

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

PATENT OWNER'S SUR-REPLY

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2181-2199		<i>Reserved</i>
2200	Beavers Declaration	Declaration of Timothy J. Beavers in Support Of Notice of Intent to Designate Provisionally Recognized PTAB Attorney as Back-Up Counsel Under 37 C.F.R. § 42.10
2201	ArcherDX v. QIAGEN Docket Report	<i>ArcherDX, LLC v. QIAGEN Sciences, LLC</i> , No. 1:18-cv-01019-MN, D. Del. (filed July 10, 2018)
2202	<i>ArcherDX v. QIAGEN</i> Accused Products List	Plaintiffs' Identification of Accused Products, <i>ArcherDX, LLC v. QIAGEN Sciences, LLC</i> , No. 1:18-cv-01019-MN (D. Del. Aug. 23, 2021), Doc. No. 451
2203	<i>ArcherDX v. QIAGEN</i> Declaration 1	Public Version of Declaration of Eric J. Rutt in Support of Plaintiffs' Motion for Partial Summary Judgment of No Invalidity as to U.S. Patent No. 10,450,597 and to Strike and Preclude Testimony, <i>ArcherDX, LLC v. QIAGEN Sciences, LLC</i> , No. 1:18-cv-010109-MN (D. Del. Mar. 8, 2021), Doc. No. 338
2204	<i>ArcherDX v. QIAGEN</i> Declaration 2	Public Version of Declaration of Eric J. Rutt in Support of Plaintiffs' Motion for Partial Summary Judgment of No Invalidity as to U.S. Patent No. 10,450,597 and to Strike and Preclude Testimony, <i>ArcherDX, LLC v. QIAGEN Sciences, LLC</i> , No. 1:18-cv-010109-MN (D. Del. Mar. 8, 2021), Doc. No. 338-1
2205	<i>ArcherDX v. QIAGEN</i> Declaration 3	Public Version of Declaration of Eric J. Rutt in Support of Plaintiffs' Motion for Partial Summary Judgment of No Invalidity as to U.S. Patent No. 10,450,597 and to Strike and Preclude Testimony, <i>ArcherDX, LLC v. QIAGEN Sciences, LLC</i> , No. 1:18-cv-010109-MN (D. Del. Mar. 8, 2021), Doc. No. 338-2
2206	QIAGEN Opposition Motion	QIAGEN'S Opposition to ArcherDX's Motion for Injunction, Ongoing Royalty, Supplemental Damages, Pre- and Post-Judgment Interest, and

Ex.	Short Name	Description
		Enhanced Damages, No. 1:18-cv-01019-MN (D. Del. Dec. 8, 2021), Doc. No. 508
2207	QIAGEN Appeal Brief	Brief for Defendants-Appellants, <i>ArcherDX, LLC v. QIAGEN Sciences, LLC</i> , No. 23-2350 (Fed. Cir. Dec. 15, 2023)
2208	Peng 2019	Quan Peng et al., <i>Targeted Single Primer Enrichment Sequencing with Single End Duplex-UMI</i> , 9 SCI REP 4810 (2019)
2209	QIAGEN Patent Application	U.S. Patent Application Publication No. 2025/0002900
2210	QIAGEN European Patent Specification	European Patent Application Publication No. EP3362577B1 for European Patent Application No. 16784755.7
2211	QIAGEN European Patent Office Reply	October 26, 2020 Reply to the Communication pursuant to Article 94(3) EPC dated 18 June 2020, European Patent Application No. 16784755
2212	'438 Patent	U.S. Patent No. 10,941,438
2213	Metzker Deposition 3	Transcript for the December 3, 2025 Deposition of Dr. Michael L. Metzker

Shapero does not disclose the methods claimed in the '012 patent nor even the same technology. Shapero uses MARA with microarrays. There is nothing in the prior art that suggested using MARA with NGS. Despite crafting an argument that uses only part of Shapero's method, Petitioner makes no effort to demonstrate why a POSA would have been motivated to abandon Shapero's microarrays. Petitioner also cannot show why a POSA would have been motivated to couple MARA with NGS.

Petitioner's arguments are at odds with its own cited references. For example, if Shapero was more effective than NGS, as Petitioner contends (*see, e.g.*, Paper 22, 17-18), a POSA would not have modified Shapero for NGS. Delseny and Syvänen also taught away from Petitioner's combination. Rather than address these teachings, Petitioner relies on new references in reply. These references demonstrate the high level of variability and tradeoffs that existed at the time. There were at least hundreds of different ways in which a POSA could have modified Shapero, but Petitioner fails to show why the POSA would have modified Shapero in the specific manner to arrive at the claimed inventions. Petitioner similarly does not meaningfully rebut Tecan's secondary considerations.

Petitioner cannot meet its burden by relying on the unsupported, hindsight-driven statements of Dr. Metzker and an overgeneralized reliance on the potential uses of NGS by 2012. Dr. Metzker and Petitioner's prior statements undermine their

current arguments. Dr. Metzker published an article in 2010 discouraging using the type of PCR amplification disclosed in Shapero for NGS. Prior to this litigation, Petitioner lauded its single-primer-enrichment NGS products as a breakthrough, publishing the unexpected results obtained from using the claimed methods. The real world evidence shows that the methods of the challenged claims were not obvious; as Petitioner described in 2018, they were “revolutionary.”

I. PETITIONER FAILS TO DEMONSTRATE A MOTIVATION TO COMBINE

Petitioner’s arguments are almost entirely based on conclusory statements. *See* Paper 22, 2 (“[B]y 2010, scientists were genotyping using NGS.”). None of Petitioner’s cited references (*i.e.*, Shapero, Delseny, and Syvänen) include such broad statements, and Petitioner fails to identify evidence in the record to support its allegations that a POSA would combine the prior art to arrive at the claimed methods. Repeatedly, Petitioner attempts to shift the burden of obviousness to hide its failure to show motivation by arguing that a “POSA would not have been steered away from” Petitioner’s combination. *See, e.g.*, Paper 22, 2. Not only is this incorrect, for the reasons explained below, but it assumes there is a motivation to combine where none exists. Petitioner cannot demonstrate that a POSA would have been motivated to (1) divorce the MARA method from microarrays, and (2) couple the MARA method with NGS in the manner claimed. Additionally, Petitioner

essentially abandons its originally relied-upon references, Delseny and Syvänen, given that they teach away from adapting methods like Shapero for use with NGS.

Petitioner's argument that "at the time of the invention ... there [was] a known problem for which there [were] a finite number of predictable solutions" is undermined by the record. Paper 22, 13-14. As Petitioner's own art demonstrates, there were hundreds, if not thousands, of potential solutions. *See, e.g.*, EX1007.0419-422; EX1012.0934; EX1025.0041-42; EX1038.0114. Far from a finite number of solutions to a known problem, NGS methods were highly variable and uncertain. Petitioner's reliance on numerous new prior art references in reply, while improper, only highlights its hindsight-driven analysis. "KSR did not do away with the requirement that there must exist a motivation to combine various prior art references in order for a skilled artisan to make the claimed invention." *Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 887 (Fed. Cir. 2024). The Petition fails to demonstrate this fundamental requirement.

A. Shapero Does Not Use or Suggest NGS

Rather than rebut Tecan's Response, Petitioner oversimplifies the inquiry and incorrectly claims that Shapero addressed the same concerns as the '012 patent. Under Petitioner's view, all combinations of every library preparation method with any sequencing platform would have been obvious, regardless of any specific characteristic of the library preparation methods or the sequencing techniques. Such

a view overlooks the complexity of this technology and is not in line with the law of obviousness.

When viewed in light of the genomic sequencing field, Shapero was solving a different problem than the claimed methods. Shapero sought to improve methods for microarrays, both for target capture and analysis. Paper 17, 20-21, 29-30. As explained in Tecan's Response, microarray technology is distinct from NGS because microarrays rely on target-specific probes to confer target specificity. *Id.*, 20-24.

The '012 patent, on the other hand, explains that prior-art microarray capture methods require "complex pools of costly long oligonucleotides and long periods (typically 48 hours) of hybridization for efficient capture," "expensive instrumentation and hardware," and "large quantities of input DNA" due to the "relatively low efficiency of the hybridization reaction." EX1001.0016 (2:4-10). Because of these limitations (among others), the specification describes "a need for improved methods for selective target enrichment that allow for low-cost, high throughput capture of genomic regions of interest without specialized instrumentation." EX1001.0016 (2:25-28).

Shapero's method suffers from all the flaws identified in the specification. Shapero used specialized instrumentation for target capture and analysis, namely the instrumentation associated with Affymetrix microarrays. Paper 17, 1, 23-24. Shapero did not attempt to avoid the numerous target-specific probes attached to the

microarray chip and instead utilized the chip to provide the desired target specificity.

Id.

The claimed methods are quite different. They promote efficiency through the incorporation of universal binding sites that can be used both for amplification and sequencing and require no specialized instruments (*i.e.*, microarrays). Despite Dr. Metzker's incorrect application of the specification (EX1121.¶5), the claimed methods specifically require that the enriched sequences be sequenced with a massively parallel sequencing platform, *i.e.*, NGS. Paper 17, 14-16. As explained in Tecan's Response and further below, the microarrays are critical to Shapero's method and data analysis, and a POSA would not have viewed the MARA method to be interchangeable with other sequencing methods.

Petitioner's arguments are flawed in part because they attempt to rewrite Shapero to divorce MARA and its data from its microarrays. Shapero does not teach that MARA can be used with anything other than an allelic-discriminatory method, like microarrays. EX1006.0001-02; *see also* EX1006.0007-08. Shapero even attributes its results (including multiplexing levels) to the combination of MARA **and** its microarrays: "In conclusion, multiplex levels for SNP genotyping that are higher than typically achieved through standard multiplex PCR have been demonstrated using MARA ***in conjunction with*** allele-specific hybridization on high-density DNA arrays." EX1006.0008 (emphasis added).

Petitioner looks beyond Shapero—to Syvänen and Jones—to claim that a POSA would have understood MARA alone could be used with other analytical platforms and methods, but these arguments are misplaced. *See* Paper 22, 13, 16. Shapero cites to Syvänen as an example of flawed prior art genotyping methods, which Shapero aspires to improve upon. Paper 17, 35-36. Jones, like Shapero, never discloses MARA without a microarray. *See, e.g.*, EX1011.0015, [0076] (explaining that the MARA “amplified product may be analyzed by hybridization to an array of probes”). The single paragraph from Jones that Petitioner cites (Paper 22, 16) describes an embodiment that uses a microarray to capture target-specific probes. EX1011.0016, [0080]. Not once does Shapero suggest that MARA can or should be used with any other instrument than its arrays. Accordingly, Petitioner’s list of out-of-context statements (Paper 22, 5-6) from the “Affymetrix experts” in “microarray technology” (EX1120.0150:20-151:1, 203:25-04:2) provides no reason to drop Shapero’s arrays for NGS. Just the opposite, Shapero is about optimizing arrays and would not support such a change.

In fact, Petitioner has not identified any publication that suggests using MARA with NGS. *See* Paper 17, 45-46. Instead, Petitioner improperly relies on Dr. Metzker’s conclusory testimony to fill in fundamental gaps in its Petition. For example, Dr. Metzker claims, without support, that the POSA would have known that the MARA amplicons could be analyzed on different platforms with no need for

a microarray. *See* EX1121.¶5. These conclusory, gap-filling assertions are insufficient. *Apple Inc. v. MPH Techs. Oy*, 28 F.4th 254, 262-63 (Fed. Cir. 2022). Further, Dr. Metzker’s opinions are inconsistent with his statements in prior publications. Paper 17, 40-41. As explained in Tecan’s Response, in 2010, Dr. Metzker discouraged the use of PCR amplification with NGS, stating: “coupling PCR with high-throughput NGS platforms for targeting strategies is not practical.” Paper 17, 40-41; EX1025.0041. Petitioner’s attempts to rewrite and explain away Dr. Metzker’s prior inconsistent statements are nothing more than self-serving hindsight. *See* Paper 22, 19.

B. Petitioner Has Failed to Establish that a POSA Would Have Been Motivated to Couple MARA with NGS

1. A POSA Would Have Been Concerned About Target Specificity

In designing an NGS library preparation method, a POSA would have been most concerned with accuracy. Paper 17, 25. It was a well-known problem that primers could bind to unwanted locations, including mispriming and primer dimers. *Id.*, 42-44. Amplification methods—especially with universal primers—can exacerbate these issues by proliferating the unwanted products from off-target binding. *Id.*; EX2107.¶55.

Unlike the microarrays used in Shapero, NGS platforms have no ability to filter off-target products. Paper 17, 20-24. Library preparation methods that result

in high levels of off-target products can diminish the accuracy of the sequencing information and are therefore undesirable. EX2107.¶¶55, 59. This is especially true where inaccurate reads comprise a large percentage of the sequencing data. *See* EX2107.¶288. Decreased accuracy increases associated costs and time, which the art, including Shapero, sought to avoid. Paper 17, 25; EX2107.¶151; *see* EX1006.0002. Petitioner does not meaningfully dispute the numerous references discussing these concerns. Instead, Petitioner raises a series of strawman arguments, many of which misrepresent the issues and Tecan's positions. None of Petitioner's arguments demonstrate a motivation to combine.

First, Tecan has not argued that "a POSA would expect an SPE library to only enrich at the 50% level" and that NGS "required enrichment levels much higher than 50%," as Petitioner alleges. Paper 22, 2; EX1121.¶7. Rather, Tecan asserts that a POSA would not have been motivated to use a sequencing method with low or unknown target specificity. Paper 17, 24. As shown consistently throughout the prior art, POSAs were concerned with achieving target specificity that improved the efficiency of sequencing runs. Paper 17, 25, 32-38, 41-45.

Second, the niche area of sequencing ancient DNA cannot be broadly applied to the sequencing field as a whole. Petitioner relies on "ancient DNA" publications, such as Green and Briggs, to argue that the POSA would have been content with sequencing results that were only 4-40% on target. Paper 22, 3. Petitioner also

mistakenly alleges that Dr. Bustamante testified that “a POSA would not be dissuaded from” using NGS where 95% of the results are off-target. *See* Paper 22, 21. Notably, this testimony was in response to questions about sequencing ancient DNA, where source material is scarce. EX1120.0161:19-164:3. As Dr. Bustamante explained, sequencing neanderthal DNA 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.” EX1120.0071:24-73:25, 161:19-164:3, 178:8-25. The concessions made for ancient DNA cannot be generalized to apply to a POSA allegedly looking for an improved NGS method. *See* Paper 17, 25, 41-44.

Third, Petitioner’s reliance on hybrid capture references are misplaced and do not support its contention regarding target specificity. Paper 22, 3 (citing EX1025.0041). Like Shapero, these papers concern microarrays, and cannot be used to infer single-primer target specificity. Paper 17, 20-24, 49-50. The same is true for Briggs, which uses hybrid capture to isolate and amplify target sequences. EX1116.0319.

Fourth, Petitioner’s conclusory arguments that the prior art had already solved target-specificity concerns are unsupported. Paper 22, 10. Petitioner relies solely on Dr. Metzker (*see e.g.*, EX1121.¶27), who 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.” EX1121.¶27.

This testimony, however, directly contradicts sworn testimony Dr. Metzker gave in a prior case. EX2213.65:1-67:4, 72:14-22. There, Dr. Metzker testified that Primer3 is used preliminarily and explained that “[a]t a minimum, you would actually do real experimental assays” because “these programs can create misinformation and they can be inaccurate.” *See* EX2203.0070:15-71:10, 72:8-11. In fact, Dr. Metzker testified that he did not use programs like Primer3 to assess mispriming. EX2203.0072:19-73:5.

Fifth, Petitioner claims that no off-target binding issues must have existed by 2012 because the '012 patent does not reference any. Paper 22, 10. This artificial requirement is of no legal significance. It is also incorrect: the claimed methods address concerns with target-specificity, which is reflected by the prosecution history. *See, e.g.*, EX2026.0029-39.

2. Shapero's Data Does Not Support Petitioner's Off-Target Claims

Petitioner relies on Shapero's data to argue that a POSA would have been motivated to use the MARA method (*see, e.g.*, Paper 2, 38), but all the data cited by the Petition comes from Shapero's microarrays. *See id.*, 36-40. There is nothing in the record that supports a claim that this data is relevant to using MARA with NGS. Paper 17, 18-31. Rather than addressing this deficiency, Petitioner misconstrues

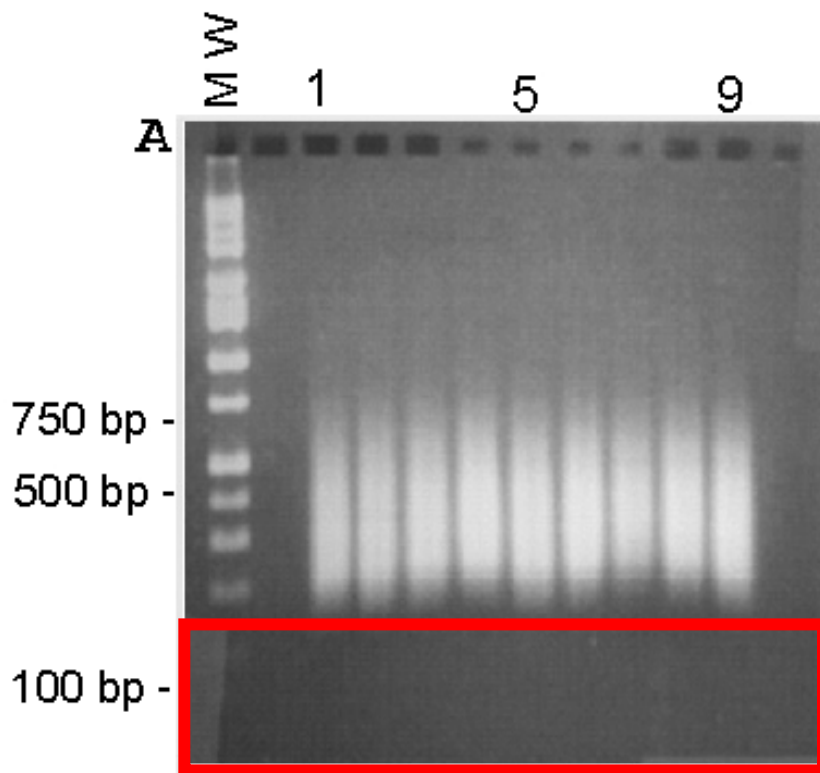
Shapero's data and Dr. Bustamante's corresponding testimony to fit its narrative. *See* Paper 22, 3-6.

As an initial matter, there is no dispute that a POSA cannot use the array data to determine what portion of the amplified library consists of off-target products that were amplified through MARA. *See* Paper 17, 28-30. As Dr. Metzker acknowledged, the array data does not show whether non-specific primer-target annealing was an issue in the MARA reaction. EX2213.0040:9-41:7. This is consistent with Dr. Bustamante's explanation. EX2107.¶215; EX1120.0139:10-17. Rather than substantively respond to this point, however, Petitioner misconstrues Dr. Bustamante's testimony. Paper 22, 3. As Dr. Bustamante testified, "[t]here is no evidence either way." EX1120.0134:21-22.

Petitioner's new arguments regarding the gel reads in Figure 2 are similarly lacking. As Dr. Bustamante testified, a POSA cannot draw any inferences as to MARA's mispriming from the gel reads. EX1120.0215:13-216:2; *see also* EX2047.4368 (noting that it would be "difficult to judge" target specificity based on a gel.). Petitioner fails to rebut this testimony. *See* Paper 22, 4. Petitioner instead tries to misconstrue the gel reads to focus on primer dimers, but a POSA cannot draw any inferences about MARA's generation of primer dimers from these gel reads for three reasons.

First, before the reads were run on the gel, Shapero used an exonuclease digestion step to remove products other than the full-length extension products. EX1006.0004. As a result, primer dimers and other partial sequences would have been removed from the mixture, reducing the chance that any small fragments would be seen on a gel.

Second, to the extent that any primer dimers remained in the solution, the data as presented did not capture them. EX1120.0228:7-15. As Dr. Bustamante explained, the 100 bp ladder band (*i.e.*, the control) was entirely missing from the gel. EX1120.0230:5-19. While the author's annotation indicates where the band was expected to be, the gel does not show the 100 bp control. The missing control suggests that there was an issue with the portion of the gel where primer dimers would have been expected, and Dr. Metzker concedes this possibility. EX1120.0229:21-230:8; EX2213.0045:12-20.



EX1006.0004 (Fig. 2(A)) (annotated). Dr. Metzker’s unmoored claim that there is a control present for the 100 bp highlights the weakness in Petitioner’s arguments (EX1121.¶15) and must be disregarded. *See Tinnus Enters., LLC v. Telebrands, Corp.*, 733 F. App’x 1011, 1022 (Fed. Cir. 2018).

Third, Petitioner misconstrues Shapero’s negative controls that excluded MARA’s locus-specific primers. Paper 22, 8-9. As Dr. Metzker admitted, “Shapero (2004)’s common primers will not produce amplification products on their own independent of the target specific primer extension through the A2 adapter.” EX1121.¶23. The negative control experiment excluded the locus-specific primers necessary for amplification, and as a result, extension products were not generated

and amplification did not occur except through experimental error. EX2107.¶¶221-226. Because the negative controls fail to amplify the sample, it is not surprising that there was not enough sample for analysis. EX2107.¶¶223-225. Both Drs. Metzker and Bustamante agreed that the “common primers did not produce quantities sufficient for the chip to detect.” EX1121.¶19; EX2107.¶225. Thus, the negative controls provide no data regarding the locus-specific primers’ target specificity and would not have motivated a POSA to use the MARA method outside the scope of Shapero’s disclosure. Paper 17, 27-28. The Board should disregard Dr. Metzker’s contradictory testimony about the conditions of the negative control experiment (EX1121.¶¶19, 23). *Interactive Comms. Int’l, Inc. v. Blackhawk Network Inc.*, IPR2024-00465, Paper 40, at 2-3 (PTAB Oct. 9, 2025).

Even accepting Petitioner’s claims regarding Shapero’s data, however, this data motivates *against* altering Shapero’s methods. If Shapero’s data was superior to other analytical methods, there would be no reason for a POSA to dissemble a method and alter it for different technology. Every supposedly favorable disclosure of data confirms that a POSA would have been motivated to continue using Shapero’s entire method, including the microarrays, and not NGS. Paper 17, 29-30.

Further, Petitioner’s dispute regarding how Shapero calculated the concordance rates distracts from the point that matters. Paper 22, 5. Petitioner does not address Dr. Bustamante’s conclusion that a POSA would have been discouraged

by MARA's four-to-five-fold discordancy when compared to Affymetrix's standard values. EX2107.¶168. Petitioner's only argument is that the methods Shapero compared used two different discrimination-score thresholds. That did not stop Shapero from evaluating MARA based on how it performed against a library method specifically designed to amplify all sequences and to avoid targeting specific loci (WGSA). Paper 17, 50-51; EX1006.0011 (describing calls obtained by MARA that differed from WGSA as "miscalled"). Petitioner fails to explain why it would not have been reasonable for a POSA to rely on Shapero's concordance rates.

3. Petitioner Ignores Delseny and Syvänen's Disclosures That Taught Away from Petitioner's Combination

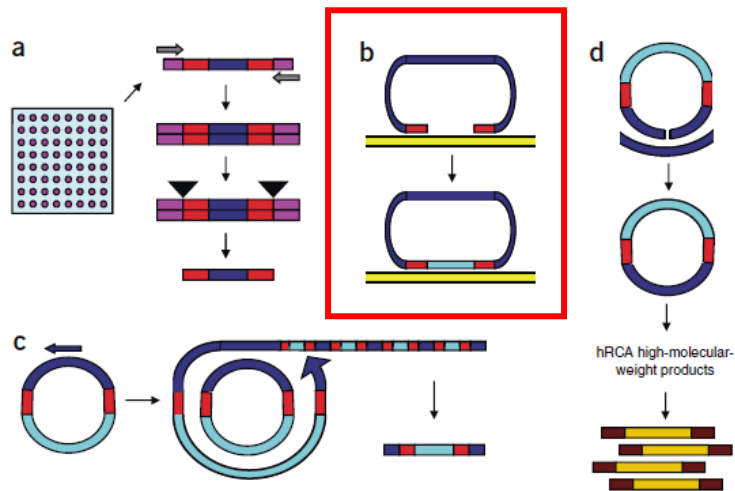
Tecan's Response identifies numerous references that teach away from the combination that Petitioner suggests and many of these arguments remain unrebutted. Paper 17, 31-41. Petitioner relies on Delseny for its obviousness argument, but does not address the reference Delseny cites, Han (EX2117), which teaches away from the claimed combination. As Dr. Bustamante testified, Han criticizes and warns against using methods like MARA with NGS. Paper 17, 32; EX2107.¶¶191-196, 238-243. These statements are uncontested.

Instead, Petitioner misconstrues Tecan's response and Delseny. Paper 22, 13-15. Contrary to Petitioner's claims, Tecan considered Delseny's "Targeted Sequencing" section. *See* Paper 17, 34-35. This section of Delseny is silent on

genotyping. While it identifies at least nine different targeted sequencing methods, none of these references discuss the use of a single target-specific primer. EX2107.¶¶178-185. Petitioner misrepresents Delseny's reliance on Porreca (EX2153), which discloses a molecular inversion probe (MIP) with two targeting arms—not a single, gene-specific primer.

Figure 1 | Schematic of multiplex exon capture.

(a) A library of 100-mer targeting oligo precursors is synthesized in parallel on a programmable microarray. Each oligo consists of common 15 nt flanking sequences (purple), unique 20 nt targeting arms (red) and a common 30 nt linker (dark blue). The oligos are released and PCR amplified with a single set of primers directed at the common flanking sequences. Double digestion with nicking restriction endonucleases (black triangles) releases a library of single-stranded 70-mers. (b) The unique targeting arms (red) of individual targeting oligos are designed to hybridize immediately upstream and downstream of each exon of interest. Hybridization to genomic DNA (yellow) is followed by an enzymatic gap-filling and ligation step, such that a copy of the sequence of interest is incorporated into a circle (light blue). The figure is not drawn to scale; the length of the gap-fill ranged from 60 to 191 bp. (c) Enrichment and amplification of exon-capture circles includes exonuclease digestion of linear material (not shown), linear rolling circle amplification and PCR amplification. Primers for the latter two steps are directed at the common linker sequence (dark blue). (d) To generate a shotgun sequencing library, amplicons are recircularized via their common linker (dark blue) and subjected to hyperbranched RCA with phi29 polymerase and random hexamers. High-molecular-weight products of the hRCA reaction are randomly sheared and appended with universal adaptors to generate the shotgun sequencing library.



EX2153.0932 (annotated) (targeting arms acting as gene-specific primers depicted as red rectangles in Figure 1(b)); EX2108.0054:10-13.

Petitioner also offers no substantive response to Syvänen's criticisms. Paper 22, 16. Syvänen's warning that future methods "should avoid the PCR amplification step" (EX1012.0940) is textbook teaching-away. *See AstraZeneca AB v. Mylan Pharmas. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021). Rather than address Syvänen's disclosures, Petitioner misconstrues the reference. Petitioner incorrectly claims that

Syvänen “recognized that PCR amplification was the workhorse in all the methods for SNP detection.” Paper 22, 16. However, from 27 different SNP-genotyping methods, Syvänen identifies several that do not use PCR amplification. EX1012.0934. Syvänen describes the lack of a PCR amplification step as the “[m]ost significant advantage” of those methods. *Id.*

Despite Syvänen’s express disclosures, Petitioner proclaims that “nothing in Syvänen would have dissuaded a POSA in 2012 from using Shapero’s MARA with NGS to detect SNPs.” Paper 22, 17. But Petitioner ignores the other limitations Syvänen identified for “selectively amplify[ing] SNP alleles.” EX1012.0935. For example, Syvänen criticizes the use of PCR amplification because “*without a consecutive target-specific detection reaction* or size-separation step, the specificity of the method might be hampered owing to primer dimers and other spurious amplification products that will not be distinguished from the actual PCR products.” EX1012.0935 (emphasis added). As discussed above, Shapero uses its microarrays as a *consecutive target-specific detection reaction*—exactly as Syvänen suggests.

Petitioner’s reliance on pyrosequencing in Syvänen fares no better. EX1121.¶44. Syvänen explains that pyrosequencing is at odds with Shapero’s goal of “highly multiplexed locus-specific SNP genotyping.” EX1006.0002. Syvänen explains that the “limitation of [pyrosequencing] is that sequential identification of bases prevents genotyping of several SNPs per reaction in diploid genomes.”

EX1012.0937; *see also* EX1012.0934 (criticizing pyrosequencing as “expensive” and “difficult to multiplex”). Thus, Delseny and Syvänen fail to support Petitioner’s claims.

4. Petitioner Improperly Turns to New References

Rather than address the deficiencies of the Petition, Petitioner has entirely shifted its arguments regarding a POSA’s motivation to combine. Petitioner now relies on the gel reads reported in Shapero despite failing to mention them once in the Petition. *See* Paper 22, 4; *supra* Section I.B.2. Similarly, 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. Paper 22, 2-3, 15, 19. These new arguments should be given little weight, since 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. *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369-70 (Fed. Cir. 2016).

5. The Other Prior Art Taught Away From and Expressed Skepticism Towards the Claimed Inventions

Petitioner and Dr. Metzker speculate, without support, that methods identical to the claimed methods “had been in use and were well proven to work” before the priority date. EX1003.¶99. There are over a hundred references in this proceeding directed to library preparation and sequencing methods, but Petitioner fails to

identify a single reference to support such a bold statement. Moreover, Dr. Metzker made this claim without considering how Petitioner previously described the art. During prosecution of one of Petitioner's patents, having a priority date of 2015, Petitioner told the European Patent Office that the use of a single target-specific primer for amplification, rather than a primer pair, is what "differentiates [Petitioner's] claimed methods from the standard prior art methods." EX2211.0002. Dr. Metzker was unaware of these representations and could not offer an explanation. EX2213.0114:3-116:1.

Petitioner's speculative claims are also at odds with what the prior art teaches. The art shows a complex landscape of varying methods with numerous publications that criticized or discouraged using single target-specific primers, PCR amplification, and universal primer pairs for amplification. Not surprisingly, Petitioner and Dr. Metzker have no response to nearly a dozen teaching-away references. For example, Devon (EX2044), Padegimas (EX2045), Arnold (EX2046), and Bower (EX2049) expressed concerns with off-target products generated by single target-specific primers and taught the need for additional safeguards. *See* Paper 17, 41-45, 55-56; EX2107.¶¶60-61, 251-254. Tsoktouridis (EX2048) criticized PCR amplification methods. Paper 17, 55. Bronner (EX2155) warned that unnecessary PCR amplification steps "should be avoided wherever possible" and advocated for PCR-free methods. Paper 17, 56. Almomani (EX2051),

Myllykangas (EX2052), Quail (EX2053), Kozarewa (EX2054), and Grunenwald (EX2056) also advocated for methods that either bypassed or limited PCR amplification. Paper 17, 45, 58; EX2107.¶¶63-64. These references are consistent with Delseny, which praises a number of “third-generation sequencing methods” that do “not require amplification of DNA fragment libraries.” EX1007.0410.

Again focused on misdirection, Petitioner raises a series of incorrect and irrelevant issues to distract from what the art teaches.

First, a reference expressly teaches away when it “criticize[s], discredit[s], or otherwise discourage[s] investigation into the invention claimed.” *Galderma Lab’ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013) (cleaned up). Contrary to Petitioner’s representations, Tecan need not show that the combination “would be unproductive” to teach away. Paper 22, 7. “Even if evidence does not rise to the level of teaching away, it is still proper for the Board to consider evidence that suggests reasons that a skilled artisan would be discouraged from pursuing such a combination.” *Lab. Corp. of America Holdings v. Ravgen, Inc.*, 2025 WL 32904, at *4 (Fed. Cir. Jan. 6, 2025). As explained in Tecan’s Response, there are many references that would have discouraged the claimed inventions. Paper 17, 41-45, 54-57.

Second, Petitioner cherry-picks and misconstrues other disclosures in a failed effort to rehabilitate the Petition. For example, Petitioner incorrectly claims that

Palka-Santini “published years before Shapero,” (Paper 22, 20), but Palka-Santini published in 2009—years *after* Shapero. EX2139.0001. Palka-Santini criticizes Shapero based on concerns about contamination that were still an issue in 2009. EX2139.0010; Paper 17, 56.

Moreover, Petitioner does not seriously dispute that the art taught away from and discouraged the use of a single target-specific primer without increasingly complicated safeguards. Paper 17, 41-45. Petitioner fails to address the criticisms that Miura (EX2047) and Sohn (EX2050) raised against genome-walking methods like Siebert (EX1101) and Fradkov (EX1112). That Miura taught the use of an algorithm to optimize conditions for some experiments is of no significance. Paper 22, 9. Miura could not replicate its algorithm for other sequences, and adjustments to the algorithm exacerbated new problems. EX2047.4366-67. Petitioner’s attempts to distinguish Bustin’s criticisms (Paper 17, 43-44) are inconsistent. Petitioner dismisses Bustin because it “describes [reverse-transcription]-PCR” (“RT-PCR”) (EX2018.0597), but then relies on Miura, which also describes a method that utilizes RT-PCR (EX2047.4364). *See* Paper 22, 9. Petitioner makes no attempt to address why a POSA would have considered the teachings of Miura but discounted Bustin’s where both utilize RT-PCR.

Petitioner concedes that Sohn “identified two problems with SPE genome walking: low amplification efficiency and non-specific amplification.” Paper 22, 8.

But Sohn uses a special linker-adaptor ligation strategy to target fragments. *See, e.g.,* EX2050.0001. Sohn rejected the prior methods due to these issues and proceeded down a path different than the claimed methods, reinforcing the non-obviousness of the claimed inventions. *See Panduit Corp. v. Dennison Mfg. Co.*, 810 F.2d 1561, 1569 (Fed. Cir. 1987).

Petitioner even attempts to contort Siebert to fit the claims, including by mischaracterizing Dr. Bustamante's testimony (*see* EX1121.¶21). Paper 22, 7-8. As discussed in Tecan's Response, genome-walking papers, including Siebert, discouraged a POSA from practicing the claimed inventions. *See* Paper 17, 41-45. Siebert does not sequence any amplicons, relies on a special adaptor and PCR suppression to generate target specificity, and does not use a universal primer pair to amplify extension products. EX1101.1087-88; EX2107.¶61. While Petitioner argues that the genome walking papers evidenced that "the field believed in SPE and continued to optimize its performance," Paper 22, 9, Petitioner ignores that researchers were continuously trying different methods in search for solutions and none used the MARA method for NGS.

With respect to the few publications citing to Shapero, Petitioner misses the point. None suggest using MARA with NGS, and many either criticize Shapero or reject it in favor of other methods. For example, Petitioner attempts to cabin Bui's criticisms (EX2138.0002) to "small-scale genotyping," but this argument falls flat

given Petitioner's contradictory argument that the claims cover small-scale genotyping and "do not require multiplexing." *See* Paper 22, 11, 22. Similarly, Petitioner misrepresents Liu (Paper 22, 11), relying on a disclosure related to a set of methods cited in 2002—three years before Shapero published. EX2141.0006.

C. The Petition Fails to Demonstrate Any Motivation to Abandon Hybrid Capture

Separate from the Petition's failure to show the requisite motivation to combine MARA with NGS, the Petition also fails to show why a POSA would have abandoned aspects of Shapero's method that provided target specificity, *i.e.*, its microarrays. Paper 17, 30. Petitioner ignores the functionality that the microarray provides in Shapero's method. Petitioner only argues that a POSA could have coupled the MARA library preparation method with NGS but offers no explanation as to why a POSA would decouple MARA from Shapero's microarrays. This is legally insufficient to demonstrate the requisite motivation to combine the references in the specific manner as the claimed inventions. *Virtek*, 97 F.4th at 886-87. The Petition must show that the POSA "would have been motivated to make the combinations or modifications of prior art to arrive at the claimed invention." *Id.* (finding a lack of motivation where the petitioner failed to show why a POSA would have substituted one approach for a separate approach that was absent from the claimed combination but disclosed in another reference).

As evidenced by the record, neither Shapero nor Delseny teach using a method like MARA with NGS *and without* a microarray. Paper 17, 28-31. Rather, there are numerous references that illustrate using microarrays, instead of the claimed methods, to isolate target sequences. For example, Briggs teaches a single primer extension technique that uses hybrid capture to isolate and amplify target sequences. EX1116.0319. Dr. Metzker recognizes that this approach is different from the claimed methods. EX1121.¶9 (“the subsequent steps to isolate and further amplify that extended fragment are different”). Petitioner, therefore, has failed to establish that a POSA would have been motivated to take only the MARA library preparation method from Shapero and sequence the results on an NGS platform.

II. PETITIONER FAILS TO SHOW A REASONABLE EXPECTATION OF SUCCESS

Given the target specificity concerns, Shapero and Delseny would not have provided a POSA with a reasonable expectation of success for Petitioner’s combination. Paper 17, 47-53. For the reasons that the record cannot sustain a finding that there was a motivation to combine, it also cannot support a finding of reasonable expectation of success.

III. PETITIONER FAILS TO REBUT TECAN’S OBJECTIVE INDICIA

Petitioner addresses the Brooks’ declaration at length, but largely ignores the other extensive evidence of nonobviousness described in Tecan’s Response. This fails to rebut Tecan’s evidence of objective indicia, further supporting a finding that

Petitioner has failed to show that any challenged claim is obvious. *See, e.g., supra* Section I.B.5.

A. There Were Several Long-Felt, Unmet Needs

Petitioner fails to address Tecan's references demonstrating the long-felt, unmet needs solved by the '012 patent. Paper 17, 57-59. Instead, Petitioner misconstrues testimony and arguments to rehash the same incorrect obviousness arguments regarding Shapero. Paper 22, 22; *supra* Section I.A. Dr. Bustamante never testified that Shapero resolved the speed or cost concerns identified by the '012 patent. Rather, he contrasted the claimed methods with Shapero: Shapero reads out off-target products through hybridization rather than through universal adaptors. EX1120.0265:18-267:14. Petitioner is also incorrect that the alleged long-felt need must be claimed. Paper 22, 22. All that is required is that the challenged claims solve the identified long-felt need. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016) (finding substantial evidence for jury verdict where articulated need was not claimed).

B. The Industry Praised the Claimed Inventions for Resolving Those Needs

Petitioner does not seriously dispute this factor. Petitioner concedes that Barchi (EX2065) and Scaglione (EX2068) praise Tecan's SPET. Paper 22, 22. It is of no moment if multiplexing is recited in the claims, as Tecan's methods enable NGS multiplexing. That Smith (EX2067) also praises Tecan's SPET for the same

reasons but subsequently includes quotes from Tecan does not diminish this praise. Petitioner fails to address Benjamino (EX2069), merely repeating its incorrect allegation that Shapero uses the same method as the '012 patent. Paper 22, 23.

C. Petitioner Copied the Claimed Inventions

“Evidence of access and substantial similarity *is* evidence of copying.” *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 70 F.4th 1331, 1340 (Fed. Cir. 2023) (emphasis original). Petitioner fails to rebut Tecan’s evidence of access, including that Petitioner “received certain detailed information on NuGEN technologies” as part of diligence in 2013 and that Tecan’s workflow became publicly available that same year. EX2170.0032; EX2171. Petitioner does not dispute that it created a substantially similar product afterwards. Paper 17, 62-64; Paper 22, 23.

Failing to rebut these facts, Petitioner instead claims that its products are not copies of the Tecan products because Petitioner’s products are more like Shapero. Paper 22, 24. Petitioner mistakenly claims that Dr. Bustamante agreed with this position, relying on out-of-context deposition testimony. EX1120.0390:2-402:9. Notably, Petitioner offered no testimony from Dr. Metzker to support this position, despite having testified about the same QIAGEN products at a prior trial. *See* EX2202; EX2205.0068. At deposition, Dr. Metzker agreed with Petitioner’s comparison between the QIAGEN method and Shapero but was unaware that QIAGEN did not disclose Shapero to the Patent Office during prosecution of its

patents covering Petitioner's SPE workflow, despite a duty to disclose relevant prior art. EX2213.0129:22-130:5; EX2212; *see also* EX2210. These inconsistencies call into question the veracity of Petitioner's and Dr. Metzker's claims that the QIAGEN method is similar to Shapero.

D. Petitioner Extolled the Claimed Inventions

There can be no dispute that Petitioner praised the benefits of a single primer enrichment method. Petitioner's only response is to suggest the praise was for benefits of Shapero, not SPET. Paper 22, 24. Even taken at face value, these arguments are inapt. Shapero obtained its benefits by using microarrays. *See supra*, Section I.A. There is nothing in Petitioner's publications that describe or praise Shapero or Jones. EX2144; EX2146; EX2147.0002; EX2148.0001-04; EX2149. While Petitioner identifies other features that Petitioner praised in one publication, that does not negate the express statements Petitioner made about using single target-specific primers. Paper 17, 64-67.

E. Petitioner Fails to Address the Unexpected Results It Obtained Using the Claimed Inventions

Petitioner entirely ignores its own prior representations about the unexpected properties of SPET. Paper 17, 68-69. Although Dr. Metzker previously testified regarding these same products, Petitioner surprisingly offers no expert testimony to rebut Tecan's evidence that Petitioner itself has claimed that the success of the SPET

methods were unexpected. EX2213.0057:6-83:15; EX2205.0068; EX2206.0025-26.

Dated: December 19, 2025

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Sur-Reply** complies with the type-volume limitation of 37 C.F.R. §§ 42.24(c)(4). The Sur-Reply contains 5,599 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system used to prepare the Sur-Reply.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on December 19, 2025, a copy of the foregoing **Patent Owner's Sur-Reply** and all supporting documents were served on the counsel of record for Petitioner by filing the same through the P-TACTS System as well as delivering a copy via electronic mail to the following addresses:

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