 286); *see also id.* at 46–47 (arguing the references “criticize or disregard MARA”) (citing Ex. 2107 ¶¶ 271–274). We find the evidence Patent Owner relies on does not support its argument.

For example, Patent Owner contends that Liu “describes Shapero’s method as ‘expensive and requir[ing] specialized equipments [sic], which cost more [than] standard primers and are not practical for assaying low- to moderate-throughput SNPs.” *Id.* at 46 (quoting Ex. 2141, 2). Similarly, Patent Owner contends that “Bui explains that Shapero is ‘impractical for assaying a selected set of SNPs in specific genomic regions’ and ‘usually beyond the reach of small to medium sized laboratories with limited resources.’” *Id.* (quoting Ex. 2138, 2).

Liu cites Shapero (reference 15) as a high-throughput SNP genotyping technique using “genome re-sequencing.” Ex. 2141, 2. So does Bui. *See* Ex. 2138, 2 (describing Shapero (reference 12) for teaching a “genome re-sequencing method[]” as “extremely powerful for large scale SNP-discrimination.”).

But re-sequencing technology here apparently refers to the microarrays. *See* Ex. 1007, 408 (“[S]equencing by hybridization is a re-sequencing technology that now seems of limited value as compared with the other technologies.”). Accordingly, if Liu and Bui criticized Shapero, they criticized the microarray aspect of the method, not MARA. Thus properly viewed, Liu and Bui in fact would have provided further reason for

a POSA to replace microarrays with another high-throughput method, such as NGS.

Patent Owner argues that

[l]ess than a year after Shapero published, Dahl acknowledges the publication but goes on to say that “[c]urrently, the only way to amplify many defined sequences in the same reaction is by combining several different PCR primer pairs.”⁸

EX2126.0001. Dahl rejects Shapero and goes on to propose a method using circularization instead. *Id.*, .0001-02.

PO Resp. 46–47 (footnote added); *see also id.* at 56 (the same).

Dahl cites Shapero (reference 7) in a string cite: “[a] few methods exist that permit the user to amplify subsets of genomes using variants of so-called adaptor PCR (6–8).” Ex. 2126, 1. It goes on to discuss reference 6 and two other references (references 9 and 10) to describe adaptor PCR. *Id.* Dahl does not discuss Shapero. Just because Dahl “present[s] an approach to enable robust amplification of large sets of selected DNA sequences” (*id.*) does not amount to criticism or discrediting of Shapero. *See Fulton*, 391 F.3d at 1201.

Patent Owner asserts that “Howell explains that Shapero fails to ‘achieve[] the ideal goal of amplifying a large set of arbitrary sequences without the production of undesired amplification products.’” PO Resp. 46 (quoting Ex. 2130, 160); *see also id.* at 56 (the same). But Howell does not single out Shapero; instead, Howell says “[n]one of the methods achieves the ideal goal” of absolute target specificity. Ex. 2130, 160. Obviousness

⁸ Dahl continues to describe that this approach has a “crucial problem” of generating amplification artifacts. Ex. 2126, 1.

does not require the ideal solution. *Intel Corp. v. Qualcomm Inc.*, 21 F.4th 784, 800 (Fed. Cir. 2021) (“[It is] not necessary to show that a combination is the *best* option, only that it be a *suitable* option.”). And, as Dr. Bustamante testified, no method, including the claimed method, achieves that unattainable goal of absolute specificity. Ex. 1120, 383:17–22, 385:1–10. Nor do the challenged claims require such specificity. *Id.* at 385:11–18. In fact, as Dr. Bustamante acknowledged, the claims “do not require you to achieve a specific level of enrichment or on target.” *Id.* at 384:6–8.

Finally, according Patent Owner, Palka-Santini teaches away because it states that “methods like MARA ‘are time consuming and prone to contamination.’” PO Resp. 46 (citing Ex. 2139, 10); *see also id.* at 56 (the same). Palka-Santini describes Shapero (reference 30) as the alternative approach to highly multiplex PCR, which has “typical hindrances” due to “[t]he complex nature of the interference between multiple primer pairs and targets.” Ex. 2139, 10. Palka-Santini recognizes Shapero’s method is the “replacement of target-specific primers with universal ones.” *Id.*

According to Palka-Santini, Shapero’s method “involves multiple steps starting with enzymatic digestion of the template DNA, ligation to adapters, primer extension and finally two subsequent PCR reactions [30,31]. Such multi-step approaches are time consuming and prone to contamination [25], and therefore, have not been recommended for bacteriological routine diagnostics.” Ex. 2139, 10. Curiously, reference 25, which Palka-Santini cites to support the alleged criticism of Shapero, was published in 2000, four years *before* Shapero was published. *See id.* at 13. Furthermore, even if we accord Palka-Santini’s statement full weight, the

criticism is limited to the field of “bacteriological routine diagnostics.” *See id.* at 10. Because a POSA would have had broad knowledge in “molecular biology, molecular genetics, bioinformatics, biochemistry, or a related field” (*see supra* Section II.B), we find Palka-Santini would not have taught away from Shapero’s MARA method or from modifying that method as proposed by Petitioner to arrive at the claimed subject matter.

In sum, we find the prior art does not teach away from Shapero.

b) Teaching Away by Delseny

Patent Owner argues that Delseny’s “concerns and endorsement of pre-NGS Sanger sequencers taught away from using target capture methods, like MARA, with NGS for the genotyping performed in Shapero, especially given the heightened need for accuracy.” PO Resp. 34 (citing Ex. 2107 ¶ 245); *see also id.* at 33 (“Delseny points to errors in base-calling, sequencing read artifacts, and higher false discovery rates.”) (citing Ex. 1007, 411–17; Ex. 2107 ¶¶ 189, 244). Dr. Bustamante testifies that Delseny “discloses that early NGS technologies suffered from a series of inaccuracies,” which according to Dr. Bustamante, “would have diminished their ability to be used for SNP genotyping.” Ex. 2107 ¶ 244. As support, Dr. Bustamante points to Delseny’s teaching that “identifying high-confidence SNPs and small InDels remains a major challenge until base-calling is improved and false discovery rate is reduced.” *Id.* (quoting Ex. 1007, 417).

Calling for improvement of a method hardly teaches away from that method. Indeed, in the paragraph right after the language quoted by Dr. Bustamante, Delseny continues that “[t]he ultimate resolution is at the base-pair level and NGSTs now open the possibility to genotype a line by

sequencing it, provided a reference genome is available.” Ex. 1007, 417. In that same paragraph, Delseny teaches that NGS “can substitute for the genotyping microarray strategy because of its higher resolution.” *Id.*

Patent Owner emphasizes that “Delseny recognizes the pre-NGS Sanger method as the ‘gold standard’ due to it having the ‘highest accuracy.’” PO Resp. 34 (citing Ex. 1007, 411). Delseny, however, also states that “this technology remained tedious and expensive. Sequencing of each of the above eukaryotic genomes cost several million US dollars and mobilized hundreds of scientists all over the world.” Ex. 1007, 408. Such disclosure demonstrates that rarely is any technology perfect, and pointing out its weakness does not teach away from an otherwise useful method. *Pro-Mold & Tool Co., Inc. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996) (“We start from the self-evident proposition that mankind, in particular, inventors, strive to improve that which already exists.”).

c) Teaching Away by Syvänen

Patent Owner argues that “Syvänen teaches away from using the PCR amplification required by the challenged claims.” PO Resp. 35. Syvänen reviews several SNP genotyping methods available at its 2001 publication date. *See* Ex. 1012. For example, Syvänen teaches that DNA-polymerase-assisted genotyping includes, among others, minisequencing and pyrosequencing. *Id.* at 935–37.

Patent Owner points to Syvänen’s statement that “[i]n practice, the requirement of a PCR amplification step to achieve sensitive and specific SNP genotyping is the principal factor that limits the throughput of assays today.” PO Resp. 36 (quoting Ex. 1012, 939). Patent Owner also points to Table 2, where Syvänen summarizes the “Features of SNP-genotyping

methods.” *Id.* (citing Ex. 1012, 934). In that table, Syvänen labels “Avoids target amplification” as a “special feature” of one method and “PCR amplification avoided” as the “Most significant advantage” of another. *Id.* at 37 (citing Ex. 1012, 934). Patent Owner emphasizes Syvänen’s advice that “[t]he next generation technology for SNP analysis should avoid the PCR amplification step.” *Id.* at 36 (quoting Ex. 1012, 940).

We previously stated that “Patent Owner’s argument related to Syvänen appears to have merit.” DI 25. In response, Petitioner argues that Syvänen’s “2001 suggestion was not followed; by 2010, using PCR amplification to prepare and sequence libraries on NGS platforms was dominant and well accepted.” Reply 16 (citing Ex. 1013, Figs. 2, 3, 4; Ex. 1121 ¶ 44; Ex. 2011, 117). On the full record, we agree with Petitioner’s argument.

Indeed, in 2004, Shapero acknowledged that the multitude of genotyping approaches can vary “in terms of how alleles are discriminated,” and “in the nature of both the assay formats and labeling and detection strategies.” Ex. 1006, 1. According to Shapero, however, many of those approaches

share a common feature in that there is a requirement for an amplification of the region harboring the polymorphism prior to actual genotyping. PCR significantly increases the copy number of the sequence to be genotyped, thereby effectively reducing the complexity of the target sequences and improving the ability to differentiate correct and incorrect genotype calls.

Id.

By 2010, it was recognized that for target enrichment, “[t]he specificity of PCR will almost certainly always exceed that of hybrid capture, and its uniformity may never be matched by either hybrid capture or

MIPs.” Ex. 2011, 117. Although “specificity and uniformity are not everything” (*id.*), they are two of several parameters to be considered in choosing the enrichment method (*id.* at 111). Undeniably, each of the enrichment methods has its “unique advantages and disadvantages,” and a POSA would have had to “find the best compromise between sensitivity, specificity and uniformity for their particular project.” *Id.*

d) Teaching Away by Other Prior Art

All that is to say that we recognize amplification has its drawbacks, but it also has strengths unmatched by other methods. Thus, for the same reason, we are not persuaded by Patent Owner’s argument that other prior art “taught away from and expressed skepticism at PCR amplification methods generally.” PO Resp. 44–45, 55–56 (citing Exs. 1025, 2042, 2047, 2048, 2050, 2053, 2054, 2071, 2155).

The numerous other references cited by Patent Owner also fail to support its argument for other reasons. For example, Patent Owner quotes Bronner for stating that “[u]nnecessary PCR amplification steps will exacerbate amplification biases, and so they should be avoided wherever possible.” PO Resp. 45 (quoting Ex. 2155, 18–19). The operative word here appears to be “unnecessary,” because Bronner actually teaches using PCR for sequencing. *See* Ex. 2155, 18–19.

Patent Owner represents that Dr. Metzker previously stated that “coupling PCR with high-throughput NGS platforms for targeting strategies is not practical.” PO Resp. 40 (quoting Ex. 1025, 41); *see also id.* at 55 (the same). Patent Owner, however, neglects the other half of the sentence: “as sample preparation would require handling tens of thousands of primers individually or in large multiplex groups to meet the needs of a single

instrument run.” Ex. 1025, 41. We credit Dr. Metzker’s testimony that “[p]ut in the proper context,” the sentence means that “if one were to enrich with standard target specific forward and reverse primer pairs, one would need on the order of tens of thousands of primer pairs to use the entire capacity of an NGS instrument[,] which at that point was not practical.” Ex. 1121 ¶ 45.

Similarly, Patent Owner quotes Aird for stating that “the best way to avoid bias during PCR is to avoid library amplification by PCR altogether.” PO Resp. 45 (quoting Ex. 2042, 11). Again, Patent Owner neglects to mention the next sentence that “[o]n the other hand, PCR-free libraries require relatively large amounts of input DNA and are thus impractical for many sample types.” *See* Ex. 2042, 11. Aird also teaches that “PCR-free protocols are not readily amenable to automation and are therefore not the best choice as the default protocol in high-throughput sequencing facilities.” *Id.* Aird further states that “[i]mproved PCR conditions like the one described [t]here will likely satisfy the vast majority of projects.” *Id.*

In another example, Patent Owner argues that Tsoktouridis “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.’” PO Resp. 44–45 (citing Ex. 2048, 885; Ex. 2107 ¶¶ 61, 252). Patent Owner, again, fails to point out that Tsoktouridis did not abandon PCR, but instead developed an efficient adaptor long-range PCR. *See* Ex. 2048, 885.

Altogether, after reviewing the numerous references Patent Owner relies on, allegedly showing that the prior art taught against using PCR amplification to enrich target sequences, we find none that actually did so.

This is because even if prior art teaches other methods to enrich target sequences, including those “without PCR amplification,” which according to Quail, “performed best” (PO Resp. 45 (citing Ex. 2053, 2054, 2071), it does not “criticize, discredit, or otherwise discourage” POSAs from using PCR amplification. *See Fulton*, 391 F.3d at 1201.

We also are not persuaded by Patent Owner’s argument that the prior art “caution[ed] against the use of a single target-specific primer for amplification, given concerns about specificity and off-target binding.” PO Resp. 42 (citing Ex. 2107 ¶¶ 57–64, 246–254). Patent Owner also relies on Miura. PO Resp. 42, 55. Patent Owner acknowledges that Miura teaches methods using only “a single unique primer in combination with a common primer,” but points out that they were often “plagued with non-specific amplification products derived from so-called ‘off-targets.’” *Id.* (quoting Ex. 2047, 4363); *see also id.* at 55 (the same).

Miura, however, teaches that “[t]hese problems may be solved by optimizing the PCR conditions, including the annealing temperature and the concentrations of Mg²⁺, dNTPs, primers and the template.” Ex. 2047, 4363. Recognizing that these solutions also have their issues, Miura states that “a reliable method is required to design more specific primers, particularly, for use in a large-scale analysis based on these PCR applications.” *Id.*

Miura further teaches “a simple algorithm to predict the performance of the primer.” *Id.* Applying its algorithm to the design of primer for 5’-RACE (rapid amplification of cDNA ends), Miura reports that primers designed using this algorithm worked “strikingly better” than those designed using a conventional method, with “[m]ore than 90% of the products

obtained using [these] primers were derived from the bona fide targets.” *Id.* at 4368.

Thus, viewed in its entirety, we agree with Petitioner’s argument that Miura does not teach away from using single primer extension (“SPE”). Reply 9. Instead, “it shows that those in the field believed in SPE and continued to optimize its performance. *Id.* (citing Ex. 1121 ¶ 25).

Patent Owner argues that prior art “would have discouraged a POSA from using a single target-specific primer given that they reflected a basic understanding in the art that target-specific *primer pairs* were necessary for PCR enrichment for NGS.” PO Resp. 43 (“[R]esearchers outright dismissed the use of a single target-specific primer for enrichment.”). As support, Patent Owner relies on Bustin. *Id.* In this 2005 article, Bustin discusses real-time reverse transcription polymerase chain reaction (RT-PCR). Ex. 2018, 597. Bustin states that the PCR step in the methods used to prime cDNA synthesis requires target-specific primers. *Id.* at 598. According to Bustin, “[w]hile the specificity of individual primers may be tested using for BLAST, no further consideration may be given to the influence of non-target sites that can result in suboptimal binding of the primers. Accurate quantification requires primer sets that facilitate maximum amplification efficiency.” *Id.*

We acknowledge Bustin’s teaching requiring primer sets to reach maximum amplification efficiency.⁹ Nonetheless, obviousness is analyzed based on the knowledge “at the time the invention was made.” 35 U.S.C.

⁹ We similarly acknowledge the skepticism expressed in the Brooks Declaration, submitted during prosecution. See PO Resp. 56 (citing Ex. 2026, 37).

§ 103(a). References published after Bustin embraced, and did not teach away from, using single target-specific primer.

An example is Sohn, published in 2011. Ex. 2050. Patent Owner refers to Sohn for stating that while “many studies have been made to improve the genome walking method,” “it is still in need of improvement.” *Id.* (quoting Ex. 2050, 2). Patent Owner argues that even in 2011, the “most serious problems of the PCR-based genome walking methods are low amplification efficiency and non-specific amplification.” *Id.* at 42, 55 (quoting Ex. 2050, 2). According to Patent Owner, Sohn noted that various methods had been developed but “satisfactory performance [had] not yet been achieved.” *Id.* at 42–43 (quoting Ex. 2050, 2). Unstated by Patent Owner, however, Sohn solved these problems. *See* Ex. 2050, 2 (“[T]he present inventors have developed a method capable of notably improving upon the above problems.”).

Sohn teaches that

[a] low amplification efficiency is caused by insufficient ligation between the restricted genomic DNA and cassette, and non-specific amplification is attributed to PCR reaction by only cassette primers in[]stead of a combination of the known region-specific primers and cassette primers. Thus, to amplify the desired region only, amplification by only cassette primers should be inhibited, and amplification by a combination of the known region-specific primers and cassette primers should only be performed. By the present inventors, the restricted genomic DNA fragment was treated with ddNTP, and ligated with a complementary cassette to increase the efficiency of ligation between the genome and cassette and to prevent nonspecific amplification, thereby completing the present invention.

Id.

Thus, Sohn solved both low amplification efficiency and non-specific amplification problems, and thus, does not teach away from using single primer extension.

e) Summary

In sum, after reviewing the voluminous prior art presented by the parties, we find the evidence shows that neither PCR amplification nor using single target-specific primer is perfect. They both, however, are useful and POSAs continued regularly to employ them in their endeavors at the time of the '012 patent invention. We also acknowledge that POSAs at the same time pursued other approaches to improve target enrichment for NGS. This, however, does not rise to the level that it “criticize[s], discredit[s], or otherwise discourage[s]” the combination of Shapero’s MARA with NGS. *See Fulton*, 391 F.3d at 1201.

ii. Long-felt, Unmet Needs

Patent Owner argues that “[b]efore the claimed methods, the field did not have an efficient solution for targeting portions of the genome for sequencing.” PO Resp. 59. The alleged needs, however, appear to be of library preparation methods. According to Patent Owner, “[t]he targeted library preparation methods at the time relied on complex, specialized instrumentation.” *Id.* at 58 (citing Ex. 2107 ¶ 289; Ex. 2009, 2–7; Ex. 2064, 1–2). Patent Owner asserts that despite considerable work in the field, the solutions developed fell short of resolving the problems, and the needs remained unmet until the claimed inventions. *Id.* at 58–59 (citing Ex. 2107 ¶¶ 289–92).

It is undisputed that Shapero’s MARA method, which generates a targeted library, is the same as the claimed enrichment steps. *See*

Tr. 97:19–20 (“The enrichment steps of the MARA method, [Patent Owner does] not dispute that they align with the patent claims.”), 50:14–18 (the same). Because Shapero’s MARA method met the alleged long-felt, but unmet needs, we accord little weight to Patent Owner’s evidence on this point.

iii. Industry Praise

Patent Owner asserts that “NuGEN¹⁰ and Tecan’s SPET products were designed to perform the claimed methods,” and “Tecan’s Ovation and Allegro products are coextensive with the claimed methods.” PO Resp. 60 (citing Ex. 2107 ¶¶ 276–284, footnote added). Patent Owner relies on Barchi (Ex. 2065), Smith (Ex. 2067), Scaglione (Ex. 2068), and Benjamino (Ex. 2069). *Id.* at 60–61.

We acknowledge that the cited references praised SPET products. We, however, note that the praise appears to focus on the enrichment method, which again, is the same as Shapero’s MARA method. *See, e.g.*, Ex. 2065, 1 (praising SPET’s “reliance on single primers, rather on primer pairs, greatly simplifies panel design”), Figure 1 (showing the “six main steps of the SPET workflow,” from “Fragment DNA” to “Amplify Library”); Ex. 2067, 1, 3 (reviewing SPET as one of the “Growing Options for Enriching Target DNA”); Ex. 2068, 548 (attributing the advantage of SPET to, among others, “a high efficiency enrichment system”). Taking all aspects in consideration, we accord evidence of industry praise some weight.

¹⁰ Patent Owner “Tecan Genomics is a subsidiary of the Tecan Group,” who “acquired NuGEN in 2018 and has continued operating NuGEN and its products as Tecan Genomics.” Ex. 2170, 2 n.1.

iv. Copying

Patent Owner asserts that Petitioner copied the claimed invention. PO Resp. 62–64 (citing Ex. 2107 ¶¶ 299–304; Ex. 2170, 31–32; Ex. 2171, 16). According to Patent Owner, “[a]ccess to an embodiment of the claimed invention in combination with similarity can create a strong inference of copying.” *Id.* at 62 (citing *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 70 F.4th 1331, 1340 (Fed. Cir. 2023)).

Patent Owner argues that “in 2013, NuGEN and QIAGEN entered into discussions related to QIAGEN’s potential acquisition of NuGEN. EX2170.0031-32. QIAGEN met with NuGEN employees and reviewed various technical documents concerning the claimed inventions, including underlying research and development documents and pending patent applications. *See id.*” PO Resp. 62. Patent Owner also points to its patent application published in 2013 and an article published online in 2015 as evidence of access. *Id.* (citing Ex. 2107 ¶ 300; Ex. 2171, 16).

According to Patent Owner, “[a]fter QIAGEN’s discussions with NuGEN and NuGEN’s publications on SPET, QIAGEN copied Tecan’s SPET methods, releasing its Single Primer Extension (“SPE”) commercial products.” *Id.* at 62–63 (citing Ex. 2107 ¶¶ 299–304). Pointing to a comparison of the workflows of its Ovation Target Enrichment and Petitioner’s QIAseq Targeted DNA Panel, Patent Owner argues that “QIAGEN’s SPE products copy the claimed features.” *Id.* at 63.

We do not find that the public availability of Patent Owner’s published patent application and online article discussing the claimed invention sufficiently shows Petitioner in fact accessed the information.

As for the alleged access through the business discussion, Petitioner admitted that “NuGEN and QIAGEN entered into discussions related to QIAGEN’s potential acquisition of NuGEN,” and that “it performed some level of due diligence regarding acquisition of NuGEN,” which “involved discussions with QIAGEN employees and reviewing various documents.” Ex. 2171, 31–32. But, Petitioner denied that it “received unfettered access to confidential information concerning NuGEN’s research and development of technologies, its entire IP portfolio, and any other trade secrets that NuGEN possessed.” *Id.*

We are mindful that circumstantial evidence showing “access and substantial similarity *is* evidence of copying.” *Medtronic*, 70 F.4th at 1340. Here, however, the evidence showing access is one level removed: Patent Owner asks us to infer that the documents reviewed by Petitioner include information about the claimed invention. Even if we do so, we cannot accord full weight to such evidence.

Citing Dr. Bustamante’s testimony, Patent Owner contends that Petitioner’s “QIAseq Targeted DNA Panel is just one of its numerous SPE products that were copied from and that are substantially similar, if not identical, to Tecan’s patented technology.” PO Resp. 64 (citing Ex. 2107 ¶ 303). Petitioner points to Dr. Bustamante’s deposition testimony, admitting that certain differences between Patent Owner’s Ovation Target Enrichment and Petitioner’s QIAseq Targeted DNA Panel. *See* Reply 24 (citing Ex. 1120, 390:2–402:9 (Dr. Bustamante explaining that the two products employ different fragmentation methods (enzymatic fragmentation v. sonification), which result in overhang v. blunt end fragments, which in turn require different procedures to attach the adaptor (direct ligation v. end

repair and then ligation)). Although these differences are “not trivial,” they do not go to the heart of the enrichment method. Thus, we find Patent Owner’s evidence shows substantial similarity between Ovation Target Enrichment and Petitioner’s QIAseq Targeted DNA Panel.

We, however, accord this evidence limited weight because the workflow in Petitioner’s QIAseq Targeted DNA Panel is also similar to Shapero’s MARA method. *See* Ex. 1120, 390:2–402:9. In fact, where Petitioner’s QIAseq Targeted DNA Panel differs from Patent Owner’s Ovation Target Enrichment, it is the same in Shapero’s MARA method. *See id.* at 394:14–396:4, 397:23–398:8.

In sum, we accord Patent Owner’s circumstantial evidence of copying, including evidence of access and evidence of substantial similarity, limited weight.

v. Unexpected Results

Patent Owner relies on the Brooks Declaration, submitted during the prosecution of the ’012 patent, as evidence of unexpected results. PO Resp. 67 (citing Ex. 2026, 38¹¹).

We are not persuaded by Patent Owner’s argument. 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

¹¹ Patent Owner cites “Ex. 2026, 4.” *See* PO Resp. 67. Although the quoted language appears on page 4 of Dr. Brooks’ Declaration, it is in fact page 38 of Exhibit 2026.

(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).

Dr. Brooks testified that

I observed unexpected results when enriched nucleic acid sequences generated using the claimed methods were sequenced by massively parallel sequencing. Based on my skepticism, using the claimed methods I expected to observe about fifty percent of sequences of interest in the sequencing results. We actually observed greater than ninety percent of on-target sequences of interest in the sequencing results. Based on my knowledge and experience in this field, I did not expect and would not have predicted this level of specificity. The results were surprising to me. I would not have thought to utilize massively parallel sequencing in this manner and did so because I was asked by NuGEN to perform the method.

Ex. 2026, 38.

Patent Owner’s reliance on Brooks Declaration is insufficient legally because it is unclear what Dr. Brooks considered to be the closest prior art when he alleged unexpected results. We also find no persuasive evidence in Brooks Declaration on the requisite nexus.

Patent Owner’s reliance on Brooks Declaration is also questionable factually. During his deposition, when asked about the “expected” fifty percent on-target rate, Dr. Bustamante answered that “I’m not sure I would agree to 50 percent.” Ex. 1120, 279:8–16.

Thus, we accord the Brooks Declaration little weight in showing unexpected results.

Patent Owner also points to Petitioner's own publication (Ex. 2149) as showing unexpected results. PO Resp. 68–69. According to Patent Owner, Petitioner published an article “comparing the sequencing coverage obtained for specific genes through NGS when using target-specific primer pairs and single target-specific primers.” *Id.* at 68 (citing Ex. 2107 ¶¶ 313–314). Citing Dr. Bustamante's testimony, Patent Owner argues that “a POSA would have expected greater coverage where target-specific primer pairs are used instead of single target specific primers,” but Petitioner's data showed using single target-specific primers, “sequencing coverage substantially increased for the target genes.” *Id.* (citing Ex. 2107 ¶¶ 312–319). According to Patent Owner, this demonstrates unexpected results. *Id.* at 68–69. We are not persuaded by this argument.

Exhibit 2149 states that non-coverage due to primer dropouts “is not an uncommon problem.” Ex. 2149, 1. It explains that

[t]he reason for primer dropouts in 2-primer amplicon designs is the interaction between the forward and reverse primers targeting a specific region to be enriched. If these primers share common sequences, there is a chance they bind to each other, thereby failing to enrich the targeted region, and resulting in coverage gaps.

Id. at 2. It further states that

[t]he solution to this problem is simple – eliminate the need for 2 region-specific primers by using only one region specific primer that targets one end of the targeted region. The other primer is a universal primer that can be shared by all the region-specific primers by binding to universal sequences introduced through library adapters.

Id. at 3.

Thus, Exhibit 2149 merely provides a “simple” solution to “an uncommon problem,” designed based on a known reason. It does not tout the results produced by such a solution as unexpected. And we do not agree that the “enhanced coverage” is equivalent to unexpected results. *See* PO Resp. 68 (citing Ex. 2107 ¶ 316).

vi. Petitioner’s Prior Statements

Patent Owner argues that Petitioner previously made statements that “describe the ‘revolutionary’ nature of using a single target-specific primer for NGS target capture.” PO Resp. 64 (citing Ex. 2107 ¶¶ 305–309; Ex. 2147, 2, 5; Ex. 2148, 1–4; Ex. 2149, 3–5; Ex. 2172, 1). According to Patent Owner, Petitioner’s “prior statements reflect how the prior art did not consider using the claimed single primer enrichment methods with NGS and how the claimed methods addressed numerous long-felt, unmet needs in the art,” and Petitioner’s “praise of its copied products is directly attributable to [Patent Owner] Tecan’s claimed inventions.” *Id.* at 66–67 (citing Ex. 2107 ¶ 309).

Petitioner responds that “[t]he benefits that QIAGEN described in its marketing materials, like high PCR multiplexing capabilities and fewer primers, were benefits that Shapero had identified.” Reply 24 (citing Ex. 1006, 1). Thus, according to Petitioner, its “marketing document stating that the approach was revolutionary simply means it was a departure from what people had generally done and does not identify when the idea came into being.” *Id.*

We acknowledge Petitioner’s prior statements touting the benefits of single primer extension. *See* Ex. 2147, 2, 5; Ex. 2148, 1–4; Ex. 2149, 4. Nonetheless, we agree with Petitioner that, the same enrichment method

employed by Shapero also has those benefits. Thus, we accord moderate weight to Patent Owner's evidence on this point.

c. Summary

In sum, we find Petitioner has shown, by a preponderance of the evidence, that the combination of Shapero and Delseny teaches each limitation of claim 1. Petitioner also has shown, by a preponderance of the evidence, that an ordinarily skilled artisan would have had a reason to combine the teachings of Shapero and Delseny, and in doing so, would have had a reasonable expectation of success to arrive at the claimed invention. In addition, according to Patent Owner's evidence of objective indicia proper weight, we do not find it outweighs the other *Graham* factors and the evidence of obviousness on this record. As a result, we find Petitioner has shown, by a preponderance of the evidence, that the combination of Shapero and Delseny renders claim 1 obvious.

2. Claims 2, 5, 6, 11–15, 17–20, and 22

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 argues the challenges to these claims fail for the same reason that Petitioner fails to show obviousness of claim 1 over the combination of Shapero and Delseny. *See* PO Resp. 53.

We find persuasive Petitioner's mapping of the dependent claims' additional limitations to the asserted prior art and adopt it as our own. *See* Pet. 43–51. For the same reasons we find Petitioner has shown that claim 1 would have been obvious over the combination of Shapero and Delseny, we find Petitioner has shown that claims 2, 5, 6, 11–15, 17–20, and 22 would have been obvious over the combination of Shapero and Delseny.

F. 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* PO Resp. 53.

We find persuasive Petitioner’s mapping of the additional limitations of claims 7–10 to the asserted prior art and adopt it as our own. *See* Pet. 51–53. Because we find no deficiencies in the challenge based on the combination of Shapero and Delseny, we similarly find Petitioner has shown that claims 7–10 would have been obvious over the combination of Shapero, Delseny, and Hamady.

G. 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* PO Resp. 53–54.

We find persuasive Petitioner’s mapping of the additional limitations of claims 3, 4, and 21 to the asserted prior art and adopt it as our own. *See* Pet. 54–55. Because we find no deficiencies in the challenge based on the combination of Shapero and Delseny, we similarly find Petitioner has shown that claims 3, 4, and 21 would have been obvious over the combination of Shapero, Delseny, and Jones.

III. MOTION TO STRIKE

Petitioner filed a Motion to Strike Exhibits 2201–2212 and “portions of the sur-reply (at 9-10, 18-19, 26-28) and Dr. Metzker’s December 3 deposition transcript that rely on or relate to these new exhibits (EX2213 at 55-131).” Paper 31 (“Mot.”). Patent Owner filed an Opposition to the Motion. Paper 33 (“Opp.”). For the reasons explained below, we grant in part and deny in part Petitioner’s Motion.

Under our Rules, “[a] sur-reply may only respond to arguments raised in the corresponding reply and may not be accompanied by new evidence other than deposition transcripts of the cross-examination of any reply witness.” 37 C.F.R. § 42.23(b). Admittedly, Exhibits 2201–2212 are new evidence not authorized under § 42.23(b).

Patent Owner argues that these exhibits are “used to challenge the credibility of Petitioner’s positions.” Opp. 2 (heading normalized). Patent Owner also points out that these exhibits were introduced during the deposition of Petitioner’s expert. *Id.* at 5. Relying on several Board cases, Patent Owner argues that such materials are permissible. *Id.* at 5–6.

We agree with Patent Owner that the Board does not categorically forbid the use of impeachment deposition materials. For completeness of the record, we deny Petitioner’s Motion and enter the challenged exhibits into the record.

We, however, emphasize that we only consider these exhibits for Patent Owner’s stated purpose of impeachment, and not for the substantive analysis of patentability. In addition, we find that challenged exhibits generally do not call into question Dr. Metzker’s credibility. *See Fed. R.*

Evid. § 607 (describing impeachment as the attack of a “witness’s credibility”).

For example, Patent Owner submitted Exhibits 2202 and 2205 to support its argument that Dr. Metzker testified about Petitioner’s products at a prior trial. Sur-reply 26. But as Patent Owner acknowledges, “Petitioner offered no testimony from Dr. Metzker to support [its] position” on copying in this proceeding. *Id.*

Patent Owner represents that “[a]t deposition, Dr. Metzker agreed with Petitioner’s comparison between the QIAGEN method and Shapero” (Sur-reply 26) but the citation “EX2213.0129:22-130:5; EX2212; *see also* EX2210” does not support that representation. Instead, it appears to support Patent Owner’s position that Dr. Metzker “was unaware that QIAGEN did not disclose Shapero to the Patent Office during prosecution of its patents covering Petitioner’s SPE workflow.” *Id.* at 26–27. Patent Owner has not explained clearly which part of Dr. Metzker’s testimony warrants the alleged impeachment by the introduction of Exhibits 2210 and 2212. *See id.*

Similarly, Patent Owner submitted Exhibits 2205 and 2206, apparently to support its argument that “Dr. Metzker previously testified regarding these same products.” Sur-reply 27–28. Again, as Patent Owner acknowledges, “Petitioner surprisingly offered no expert testimony to rebut Tecan’s evidence” on this point. *Id.* at 27. Patent Owner has not explained clearly which part of Dr. Metzker’s testimony warrants the alleged impeachment by the introduction of Exhibits 2205 and 2206.

In another example, Patent Owner argues that Dr. Metzker “claims that the POSA would have believed that no mispriming issues remained because of Shapero’s disclosure of Primer3 and Miura’s ‘new algorithm for

the target specific design.” Sur-reply 9 (citing Ex. 1121 ¶ 27). According to Patent Owner, “[t]his testimony, however, directly contradicts sworn testimony Dr. Metzker gave in a prior case.” *Id.* at 10. To support its position, Patent Owner introduces Exhibit 2203.

We disagree with Patent Owner’s representation of Dr. Metzker’s testimony. Dr. Metzker testifies that

[o]ne of ordinary skill in the art reading the ’012/’108 Patents in 2012 would come away believing that there were no problems with existing SPE forms of enrichment like Shapero (2004) that would have discouraged or prevented one of ordinary skill in the art from analyzing a Shapero (2004) prepared library on an NGS platform because such an enrichment technique produced high rates of off-target products.

Ex. 1121 ¶ 27.

Dr. Metzker, however, does not reason, as Patent Owner alleges, that this is “because of Shapero’s disclosure of Primer3 and Miura’s ‘new algorithm for the target specific design.’” Sur-reply 9. Instead, he testifies that “the ’012/’108 Patents do[es] not teach any specifics regarding the target specific primer design indicating that there is a problem with creating such primers to produce on-target events.” Ex. 1121 ¶ 27. He goes on to testify that

Shapero (2004), in pointing to Primer 3 program and the length of the 3’ end of the target-specific primer, and Miura (2005) describing their new algorithm for the target specific design which also focused on the 3’-end, both discussed previously, were much more informative to one of ordinary skill in the art about how to achieve specificity with SPE than the ’012/’108 Patents are.

Id.

Because Dr. Metzker does not testify as Patent Owner represents, we find that Exhibit 2203 does not properly serve the purpose of impeachment.

In sum, we deny Petitioner's Motion to Strike and enter Exhibits 2201–2212 into the record for impeachment purposes. We, however, find Patent Owner has not clearly explained how these exhibits undermine Dr. Metzker's credibility. We, therefore, accord Dr. Metzker's proper weight.

IV. CONCLUSION¹²

After reviewing the entire record, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1–15 and 17–22 of the '012 patent are unpatentable.

¹² Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

In summary:

Claims	35 U.S.C. §	References	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1, 2, 5, 6, 11–15, 17–20, 22	102	Shapero, Delseny	1, 2, 5, 6, 11–15, 17–20, 22	
7–10	103(a)	Shapero, Delseny, Hamady	7–10	
3, 4, 21	103(a)	Shapero, Delseny, Jones	3, 4, 21	
Overall Outcome			1–15, 17–22	

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has shown, by a preponderance of the evidence, that claims 1–15 and 17–22 of the '012 patent are unpatentable;

FURTHER ORDERED that Petitioner's Motion to Strike is denied;
and

FURTHER ORDERED that, because this is a Final Written Decision, parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2025-00028
Patent 10,036,012 B2

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