

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN Sciences, LLC,
Petitioner,

v.

Tecan Genomics, Inc.,
Patent Owner.

Case IPR2025-00028

U.S. Patent No. 10,036,012

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. THERE WAS NO TEACHING AWAY FROM USING SHAPERO’S MARA ON NGS PLATFORMS	1
A. Shapero and the ’012 Patent Address the Same Concerns.....	1
B. Enrichment Levels Did Not Teach Away From Analyzing Shapero Enriched Libraries With NGS	1
C. Shapero’s Data Indicates High On-Target Rates	3
III. PRIOR PCR ART DOES NOT TEACH AWAY FROM SHAPERO.....	6
A. General PCR and SPE Produced Target-Specific Amplicons	7
B. The Inventors Did Not Believe SPE Had Problems	10
C. The Prior Art Did Not Criticize Shapero	10
IV. MOTIVATION TO COMBINE AND EXPECTATION OF SUCCESS	13
V. SECONDARY CONSIDERATIONS DO NOT SUPPORT NON- OBVIOUSNESS.....	20
A. There Was No Teaching Away or Relevant Skepticism.....	20
B. No Long-Felt Unmet Need Existed.....	22
C. Industry Praise Does Not Support Non-Obviousness	22
D. QIAGEN Did Not Copy The Claimed Inventions	23
E. QIAGEN’s Statements Do Not Support Non-Obviousness.....	24
F. There Were No Unexpected Results	24
VI. CONCLUSION.....	25

TABLE OF AUTHORITIES

	<u>Page</u>
<u>Cases</u>	
<i>In re Ethicon, Inc.</i> , 844 F.3d 1344 (Fed. Cir. 2017)	19, 20, 21, 22, 24, 25
<i>In re Fulton</i> , 391 F.3d 1195, 73 USPQ2d 1141 (Fed. Cir. 2004)	10, 11, 12
<i>Galderma Lab’ys, L.P. v. Tolmar, Inc.</i> , 737 F.3d 731 (Fed. Cir. 2013)	2, 6
<i>Geo. M. Martin Co. v. All. Mach. Sys. Int’l LLC</i> , 618 F.3d 1294 (Fed. Cir. 2010)	22, 23
<i>InTouch Tech., Inc. v. VGO Communications Inc.</i> , 751 F.3d 1327 (Fed. Cir. 2014)	19
<i>KSR Intern. Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007)	13
<i>Leo Pharmaceutical Prods., Ltd. v. Rea</i> , 726 F.3d 1346 (2013)	19
<i>Nike, Inc. v. Adidas AG</i> , 955 F.3d 45, 55 (Fed. Cir. 2020)	21
<i>Virtek Vision Intern. ULC v. Assembly Guidance Systems, Inc.</i> , 97 F.4 th 882 (Fed. Cir. 2024)	19

TABLE OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 10,036,012 (the “’012 patent”)
1002	Prosecution History of U.S. Patent No. 10,036,012
1003	Expert Declaration of Michael L. Metzker, Ph.D.
1004	<i>Curriculum vitae</i> of Dr. Michael Metzker, Ph.D.
1005	Expert Declaration of Sylvia Hall-Ellis, Ph.D.
1006	Shapero, Michael H., <i>et al.</i> , <i>MARA: a novel approach for highly multiplexed locus-specific SNP genotyping using high-density DNA oligonucleotide arrays</i> , NUCLEIC ACIDS RES., 32:e181 pp. 1-9 (2004) (“Shapero”).
1007	Delseny, Michel, <i>et al.</i> , <i>High throughput DNA sequencing: The new sequencing revolution</i> , PLANT SCIENCE, 179:409-422 (2010) (“Delseny”).
1008	Gormley, <i>et al.</i> , <i>Method of preparing libraries of template polynucleotides</i> , U.S. Patent No. 7,741,463 (2010).
1009	U.S. Patent No. 10,876,108 (the “’108 patent”)
1010	U.S. Patent No. 9,650,628 (the “’628 patent”)
1011	U.S. Patent Publication No. 2005/0142577 (“Jones”)
1012	Syvänen, Ann-Christine., <i>Accessing genetic variation: genotyping single nucleotide polymorphisms</i> , NATURE REV. GEN. 2:930-942 (2001).
1013	Tucker <i>et. al.</i> , <i>Massively parallel sequencing: the next big thing in genetic medicine</i> , THE AM. J. HUMAN GEN., 85:142-154 (2009).
1014	Metzker, Michael L., <i>Emerging technologies in DNA sequencing</i> , GENOME RESEARCH, 15:1767-76 (2005).
1015	Metzker & Caskey, <i>Polymerase Chain Reaction</i> , In ENCYCLOPEDIA OF MEDICAL DEVICES AND INSTRUMENTATION, Second Edition, Volume 5, pp. 380-387 (2006).
1016	Sanger, <i>et al.</i> , <i>DNA sequencing with chain-terminating inhibitors</i> ,

Exhibit No.	Description
	PROC. NAT’L ACAD. SCI. USA, 74:5463-5467, 1977.
1017	Ju, <i>et al.</i> , <i>Fluorescence energy transfer dye-labeled primers for DNA sequencing and analysis</i> , PROCEEDINGS IN THE NATIONAL ACADEMY OF SCIENCES IN THE USA, 92:4347-4351 (1995).
1018	Mardis, Elaine R., <i>Capillary electrophoresis platforms for DNA sequence analysis</i> , JOURNAL OF BIOMOLECULAR TECHNIQUES, 10:137-143 (1999).
1019	Smith, <i>et al.</i> , <i>Fluorescence detection in automated DNA sequence analysis</i> , NATURE, 321:674-679 (1986).
1020	Prober, <i>et al.</i> , <i>A system for rapid DNA sequencing with fluorescent chain-terminating dideoxynucleotides</i> , SCIENCE, 238:336-341, 1987.
1021	Gibbs <i>et al.</i> <i>Multiplex DNA deletion detection and exon sequencing of the hypoxanthine phosphoribosyltransferase gene in Lesch-Nyhan families</i> , GENOMICS 7:235-244 (1990) (“Gibbs (1990)”).
1022	Bentley, <i>et al.</i> , <i>Accurate whole human genome sequencing using reversible terminator chemistry</i> , NATURE, 456:53-59 (2008).
1023	Rothberg, <i>et al.</i> , <i>An integrated semiconductor device enabling non-optical genome sequencing</i> , NATURE, Vol. 475:348-352 (2011).
1024	<i>Technology Spotlight: Illumina Sequencing</i> , Illumina, Inc. (2010).
1025	Metzker, Michael L., <i>Sequencing technologies - the next generation</i> , NAT REV GENET., 11(1):31-46 (2010).
1026	Saiki, <i>et al.</i> , <i>Enzymatic amplification of β-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia</i> , SCIENCE, 230:1350-1354 (1985) (“Saiki 1985”).
1027	Saiki, <i>et al.</i> , <i>Primer-directed enzymatic amplification of DNA with a thermostable DNA polymerase</i> , SCIENCE, 239:487-491 (1988) (“Saiki 1988”).
1028	Gibbs, <i>et al.</i> , <i>Detection of single DNA base differences by competitive oligonucleotide priming</i> , NUCLEIC ACIDS RESEARCH 17:2437-2448 (1989) (“Gibbs (1989)”).
1029	Newton, <i>et al.</i> , <i>Analysis of any point mutation in DNA: The amplification refractory mutation system (ARMS)</i> , NUCLEIC ACIDS

Exhibit No.	Description
	RESEARCH 17:2503-2516 (1989) (“Newton (1989)”).
1030	Chamberlain, <i>et al.</i> , <i>Deletion screening of the Duchenne muscular dystrophy locus via multiplex DNA amplification</i> , NUCLEIC ACIDS RESEARCH 16:11141-11156 (1988) (“Chamberlain (1988)”).
1031	Grompe, Markus, <i>The rapid detection of unknown mutations in nucleic acids</i> , NATURE GENETICS 5:111-117 (1993) (“Grompe (1993)”).
1032	Jain <i>et al.</i> , <i>Improved data analysis for the MinION nanopore sequencer</i> , NATURE METHODS 12:351-356 (2015).
1033	Hamady, Micah and Knight, Rob, <i>Microbial community profiling for human microbiome projects: Tools, techniques, and challenges</i> , GENOME RES., 19:1141-1152 (2009) (“Hamady”).
1034	<i>Tecan Genomics, Inc. v QIAGEN Sciences, LLC et al</i> , 1:23-cv-01115-GBW, D.I. 1-1 (D. Del. Oct. 6, 2024).
1035	<i>TruSeq RNA and DNA Sample Preparation Kits</i> , Illumina, Inc. (2010).
1036	<i>Multiplexed Sequencing with the Illumina Genome Analyzer System</i> , Illumina, Inc. (2008).
1037	<i>Ion Torrent Amplicon Sequencing</i> , Life Technologies, Corp. (2011).
1038	Mamanova <i>et al.</i> , <i>Target-enrichment strategies for next-generation sequencing</i> , NATURE METHODS 7:111-118 (2010) (“Mamanova (2010)”).
1039	Turner <i>et al.</i> , <i>Methods for genomic partitioning</i> , ANNUAL REVIEW OF GENOMICS AND HUMAN GENETICS 10:263-284 (2009) (“Turner (2009a)”).
1040	Edwards & Gibbs, <i>Multiplex PCR: Advantages, development, and applications</i> , GENOME RESEARCH 3:S65-S75 (1994) (“Edwards (1994)”).
1041	Ewing <i>et al.</i> , <i>Base-calling of automated sequencer traces using Phred. I. Accuracy assessment</i> , GENOME RESEARCH 8:175-185 (1998) (“Ewing (1998a)”).
1042	Ewing & Green, <i>Base-calling of automated sequencer traces using Phred. II. Error probabilities</i> , GENOME RESEARCH 8:186-194 (1998) (“Ewing (1998b)”).
1043	Markham <i>et al.</i> , <i>A method for the amplification of nucleotide</i>

Exhibit No.	Description
	<i>sequences</i> , European Patent Application No. 0 356 021 (1990) (the “EP ’021 Patent (Markham)”).
1044	Siebert <i>et al.</i> , <i>An improved PCR method for walking in uncloned genomic DNA</i> , Nucleic Acids Research 23:1087-1088 (1995) (“Siebert (1995)”).
1045	Chenchik <i>et al.</i> , <i>Method for suppressing DNA fragment amplification during PCR</i> , United States Patent No. 5,565,340 (1996) (the “’340 Patent (Chenchik)”).
1046	Albert <i>et al.</i> , <i>Direct selection of human genomic loci by microarray hybridization</i> , NATURE METHODS 4:903-907 (2007) (“Albert (2007)”).
1047	Hodges <i>et al.</i> , <i>Genome-wide in situ exon capture for selective resequencing</i> , NATURE GENETICS 39:1522-1527 (2007) (“Hodges (2007)”).
1048	Gnirke <i>et al.</i> , <i>Solution hybrid selection with ultra-long oligonucleotides for massively parallel targeted sequencing</i> , NATURE BIOTECHNOLOGY 27:182-189 (2009) (“Gnirke (2009)”).
1049	Porreca <i>et al.</i> , <i>Multiplex amplification of large sets of human exons</i> , NATURE METHODS 4:931-936 (2009) (“Porreca (2007)”).
1050	Krishnakumar <i>et al.</i> , <i>A comprehensive assay for targeted multiplex amplification of human DNA sequences</i> , PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE USA 105:9296-9301 (2008) (“Krishnakumar (2008)”).
1051	Tewhey <i>et al.</i> , <i>Microdroplet-based PCR enrichment for large-scale targeted sequencing</i> , NATURE BIOTECHNOLOGY 27:1025-1031 (2009) (“Tewhey (2009)”).
1052	Turner <i>et al.</i> , <i>Massively parallel exon capture and library-free resequencing across 16 genomes</i> , NATURE METHODS 6: 315-316 (2009) (“Turner (2009b)”).
1053	Quail <i>et al.</i> , <i>Improved protocols for the Illumina Genome Analyzer sequencing system</i> , CURRENT PROTOCOLS IN HUMAN GENETICS 18.2.1-18.2.27 (2009) (“Quail (2009)”).
1054	(“Locus-specific oligonucleotides were designed using Primer 3 (27).”) I note that reference (27) is Rozen & Skaletsky, <i>Primer3 on the WWW for general users and for biologist programmers</i> , In METHODS IN MOLECULAR BIOLOGY, BIOINFORMATICS METHODS AND PROTOCOLS (Ed. Misener & Krawetz), Humana Press, Totowa New Jersey 132:365-386 (2000) (“Rozen (2000)”).

Exhibit No.	Description
1055-1110	<i>Reserved</i>
1101	(Copy of Exhibit 1044) Siebert et al., An improved PCR method for walking in uncloned genomic DNA, Nucleic Acids Research 23:1087-1088 (1995) (“Siebert (1995)”)
1102	Green et al., A Draft Sequence of the Neandertal Genome, Science 328:710-722 (2010) (“Green”)
1103-1111	<i>Reserved</i>
1112	Fradkov et al., Sequence-Independent Method for in Vitro Generation of Nested Deletions for Sequencing Large DNA Fragments, Analytical Biochemistry 258:138-141 (1998) (“Fradkov”)
1113-1115	<i>Reserved</i>
1116	Briggs et al., Targeted Retrieval and Analysis of Five Neandertal mtDNA Genomes, Science 325:318-321 (2009) (“Briggs”)
1117-1119	<i>Reserved</i>
1120	Bustamante Deposition Transcript, October 7, 2025
1121	Second Expert Declaration of Michael L. Metzker, Ph.D.

I. INTRODUCTION

Shapero solved the same problem, in the same way as the ’012 patent purports to. Each taught preparing an enriched library to be used on subsequent analysis platforms, by using multiplex PCR with a single target specific primer and universal primers. Patent Owner (“PO”) argues that a POSA reading Shapero would suspect the enrichment results were so poor that it would not attempt to analyze the enriched library using NGS. No facts support PO’s claim.

Secondary considerations do not save the validity of the ’012 patent. No evidence of copying, unexpected results, skepticism or praise, linked to claimed elements exists.

II. THERE WAS NO TEACHING AWAY FROM USING SHAPERO’S MARA ON NGS PLATFORMS

A. Shapero and the ’012 Patent Address the Same Concerns

Both Shapero and the ’012 patent teach preparing a PCR enriched library for subsequent analysis. EX1121.¶4-6. Both increase the number of target regions that can be enriched in the same reaction (*i.e.* ‘multiplexing) over what traditional PCR primer pairs allowed.¹ *E.g.*, EX1006.6,7 (“MARA may serve as a target preparation method for highly multiplexed locus specific SNP genotyping that far exceeds the capacity of standard traditional multiplex PCR”); EX1001.6:12-16; EX1121.¶4-6.

¹ The ’012 claims are not limited to multiplexed reactions particular enrichment levels. EX1120.297:21-298:6; 160:9-161:11; 384:6-9.

Shapero recognized that his enrichment methodology had wide application because regardless of the method used to ultimately identify SNPs, “they all share a common feature in that there is a requirement for amplification of the region harboring the polymorphism prior to actual genotyping.” EX1006.6.

Dr. Bustamante testified that by 2010, scientists were genotyping using NGS. EX1120.367:18-23. Similarly, the ’012 patent recognizes that either Affymetrix chips or NGS can analyze enriched libraries prepared in the same way as MARA and ’012 patent. EX1120.307:13-314:20; EX1001.28:8-29:53. Numerous early NGS articles described below explained that enriched libraries were important in NGS applications like genotyping. EX1121.¶6-9. Given that Shapero’s data is consistent with high levels of on-target amplification and enrichment, a POSA would not have been steered away from analyzing a Shapero library on an NGS platform. *Galderma Lab ’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (finding art did not teach away when it did not “indicate [the claimed combination] would be unproductive, nor ... indicate in any way the [drawbacks] would be serious enough to dissuade the development.”).

B. Enrichment Levels Did Not Teach Away From Analyzing Shapero Enriched Libraries With NGS

PO argues 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; EX1121.¶4-12. PO’s expert, Dr.

Bustamante, disagrees. EX1120.279:6-16. He identified a well-known 2010 article reporting libraries enriched between 4-30% being sequenced successfully on an Illumina platform. EX1102.712; EX1120.165:22-169:10. A 2009 publication used SPE to enrich for mtDNA to between 18-40% before NGS. EX1121.¶7-9 (citing EX1116.319). Dr. Metzker’s 2010 NGS review paper (EX1025.41) cited two other publications where NGS platforms sequenced samples enriched to around 50%-60%. Ex.1120-322:25-324:3.

This is consistent with Garber’s 2008 publication stating that tight specificity in a target library may not be important in NGS given its declining cost as people would not care if half the sequencing reads were off-target and thrown away. EX2029.1103; EX1120.181:22-182:19. Going even further, Dr. Bustamante testified that by 2010 people could sequence on an Illumina NGS platform and get useful results even when 75% or 95% of the reads were off-target. EX1120.71:24-73:20,178:8-25.

C. Shapero’s Data Indicates High On-Target Rates

PO then claims that a POSA would interpret Shapero as producing off-target products “at a relatively high rate that would flood the sequencing system and confound the analysis.” POR.56. PO’s expert, however, could point to no Shapero data in the 250-plex experiments showing high off-target rates. EX1120.134-135.

Dr. Bustamante eventually admitted Shapero’s data were actually consistent with high on-target, not off-target effects.

First, Dr. Bustamante admitted primer-dimers are a major contributor to off-target effects. EX1120.216:20-218:4, 350:10-19; EX1001.1:51-53. He testified a common way for POSAs to detect unwanted amplicons before 2012 was to run them on a gel. EX1120.183:9-185:18. Dr. Bustamante testified one would expect any Shapero primer-dimers to be below 100 base pairs, but Shapero’s Fig.2a gel showed no such products. EX1120-228:19-229:13, 229:14-231:7. Dr. Metzker agrees. EX1121.¶13-16.

Second, Fig.2a also indicates that Shapero’s target-specific primers (“TSP”) hybridized on-target. Shapero found reproduceable smears in the expected size range of 150-500 bp, indicating that the TSPs hybridized on-target. EX1006.4. Dr. Metzker agrees. EX1121.¶16. So does Dr. Bustamante: “what I said is what they’re reporting here is a size distribution consistent with what they expected giving a wide range of product lengths between 150 to 500 base pairs consistent with on-target priming. **I’m happy to agree with the experts that this is strong evidence of on-target priming.**” EX1120.215:13-21 (emphasis added).

Shapero’s high on-target rates are also consistent with his discrimination and concordance scores. EX1121.¶¶17. Nonetheless, PO claims that the discrimination scores of 99.4%, call rates of 96.2%, and concordance rates of 98.6% between

MARA and the prior “WGSA” preparation method would have indicated that WGSA was much more accurate and steered a POSA away from believing that MARA was an acceptable library preparation method for NGS. POR.26-27; EX2107.¶226-227. That is not the case.

The slight differences in discrimination and concordance scores between MARA and WGSA are not significant and would not have indicated to a POSA that MARA was unacceptable for NGS. EX1121.¶¶16-17. That is especially true because the MARA experiments used a discrimination score threshold of .08 whereas WGSA used a threshold more than 50% lower: .03. EX.1006.Table1.Caption; EX1121.¶¶16-19. Dr. Bustamante had not properly considered the different thresholds before his deposition. EX1120.124:23-128:22, 145:7-146:14-20 (less SNPs called when DS increased).

Dr. Bustamante called the Shapero authors experts in the types of experiments they were performing. EX1120-150:20-25, 203:25-2045:10. POSAs would as well. EX1121.¶20. There is no reason that given all the data presented in Shapero that a POSA would discount the conclusions the Shapero experts reached about the success of MARA:

- “MARA may serve as target preparation method for highly multiplexed locus-specific SNP genotyping that far exceeds the capacity of standard traditional multiplex PCR” EX1006.2²
- “MARA is a method designed to generate locus-specific DNA target sequences in a highly multiplexed manner” *Id.*3.
- “These 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.*5.
- “Thus, unique locus-specific products are all in a form that allows re-amplification in a universal secondary reaction using a pair of common primers. Importantly, unwanted generic amplification of all input genomic DNA restriction fragments is uncoupled from amplification of selected fragments harboring SNPs of interest that are targeted with locus-specific primers, resulting in a reduced-complexity DNA fraction containing sequences of interest.” *Id.*7
- “Since the efficiency of the primers in MARA did not decrease as the level of multiplexing increased from 1000 to greater than 4000-plex, it is conceivable that MARA could function at the level of 10,000-plex...” *Id.*8.

III. PRIOR PCR ART DOES NOT TEACH AWAY FROM SHAPERO

PO argues a POSA would avoid using Shapero’s enrichment method for NGS because numerous articles allegedly criticize PCR and single primer extension-based

² Pages refer to x/9

preparation methods. EX1121.¶¶21-52. PO also claims numerous references citing Shapero criticize its results or fail to specifically teach combining it with NGS. PO’s citations do not establish teaching away which requires a showing that the claimed combination “would be unproductive.” *Galderma*, 737 F.3d at 739. In fact, as explained below, when the issue of specificity for NGS is addressed at all in the cited references, they support that a POSA would have had the motivation to combine Shapero’s highly-multiplexed methodology with NGS.

A. General PCR and SPE Produced Target-Specific Amplicons

PO claims multiple references teach that because SPE produced high off-target results the field moved away from SPE by 2012. POR.42-43; EX2107.¶60-62. PO ignores a reference from Petitioner showing the opposite. Further, PO’s references show SPE produced high on-target rates and a continuing interest to improve the method even further. For example, Siebert, EX1044/1101, is a reference that used SPE to enrich regions of interest and prepare them for sequencing. EX1101.1088; EX1121.¶21. Just like the ’012 patent, Siebert taught: ligating adaptors, performing SPE, and amplifying the extension product with a common primer annealing to adaptor sequence complements. EX.1120.333:8-334:14.

Dr. Bustamante agreed with Siebert’s conclusion that the method produced high-specificity, and no off-target binding. *Id.*345:15-19; EX1101.1088(“the high

specificity of the method described...”). High on-target binding and specificity were reported two years later in other Siebert group publications utilizing SPE. EX1045.16:30-42;16:56-17:29 (discussing sequencing the products after SPE); EX1112.138 (SPE with suppression adaptors increases specificity and resulted in no detectable background in sequenced products). EX1121.¶21.

Similarly, references PO cited confirm SPE was a viable enrichment method that produced high on-target results. For example, PO claims Sohn’s statement that SPE gene walking could be improved would have steered a POSA away from using SPE. POR.42. The opposite is true. Sohn identified two problems with SPE genome walking: low amplification efficiency and non-specific amplification. EX2050.¶8. Rather than giving up on SPE, Sohn solved the problems. By increasing adaptor ligation efficiency, Sohn alleviated low amplification efficiency. *Id.*¶10. He minimized non-specific amplification using a 3’ OH block on the adaptor. *Id.*¶63. Thus, Sohn would not dissuade a POSA from using SPE. EX1121.¶¶22-24.

Notably, Shapero experienced neither of the problems Sohn identified: Shapero produced sufficient amplification products, and he minimized non-specific amplification products by using a 3’ blocking group on the adaptors to prevent the common primers from independently amplifying. EX1006.Fig.1(“The 3’ amino block helps to prevent background genomic amplification.”);EX1120.356:5-16 (Shapero’s common primers will not produce amplification products on their own

independent of the target specific); *see also* EX1101.1087(identifying an amine blocking group);). EX1121.¶¶22-24.

PO’s citation to Miura also does not demonstrate a teaching away from using SPE. POR.42; EX1120.34-35. As with Sohn, it shows that those in the field believed in SPE and continued to optimize its performance. EX1121.¶25. Miura addressed off-target events by designing a primer optimization algorithm that improved specificity by focusing on the 3’ end of the primer. EX2047.4363; EX1121.¶25. Using the new algorithm, 90% of the amplification products Miura produced with SPE were on-target. *Id.*; EX1120.356:17-357:16. Shapero also focused on the 3’ end as of the TSP. EX1006.7(Materials and Methods); EX1121.¶25. Consequently, Miura encourages, not discourages, a POSA to use SPE by teaching primer optimization strategies if problems are encountered. EX1121.¶25.

Therefore, PO’s claim that “researchers outright dismissed the use of a single target specific primer for enrichment” is unfounded. POR.43; EX2107.¶94 (both citing Bustin, EX2018). No reading of Bustin supports these conclusions. EX1121.¶26. Bustin describes RT-PCR, not creating enriched libraries for analysis in a separate assay, like Shapero and the ’012 patent. EX1121.¶26. There is no rejection of using SPE to create an enriched library as it is not discussed at all. *Id.* Bustin focuses on creating amplicons, not necessarily multiplexed ones, using

traditional primer pairs that have been designed to optimize their specificity. EX2018.598; EX1121.¶26.

B. The Inventors Did Not Believe SPE Had Problems

It is not credible that a POSA believed existing SPE methods like Shapero produced so many off-target events that NGS could not sequence such libraries. Surely, if there were well-known problems as PO now claims, the ’012 patent would have identified them and offered solutions. Despite being given multiple opportunities, however, Dr. Bustamante could find no identification of existing SPE problems in the ’012 patent nor any solutions to those alleged problems. EX1120:241:3-269:20. That is because references like Shapero, Siebert, Sohn, and Miura had already solved any problems. EX1121.¶27. The only reasonable conclusion, therefore, is that the problems PO claims a POSA would have recognized with SPE did not exist when the ’012 patent was filed.

C. The Prior Art Did Not Criticize Shapero

PO claims numerous publications specifically criticize Shapero’s MARA enrichment. POR.46. Mere suggestions of alternatives for particular applications or providing optimization suggestions does not establish teaching away. *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”).

For example, Liu, while focusing on the overall Shapero process, not just the enrichment method, said that while techniques for high-throughput identification of large numbers of SNPs are “highly efficient,” other methods may be more practical for identifying low to moderate numbers of SNPs. EX2141.2,6; EX1121.¶¶28-29. Liu never identifies the enrichment methodology of Shapero as being flawed. *Id.* Notably, Liu recognizes that both NGS and array resequencing like Shapero can be used to identify SNPs. *Id.*

Bui makes similar observations. He recognizes how powerful techniques such as Shapero (ref.12) are for large scale SNP discrimination. EX2138.2. He simply proposes a methodology he believes is better for small-scale genotyping. EX2138.Abstract; EX1121.¶30.

Palka-Santini also does not criticize the enrichment results of Shapero. It recognizes that Shapero (ref.30) allows for highly-multiplexed PCR by replacing a TSP with a common one. EX2139.10; EX1121.¶31. The claim that the process is time consuming because it requires multiple steps like digestion and ligation of adaptors (*id.*) is not one that would dissuade a POSA from using it for enrichment, especially given the time-consuming alternatives for highly-multiplexed reactions. EX1121.¶31. Further, the statement that multi-step processes are prone to

contamination, citing to ref.25, also would not dissuade a POSA from using Shapero’s enrichment method. EX1121.¶31. Ref.25 was published four years before Shapero and thus could not support a finding that Shapero’s methodology was prone to contamination. EX1121.¶31.

Dahl discusses “padlock probes” to create enriched libraries and Howell is a book chapter by multiple Dahl authors covering various SNP detection methodologies. Neither publication states that Shapero results in high rates of off-target amplicons or that it is “rejecting Shapero” as PO claims. POR.46-47. Dahl never specifically discusses Shapero. Rather, Shapero is part of a string cite about methods that allow subsets of genomes to be amplified using adaptor PCR. EX2167.1. EX1121.¶32. Later, Dahl states that the only current way to amplify many defined sequences in the same reaction is using primer pairs. *Id.* If that was interpreted to mean Shapero does not teach multiplexing, as PO claims, it would contradict the explicit teaching in Shapero and later statements by the same authors. EX1121.¶32.

In Howell, three of the five Dahl authors state that Shapero (ref. 135) achieved amplification of specific genomic sequences with a single TSP and a common primer. EX2130.160; EX1121.¶¶33-34. Howell’s statement that none of the enrichment methods to date have achieved the ideal goal of amplifying large sets of sequences without any undesired amplification products also does not denigrate

Shapero. *Id.* EX1121.¶¶33. As Dr. Bustamante admitted, no method, including the claimed “unexpected results” of PO’s product, is capable of producing no undesired amplification products. EX1120.382:19-385:24.³ Importantly, Howell recognizes that while genotyping SNPs in clinical settings has generally focused on known SNPs, the methods discussed can be used in combination with, or be replaced entirely with, new economical sequencing techniques that can provide the exact nature and position of genetic sequences, including unknown SNPs information. EX2130.160,163. EX1121.¶¶33-34.

IV. MOTIVATION TO COMBINE AND EXPECTATION OF SUCCESS

PO claims no motivation exists to combine Shapero’s highly-multiplexed enrichment method with NGS systems. POR.16,46. That is not true. EX1121.¶¶35-52. PO cannot dispute that Shapero teaches his enriched libraries can be analyzed for SNPs, not just with an Affymetrix chip, but by sequencing, through his specific reference to Synvanen. PO does not dispute that Delseny teaches that NGS, the generation of sequencing after Synvanen’s time, can also be used for genotyping. POR.32. Even Dr. Bustamante admitted NGS was used to genotype by 2010. EX1120.367:18-24. These facts satisfy the requirements for finding obviousness that the Supreme Court identified in *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398,

³ For the same reason, Shapero’s statement that “absolute specificity” is not required does not indicate it produces high rates of off-target amplicons. EX1121.¶¶33.

420-421(2007) (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).

More specifically, Dr. Metzker explains that the same reasons that would have led a POSA to analyze a library enriched by Shapero’s method with earlier sequencing methods would have led them to analyze the library on the NGS platforms. EX1121.¶35. And there would have been an expectation of success. *Id.* Nonetheless, PO crafts a lack of motivation to combine argument by misreading Delseny, in a way which, even if true, is irrelevant because it relies on non-existent claim limitations.

PO argues that Delseny encourages genotyping by sequencing only when genomes were previously sequenced. POR.32. Even if that was true, which it is not, it still falls within the scope of the claims.⁴ And, Delseny identifies a benefit of genotyping by sequencing allegedly known genomes: hybridization techniques like the Affymetrix chip will miss InDels and repeats whereas sequencing will not. EX1007.¶4.3; EX1121.¶37.

PO also claims that a POSA would have understood Delseny to at most teach that NGS could be used for whole genome sequencing. POR.33. This argument

⁴ All the examples in the patent call for sequencing the 16s bacterial loci, which had been well characterized by 2012. EX1121.¶39.

ignores the entire section in Delseny entitled “Targeted Sequencing.” EX1007.§4.4. Delseny explains how targeted sequencing is important for patients in medicine, and how it will surely be applied to plants as well. *Id*; EX1121.¶¶38-39. Delseny cites Porreca [ref. 128] as one example of a targeted enrichment method. *Id*. Dr. Metzker explains that Porreca extends a single target specific primer to prepare an enriched library for sequencing. EX1121.¶40.

PO further argues 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. First, this ignores Delseny’s express recommendation to sequence targeted loci by NGS. EX1007.§4.4. Second, it ignores PO’s own references which teach that while raw sequence error rates were initially higher in NGS than Sanger, the raw error rates were offset by the higher read depths available in NGS, which can detect variants that Sanger cannot. EX2169.7; EX1121.¶¶41-42.

Tucker reached the same determination about the raw error rates and read depths while discussing various enrichment schemes for NGS and concluded that even in clinical diagnostic settings, the accuracy of NGS was high enough that it could replace Sanger sequencing when looking for genetic mutations. EX1013.144-145; EX1121.¶43.

Syvänen also does not teach away from using MARA for NGS. Shapero teaches that MARA is a highly multiplexed targeted library preparation method that far exceeds typical multiplexed PCR in preparing a targeted library for SNP genotyping. EX1006.1,2. Shapero cites Syvänen for various ways to accomplish SNP genotyping. EX1006.1[ref.5]. That citation is consistent with the Shapero group’s earlier disclosure in Jones EX1011.¶80 (“The amplified sample may be analyzed by any method known in the art, for example.... For other methods of genotyping analysis *see* Syvänen ...,”).

Syvänen described numerous methods for detecting SNPs, with PCR being used to amplify the targeted region and provide the sensitivity and specificity for detecting SNPs. EX1012.4; EX1121.¶44. Syvänen describes Pyrosequencing (ref 72,74) which can sequence 50 bp fragments, as one SNP genotyping method. EX1012.5. While Syvänen recognized that PCR amplification was the workhorse in all the methods for SNP detection, she suggested that future methods may be better served if they avoided amplification. EX1012.11. Her 2001 suggestion was not followed; by 2010, using PCR amplification to prepare and sequence libraries on NGS platforms was dominant and well accepted.⁵ EX1121.¶44; EX1013 (Figs. 2,

⁵ PO cites Arid (EX2042.011) to claim a POSA would avoid PCR amplification. POR.45. While Arid states that avoiding PCR would avoid any bias it introduces, it also states that is not practical for applications and his improved PCR conditions should alleviate most of the PCR bias issues. Thus, Arid would not teach away from using Shapero to prepare an enriched library for NGS. EX1121.¶44.

3, 4 identifying NGS sequencing based on amplification); EX2011.117 (identifying numerous amplification-based target enrichment methods used for NGS and stating “the 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”). Consequently, nothing in Syvänen would have dissuaded a POSA in 2012 from using Shapero’s MARA with NGS to detect SNPs. EX1121.¶44.

The same is true for Metzker’s 2010 NGS sequencing review article that PO claims “echoed” Syvänen’s teaching away from using PCR amplification with NGS. POR.40. PO cropped a quote from Dr. Metzker’s paper to make its echoing argument. In the full quote, Dr. Metzker said that standard primer pair PCR would require tens of thousands of multiplexed PCR primers to use the entire capacity of NGS sequencing systems, which at that point was not practical. EX1025.41. That is merely a recognition of the problem that Shapero and others had stated by 2005: standard multiplexed PCR could not be enabled beyond several dozen loci per reaction. EX1006.1,7; EX1121.¶45. That statement is not a teaching that Shapero’s PCR enrichment technique could not be used with NGS. Rather, it is a motivation to use it. EX1121.¶45.

MARA enabled 250, 750, 1110 and 4365 loci to be enriched in a single reaction, with all the reported evidence indicating high on-target rates. EX1121.¶45. Further Shapero suggested their results demonstrated that MARA could even

function at levels of 10,000-plex. EX1006.13; EX1121.¶45. As Dr. Metzker explains, this would be further motivation for a POSA to have used MARA enriched libraries with NGS. EX1121.¶45.

In 2010, the state of the art in PCR multiplexed enriched libraries was the Raindance system. EX1025.11; EX1121.¶46. It reported simultaneous amplification of 3976 products using microdroplet PCR. *Id.* This is less than the 4365-plex experiment Shapero conducted with good results. EX1121.¶46. Moreover, the Raindance methodology required a special instrument system to create the individual droplets that would act as individual reaction vessels for each PCR reaction. *Id.* MARA avoided that special instrument cost. *Id.*

MARA also provided advantages over hybrid capture methods of enrichment that would have motivated a POSA to use it. Hybrid capture required primers of hundreds of bases, at least double the length of MARA primers. EX1121.¶47. Hybrid capture also required many primers and a complex method of capturing, segregating and then amplifying the captured products. *Id.* The other prominent enrichment method, padlock probes experienced problems with target coverage. *Id.*

The MARA methodology, however, could be performed with standard reagents, more manageable primers, and technology that was present in the laboratories of scientists who performed PCR, a widely used technique. *Id.* Both coverage and on target rates were understood to be good. *Id.*

Given the results presented in Shapero and the capabilities of NGS systems by 2012, a POSA would have had an expectation of success in combining a MARA enriched library with NGS to sequence regions that were of interest, whether for SNP detection or otherwise. EX1121.¶48. A POSA would not have been dissuaded from this combination because of the capacity of an NGS instrument or the cost of using that entire capacity in a sequencing run.

By 2010, a single investigator’s experiment to sequence an enriched library did not use the entire capacity of an NGS systems. EX1121.¶49. As Tucker pointed out in 2009, investigators could pool their samples on NGS systems and use barcodes to keep track of which results belonged to which investigator. EX1013.8 (citing Varley 2008). Dr. Bustamante confirmed that by 2011, core facilities pooled samples from different investigators into one run and then split the cost of a sequencing run. EX1120.282-284; EX1121.¶¶49-50. For all these reasons, combining MARA with NGS was obvious.

The cases PO cites do not dictate a different result. In *Virtek Vision Intern. ULC v. Assembly Guidance Systems, Inc.*, 97 F.4th 882, 888 (Fed. Cir. 2024), and *InTouch Tech., Inc. v. VGO Communications Inc.*, 751 F.3d 1327, 1351-352 (Fed. Cir. 2014), the experts only provided bare conclusions and failed to provide an articulated rational underpinning for combining references. Here, Dr. Metzker laid out myriad reasons why a POSA would be motivated to use a Shapero library for

NGS. EX1121.¶¶4-51; EX1002.¶¶157-218. In *Leo Pharmaceutical Prods., Ltd. v. Rea*, 726 F.3d 1346 (2013), the prior art did not even recognize the problem or offer a solution. *Id.* at 1353. Here, Shapero identified and solved the same problem as the ’012 patent. Further, while the passage of many decades between the prior art reference and the Leo invention suggested hindsight analysis, Shapero was published only 8 years before the priority date. *Cf. In re Ethicon, Inc.*, 844 F.3d 1344, 1352 (Fed. Cir. 2017) (“The mere age of the references is not persuasive of the unobviousness of the combination of their teaching” without evidence the art tried and failed to solve the problem).

V. SECONDARY CONSIDERATIONS DO NOT SUPPORT NON-OBVIOUSNESS

A. There Was No Teaching Away or Relevant Skepticism

As discussed previously, the articles that PO relied on like Miura, Sohn, Metzker and Syvänen did not teach away from using Shapero’s MARA method. At most, they identified areas in SPE that could be optimized and taught how to do so. Other references, in addition to not being consistent with PO’s reading, lack the required legal and factual nexus for a secondary consideration.

EX2139, published years before Shapero, could not be commenting on his results. EX2130 is only stating that Shapero does not produce zero undesired amplification products, a requirement that is not in the claims and that no one, including the inventors, have achieved. EX1120.383:11-385:24; *see also Ethicon*,

Inc., 844 F.3d at 1352 (rejecting secondary considerations that rely on unclaimed features).

Dr. Bustamante admitted that the claims required no particular level of enrichment, and no levels were discussed as preferred in the specification. EX1120.160:9-161:11. PO’s reliance (POR.56-57) on Dr. Brooks’ personal skepticism (EX2026.37-38) about levels of enrichment is, therefore, legally irrelevant. *Ethicon* 844 F.3d at 1352 (rejecting secondary considerations that rely on expert’s personal beliefs rather than what a POSA would believe.)

Factually, neither Dr. Bustamante nor Dr. Metzker agree with Dr. Brooks’ 50% enrichment level expectation. EX1120.279:6-16,280:6-281:7; EX1121.¶7. Similarly, Dr. Bustamante stated that even if 95% of the material generated during amplification was off-target, one could still get useful information off an NGS sequencing instrument and a POSA would not be dissuaded from doing so. *Id.*161:19-164:3. This factually contradicts Dr. Brooks’ claim that at enrichment levels of 50% would “confound” NGS sequencing. EX.2026.¶14. Unlike Dr. Brooks’ bare personal conclusion, Dr. Bustamante pointed to published papers, that showed useful sequencing data was obtained on Illumina sequencers prior to 2012 even with levels of enrichment well below or at the 50% level. EX1120:162:5-167:7(referencing EX1102), 321:5-10, 324:9-326:14(referring to publications cited in EX1025).

Dr. Brooks’ declaration is factually and legally insufficient to establish teaching away and skepticism.

B. No Long-Felt Unmet Need Existed

PO’s unmet need argument focuses on the desire for faster and more cost-effective methods for preparing enriched libraries. POR.57-59. Shapero had already disclosed the exact same library preparation enrichment steps of the ‘012 patent claims. EX1120.265:7-17. Thus, PO cannot argue that the ’108 patent solved an unmet need when the solution already existed. *Nike, Inc. v. Adidas AG*, 955 F.3d 45, 55 (Fed. Cir. 2020) (finding no unmet need because “other methods” to meet the need “existed before the date of invention”). Moreover, it is improper to rely on unclaimed elements to support a secondary consideration. *Ethicon* 844 F.3d at 1352. Here the ‘012 patent claims have no speed or cost requirements. In any event, Shapero solved the cost and speed issues by teaching the preparation enriched multiplex libraries using SPE years before the ‘012 patent drafted claims covering SPE but not limited to multiplexing. EX1120.297:21-300:8, 342:13-345:19

C. Industry Praise Does Not Support Non-Obviousness

PO cites Barchi (EX2065) and Scaglione (EX2068) as praising its commercial product. But what PO describes these articles praising is the library preparation method that relies on SPE because it simplifies panel design and allows higher levels of multiplexing. POR.60. Again, the ’012 claims do not require multiplexing.

Further, Shapero prepared libraries in the same way as the ’012 patent and published the exact same benefits that PO now espouses. EX1006. Another article PO relies on, EX2067.3, identifies the same benefits as Barchi and Scaglione and then quotes Tecan’s own product manager to hype the benefits of the product. *Geo. M. Martin Co. v. All. Mach. Sys. Int’l LLC*, 618 F.3d 1294, 1305 (Fed. Cir. 2010) (dismissing “self-serving statements”). These instances of “praise” are factually and legally insufficient to establish non-obviousness.

D. QIAGEN Did Not Copy The Claimed Inventions

PO cites no facts establishing copying. That details of its product were available to the public in 2015 does not show that anyone at QIAGEN accessed that information. POR.62. Similarly insufficient is PO’s claim that QIAGEN had access to technical documents about the ’012 patent and other pending patent applications during diligence exploring the purchase of PO’s predecessor in 2013. PO cites QIAGEN’s answer to the complaint as support for the preceding allegation. EX2170.31-32. But QIAGEN denied that it received unfettered access to confidential information about Nugen’s technology and trade secrets and IP. *Id.* It further denied that it had received lists of all pending patent applications and file histories. *Id.* Nothing in these denials establishes that QIAGEN copied the ’012 inventions.

Last, PO points to a side-by-side comparison of the library preparation steps in PO’s product and QIAGEN’s products and claims similarities establish copying. POR.63-64. Dr. Bustamante admitted, however, the QIAGEN workflow is closer to the Shapero workflow than PO’s. EX1120.390:2-402:9.

E. QIAGEN’s Statements Do Not Support Non-Obviousness

The benefits that QIAGEN described in its marketing materials, like high PCR multiplexing capabilities and fewer primers, were benefits that Shapero had identified. EX1006.1. Thus, QIAGEN’s 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. Moreover, QIAGEN also attributed the robustness of its product to the use of UMI’s and primer design, elements that are not part of the ‘012 claims. EX2147.2,5. Because QIAGEN was pointing to non-claimed elements and benefits recognized in Shapero these statements do not support non-obviousness. *Ethicon*, 844 F.3d at 1352.

F. There Were No Unexpected Results

As with other secondary considerations, for unexpected results to be legally relevant, PO must prove they are due to a claimed rather than unclaimed feature. *Ethicon*, 844 F.3d at 1352. Here the purported unexpected result is achieving 90% on target reads while expecting only 50%. POR.67. In the first instance, Dr. Brooks refers to his own expectations rather than the required POSA’s. EX2026.¶14 (“I was

skeptical ... I thought ... I thought ... I thought ...”). It is only a POA’s expectation that can establish this secondary consideration. *Ethicon*, 844 F.3d at 1352 (“Ethicon’s expert never even opined that the results ... would have been unexpected to a person of ordinary skill in the art”).

Drs. Bustamante and Metzker refute Dr. Brooks’ personal expectation from a factual standpoint. EX1120.279:6-16,280:6-281:7; EX1121.¶7. More specifically, given that all the data in Shapero indicates it is free of primer-dimers, produces amplicons of the expected size and gives detection results that cover virtually everything it is supposed to, there is no basis to expect it was only producing 50% on target. EX1121.¶¶15-16. Additionally, because the ‘012 claims do not require any level of enrichment the “unexpected 90% enrichment” is not relevant because it is not tied to a claim element. *Ethicon*, 844 F.3d at 1352.

VI. CONCLUSION

For the foregoing reasons, the Board should determine that all challenged claims are unpatentable.

DATED: November 12, 2025 Respectfully submitted,

By /Matthew A. Traupman/
Matthew A. Traupman (Reg. No. 50,832)
matthewtraupman@quinnemanuel.com
QUINN EMANUEL URQUHART
 & SULLIVAN LLP
51 Madison Avenue, 22nd Floor
New York, NY 10010
Tel: (212) 849-7000
Fax: (212) 849-7100

Attorney for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(a) and (d), the undersigned hereby certify that the **PETITIONER’S REPLY TO PATENT OWNER’S RESPONSE** complies with the type-volume limitation of 37 C.F.R. § 42.24(a)(i) and (b)(i) permitting a preliminary response of up to 5,600 words because, exclusive of the exempted portions, it contains 5,295 words as counted by the word processing program used to prepare the paper.

Date: November 12, 2025

Respectfully submitted,

By: /Matthew A. Traupman/
Matthew A. Traupman (Reg. No. 50,832)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
51 Madison Avenue, 22nd Floor
New York, New York 10010
matthewtraupman@quinnemanuel.com

Attorney for Petitioner

CERTIFICATE OF SERVICE

I certify that on November 12, 2025, true and correct copies of the foregoing
Petitioner’s Reply to Patent Owner’s Response were served via electronic mail on the
following counsel of record for the Patent Owner:

Linnea P. Cipriano
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018
Phone: (212) 813-8800
Fax: (212) 355-3333
LCipriano@goodwinlaw.com

John P. Padro
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018
Phone: (212) 459-7349
Fax: (212) 428-6751
JPadro@goodwinlaw.com

Scott T. Weingaertner
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018
Phone: (212) 459-7067
Fax: (212) 202-6268
SWeingaertner@goodwinlaw.com

Timothy J. Beavers
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018
Phone: (212) 459-7208
Fax: (212) 355-3333
Tbeavers@goodwinlaw.com

Date: November 12, 2025

/Matthew A. Traupman/
Matthew A. Traupman (Reg. No. 50,832)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
51 Madison Avenue, 22nd Floor
New York, New York 10010
matthewtraupman@quinnemanuel.com

Attorney for Petitioner