

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

QIAGEN Sciences, LLC,
Petitioner,

v.

Tecan Genomics, Inc.,
Patent Owner

Case IPR2025-00029
U.S. Patent No. 10,876,108

PATENT OWNER'S PRELIMINARY RESPONSE

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2002	Introduction to Affymetrix Microarrays	<i>Introduction to Affymetrix Microarrays</i> , GENSTAT, https://genstat.kb.vsnl.co.uk/knowledge-base/affymetrix-introduction/ (last visited February 19, 2025)
2003	Microarray Affymetrix Chips	<i>Microarray Affymetrix Chips</i> , GENSTAT, https://genstat.kb.vsnl.co.uk/knowledge-base/affymetrix-chips/ (last visited February 19, 2025).
2004	Dalma-Weiszhausz 2006	Dennise D. Dalma-Weiszhausz et al., <i>The Affymetrix GeneChip® Platform: An Overview</i> , 410 METHODS IN ENZYMOLOGY 3 (2006).
2005	Evans 2009	Mark F. Evans, <i>The Polymerase Chain Reaction and Pathology Practice</i> , 15 DIAGNOSTIC HISTOPATHOLOGY 344 (2009).
2006	NHGRI 2021	<i>The Cost of Sequencing a Human Genome</i> , NATIONAL HUMAN GENOME RESEARCH INSTITUTE, https://www.genome.gov/about-genomics/fact-sheets/Sequencing-Human-Genome-cost (last visited February 19, 2025).
2007	Goodwin 2016	Sara Goodwin et al., <i>Coming of Age: Ten Years of Next-Generation Sequencing Technologies</i> , 17 NAT. REV. 333 (2016).
2008	Mardis 2017	Elaine R. Mardis, <i>DNA Sequencing Technologies: 2006-2016</i> , 12 NAT. PROTOC., 213 (2017).
2009	Ernani 2009	<i>Bringing Cost and Process Efficiency to Next Generation Sequencing</i> , DRUG DISCOVERY WORLD, https://www.ddw-online.com/bringing-cost-and-process-efficiency-to-next-generation-sequencing-731-200908/ (last visited February 19, 2025)
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2013	Shokralla 2012	Shadi Shokralla et al., <i>Next-Generation Sequencing Technologies for Environmental DNA Research</i> , 21 MOL. ECOL. 1794 (2012).
2014	QIAGEN 2010	<i>QIAGEN® Multiplex PCR Handbook</i> , QIAGEN (2010).
2015	Han 2006	Sangjo Han et al., <i>AtRTPrimer: Database for Arabidopsis Genome-Wide Homogeneous and Specific RT-PCR Primer-Pairs</i> , 7 BMC BIOINFORMATICS 179 (2006).
2016	Matz 1999	Mikhail V. Matz et al., <i>Amplification of cDNA Ends Based on Template-Switching Effect and Step-out PCR</i> , 27 NUCLEIC ACIDS RES. 1558 (1999).
2017	Bru 2008	D. Bru et al., <i>Quantification of the Detrimental Effect of a Single Primer-Template Mismatch by Real-Time PCR Using the 16S rRNA Gene as an Example</i> , 74 APPL. ENVIRON. MICROBIOL. 1660 (2008).
2018	Bustin 2005	Stephen A. Bustin et al., <i>Quantitative Real-time RT-PCR – A Perspective</i> , 34 J. MOL. ENDOCRINOL. 597 (2005).
2019	Duncavage 2011	Eric J. Duncavage et al., <i>Hybrid Capture and Next-Generation Sequencing Identify Viral Integration Sites from Formalin-Fixed, Paraffin-Embedded Tissue</i> , 13 J. MOL. DIAGNOSTICS. 325 (2011).
2020	Brownie 1997	Jannine Brownie et al., <i>The Elimination of Primer-Dimer Accumulation in PCR</i> , 25 J. NUCLEIC ACIDS. RES. 3235 (1997).
2021	Mertes 2011	Florian Mertes et al., <i>Targeted Enrichment of Genomic DNA Regions for Next-Generation Sequencing</i> , 10 BRIEF. FUNCT. GENOM. 374 (2011).

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2023	Deutsche 2011	Ulla Deutsch et al., <i>Streamlining Multiplex PCR Analysis</i> , GENETIC ENGINEERING & BIOTECHNOLOGY, Dec. 1, 2011, https://www.genengnews.com/insights/streamlining-multiplex-pcr-analysis/ .
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2025	'768 Prosecution History	Prosecution History of U.S. Patent Application No. 13/750,768
2026	'785 Prosecution History	Prosecution History of U.S. Patent Application No. 15/471,785
2027	'340 Prosecution History	Prosecution History of U.S. Patent Application No. 16/017,340
2028	Bustamante Declaration	Declaration of Carlos D. Bustamante, Ph.D.
2029	Garber 2008	Ken Garber, <i>Fixing the Front End</i> , 26 NAT. BIOTECHNOL. 1101 (2008).
2030	Illumina 2014	<i>TruSeq® DNA Library Prep Kits</i> , Illumina, Inc. (2014).
2031	Matsuzaki 2004	Hajime Matsuzaki et al., <i>Parallel Genotyping of Over 10,000 SNPs Using a One-Primer Assay on a High-Density Oligonucleotide Array</i> , 14 GENOME RES. 414 (2004).
2032	Risen 2021	Clay Risen, <i>Andrew Brooks, Who Developed a Rapid Covid Test, Dies at 51</i> , N.Y. TIMES, Jan. 31, 2021, https://www.nytimes.com/2021/01/31/science/andrew-brooks-dead.html .
2033	Affymetrix Assay Kit	<i>GeneChip® Human Mapping 10K Array and Assay Kit</i> , Affymetrix, Inc. (2003).

Ex.	Short Name	Description
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2035	Kennedy 2003	Giulia C. Kennedy et al., <i>Large-Scale Genotyping of Complex DNA</i> , 421 NAT. BIOTECHNOLOGY 1233 (2003).

I. INTRODUCTION

Pursuant to 35 U.S.C. § 323 and 37 C.F.R. § 42.107, Patent Owner Tecan Genomics, Inc. (“Patent Owner” or “Tecan”) submits this Preliminary Response to QIAGEN Sciences, LLC’s (“Petitioner” or “QIAGEN”) petition (“Petition”) challenging claims 1-12 and 14-19 (the “Challenged Claims”) of U.S. Patent No. 10,876,108 (“the ’108 patent”). Petitioner has not met its burden of establishing that there is a reasonable likelihood that it would prevail with respect to at least one challenged claim, and therefore, the Board should deny the Petition.

As an initial matter, Petitioner raises substantially the same art and arguments as were previously considered during prosecution, making denial pursuant to 35 U.S.C. § 325(d) appropriate. Petitioner claims that the cited art includes a set of experimental data that was not before the Examiner, justifying reconsideration of the Office’s prior determination. However, as explained in more detail below, the allegedly new data does not address the issues that led the Examiner to withdraw the obviousness arguments raised during prosecution, and Petitioner has failed to show that the Examiner materially erred. The Board should, therefore, deny the Petition.

Further, Petitioner’s argument that a POSA would have been motivated to take a method used with hybridization arrays and modify it to be used with next generation sequencing (or “NGS”) is based purely on hindsight and runs contrary to teachings at the time. The prior art discouraged such a modification due to concerns

with target specificity, off-target binding, and sequencing errors. Petitioner relies on the data in Shapero to argue that these issues would not have been a concern, but Shapero's data does not provide any information regarding the use of NGS. Indeed, the equipment necessary for NGS was not commercially available at the time. Petitioner, therefore, has failed to demonstrate that a POSA would have had a motivation to combine the cited references to arrive at the Challenged Claims with a reasonable expectation of success. Thus, the Board should deny the Petition.

II. TECHNOLOGY BACKGROUND

Genetic sequencing, the assessment of genetic information through methods that characterize the sequence of an organism's genetic code, is an important tool for the understanding of biology and medicine. EX2028.¶31. One way in which researchers have sought to study genetic information is through genotyping. EX2028.¶40. Genotyping analyzes DNA to identify the presence of certain genetic markers and to identify genetic differences between individuals and populations. *Id.* Some of the methods in which researchers genotype include using hybridization

arrays and sequencing technologies (such as Sanger sequencers and NGS).
EX2028.¶38.

A. Hybridization Arrays¹

Hybridization arrays are silica chips where hundreds of billions of target-specific probes are affixed to the array's surface. *Id.*, ¶42. These probes bind to the complementary sequences of targets as samples are washed over the arrays. *Id.* These probes are typically used to screen for single nucleotide polymorphisms ("SNPs"). *Id.* SNPs are variations in a single nucleotide in a genetic sequence. *Id.*, ¶39. Researchers are interested in SNPs in the human genome because these variations can result in profound downstream implications, such as driving certain diseases. *Id.*, ¶41.

Researchers are able to identify the presence of SNPs by running samples over the surfaces of the hybridization array. *Id.*, ¶42. If a specific SNP is present in the sample, it will bind to a probe that is specific to that SNP. *Id.* Where there is no complementary probe, the sequence is filtered from the array. *Id.* Various technologies and software have been developed to allow researchers to assess the

¹ Hybridization describes the process by which complementary single strands of DNA bind together. EX2028.¶42. This concept is utilized by various genotyping and sequencing technologies, including hybridization arrays and NGS.

presence of SNPs based on what sequences have bound to the SNP-specific probes. *Id.*, ¶¶43-51.

B. Pre-NGS Nucleic Acid Sequencing Technology

Another way to genotype is to identify the various nucleotides that make up the sequence—commonly referred to as sequencing. EX2028.¶52. Several methods have been developed over the years to accurately and efficiently sequence DNA, starting with traditional sequencing methods that are now referred to as “pre-next-generation sequencing” (“Pre-NGS”) technologies. *Id.*, ¶¶53-56. The gold standard of these Pre-NGS technologies was Sanger Sequencing, developed in 1977. *Id.*, ¶53. Sanger Sequencing was the first method that allowed for a DNA sequence to be determined. *Id.*, ¶53. In this method, the DNA was amplified in the presence of dye-labeled, chemically-modified nucleotides that, when incorporated into the sequence, would prevent further strand elongation. *See id.*, ¶56. These modified nucleotides would be incorporated at random throughout the duplication process, yielding a variety of smaller fragments, each with a modified nucleotide at its end. *Id.* Each terminal nucleotide could be identified based on the dye-labeled nucleotides. By correlating the length of the fragments and the identification of the dye-labeled nucleotides, one could determine the nucleotide sequence of the original

template DNA strand. *Id.* Although revolutionary, Sanger Sequencing was expensive and ill-suited for large-scale applications. *Id.*, ¶57.

C. Next-Generation Technologies

Starting in the early 2000s, the field of genetics was revolutionized by the invention of next-generation sequencing (“NGS”). EX2028.¶58. Compared to traditional, Pre-NGS sequencing methods, NGS utilized a new design that no longer relied upon disassembling and then piecing together a single original template DNA strand. *Id.* Instead, NGS now allowed for hundreds of thousands of original template strands to be sequenced in the same reaction. With NGS, a user could perform massively parallel sequencing, allowing for elements of the genome to be sequenced in a fast, scalable manner. *Id.*, ¶59. As compared to Sanger Sequencing, NGS was cheaper, more efficient, and capable of assessing both larger genetic samples and longer portions of the human genome in high fidelity. *Id.*

However, early NGS methods had their drawbacks. NGS was limited to shorter individual sequencing reads than Sanger Sequencing, which greatly increased the difficulty in mapping the sequencing reads to a full genome. *Id.*, ¶61. Additionally, NGS platforms exhibited a higher error rate than Sanger Sequencing. *Id.* For example, the 454 Sequencer, which was released in 2004, suffered from a relatively high error rate, especially when sequencing homopolymer regions (long stretches of the same mononucleotides). *Id.*, ¶131.

D. Targeted Enrichment

Targeted enrichment methods became one way to mitigate some of the issues associated with characterizing a sequence of a genomic area of interest, including platform-specific issues. EX2028.¶¶62-63. Rather than amplifying and sequencing the larger, full genome, targeted enrichment was a method of sample preparation in which smaller genomic areas of interest, such as individual genes, were amplified. *Id.*, ¶64. By doing so, researchers hoped to reduce the errors and noise caused by sequencing broad swathes of genomic data. As of the priority date, the prior art methods consisted of capture-by-hybridization,² PCR-based target enrichment, and capture-by-circularization. *Id.*, ¶65; EX1001.0016 (1:44-49).

Hybrid capture methods relied on the selective hybridization of a target genomic region to a custom designed oligonucleotide. EX2028.¶76; EX1001.0016 (1:66-2:01). The oligonucleotide could be immobilized to a surface or contain a ligand that could be immobilized (such as biotin). EX2028.¶76; EX1001.0016

² Hybrid capture methods rely on the same use of hybridization to target samples as with hybridization arrays. The difference is that hybridization arrays target sequences as part of the analytical step, not during sample preparation. Hybrid capture instead seeks to target sequences during sample preparation so that the targeted sequences can be isolated and enriched. EX2028.¶76.

(2:01-06). These methods, however, required complex pools of long, expensive oligonucleotides and long periods of hybridization for efficient capture, as well as the use of expensive instruments. EX2028.¶77; EX1001.0016 (2:06-12). One additional problem was that due to low levels of efficiency, these methods required large quantities of input nucleic acid. *Id.*

In contrast, PCR-based target enrichment methods employed the use of a corresponding pair of unique, sequence-specific primers for each target sequence. EX2028.¶66; EX1001.0016 (1:50-52). The need for numerous primer pairs made multiplex PCR impractical due to high levels of non-specific amplification and primer-primer interactions. EX2028.¶71; EX1001.0016 (1:53-55). One attempt at addressing these issues was through microdroplet PCR where each amplification reaction is physically separated into an individual droplet. EX2028.¶72; EX1001.0016 (1:53-58). That method, however, required special instruments, had limited throughput, and required a large number of individual primer pairs when enriching for multiple regions of interest, which made target enrichment expensive. EX2028.¶73; EX1001.0016 (1:55-60).

Circularization capture (also referred to as molecular inversion probe or MIP) methods relied on numerous single-stranded linear oligonucleotide probes with a common linker flanked by target-specific sequences. EX2028.¶78; EX1001.0016 (2:13-18). Once the probe annealed to a target sequence, the gap region was filled

by polymerization and ligation, resulting in a circularized probe. EX2028.¶78. These probes were then amplified using primers specific to the common linker region. EX2028.¶78.; EX1001.0016 (2:18-20). These methods, however, exhibited high variability in sequence coverage across target regions and required a large number of target-specific oligonucleotides, driving up costs. EX2028.¶79; EX1001.0016 (2:20-26).

In this backdrop, there was “a need for improved methods for selective target enrichment that allow for low-cost, high throughput capture of genomic regions of interest without specialized instrumentation.” EX1001.0016 (2:27-30). There was “also a need for high efficiency nucleic acid library generation.” *Id.* (2:30-31). The claimed methods of the ’108 patent fulfilled these needs.

III. THE ’108 PATENT

A. Overview

The ’108 patent is directed to methods for sequencing an enriched nucleic acid sequence of interest with a massively parallel sequencing platform (NGS) where a single oligonucleotide is used to select for a target sequence of interest and a common pair of primers is used to selectively amplify the target sequence of interest, thus enriching for that sequence. EX1001.0033. The ’108 patent discloses methods that “can be used for the selective enrichment of a plurality of defined target sequences from complex [nucleic acids] with a set of common primers and adaptors,

thus circumventing the need for multiplex PCR and multiple primer pairs.” EX1001.0018 (6:14-18). The claimed methods, therefore, improve on the then-existing methods by allowing for the selection of a sequence of interest using a single target-specific primer as opposed to two target-specific primers. The claimed methods also allow for enrichment through amplification and sequencing of the sequence of interest with a non-target specific set of primers, avoiding the time and expense associated with generating multiple target-specific primers. The claimed methods improve upon the prior art sequencing methods by creating “a simple, low cost, high throughput system for target enrichment and library preparation.” *Id.*, (6:27-29).

B. Independent Claim 1

The sole independent claim of the '108 patent, claim 1, is reproduced below.

Claim Element	Claim Language
1[pre]	A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
1[a]	annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in a nucleic acid fragment, wherein the reaction mixture comprises a plurality of nucleic acid fragments, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest comprises a first adaptor sequence,

Claim Element	Claim Language
	wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;
1[b]	extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment comprising the first adaptor sequence with a polymerase, in the reaction mixture, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;
1[c]	amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest; and
1[d]	sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

C. Level of Ordinary Skill in the Art

Petitioner proposes a level of skill in the art that is higher than the level of ordinary skill in the art as of the priority date of the '108 patent. Petitioner's definition of a person of ordinary skill in the art ("POSA") requires that the POSA either hold "(i) a Ph.D. in molecular biology, molecular genetics, bioinformatics, biochemistry, or a related field and at least two years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and sequencing experience," or "(ii) a Master's degree in one of the same fields with at least four years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and high-throughput sequencing technologies." Petition, 13-14; *see also* EX1003.¶39. By 2008, NGS sequencing technologies were performed in laboratories according to published protocols and would have been accessible to experienced laboratory technicians and graduate students. Petitioner's definition requiring that a POSA have both a Ph.D. or Master's degree and several years of experience is therefore higher than ordinary. EX2028.¶¶88-91.

Patent Owner proposes that the appropriate level of ordinary skill in the art requires that the POSA would have a Ph.D. in a field related to molecular biology, or a B.S. or M.S. degree with three-to-five years of experience working in a molecular biology lab. To the extent there are any differences between Petitioner's

definition and Patent Owner's definition, under either definition, Petitioner has failed to establish a reasonable likelihood of success on at least one challenged claim.

Further, Dr. Carlos D. Bustamante, who has submitted a declaration in support of Tecan's preliminary response, would have been a POSA as of the priority date under either definition. *See* EX2028.¶¶6-20, 91; *see also* Ex. A.

D. Claim Construction

The Petition does not ask the Board to explicitly construe any terms of the Challenged Claims. As such, the Board need not construe any terms for purposes of resolving the instant dispute.

E. Relevant Prosecution History

The '108 patent issued from U.S. Patent Application No. 16/017,340 ("the '340 application"), which was filed on June 25, 2018. EX1001.0001. The '340 application ultimately claims priority to Provisional Application No. 61/591,241, which was filed on January 26, 2012. *Id.* The '340 application is a continuation of U.S. Patent Application No. 15/471,785 ("the '785 application"), filed on March 28, 2017, which issued as U.S. Patent No. 10,036,012 ("the '012 patent") on July 31, 2018. *Id.* The '785 application is a continuation of U.S. Patent Application

No. 13/750,768 (“the ’768 application”), filed on January 25, 2013, which issued as U.S. Patent No. 9,650,628 (“the ’628 patent”) on May 16, 2017. *Id.*

During the prosecution of the grandparent ’768 application, the Examiner issued anticipation and obviousness objections based on two patent applications that named Keith W. Jones and Michael H. Shapero as co-inventors (the authors of the Shapero reference cited in the Petition), including U.S. Patent Publication No. 2005/0142577 (“Jones”) (EX1011). In the first series of rejections, the Examiner argued that “Jones teaches a method for enriching a nucleic acid sequence of interest in a sample comprising nucleic acids” and that the method comprised the claimed steps. EX2025.0010. The Applicant traversed the rejections and proposed amendments clarifying that methods were directed to the use of NGS. *Id.*, .0028-30. In response, the Examiner conceded that Jones “does not disclose massively parallel sequencing” and withdrew the anticipation rejections. *Id.*, .0045. However, the Examiner raised new obviousness rejections based on Jones in view of Tucker et al. “Massively parallel sequencing: the next big thing in genetic medicine” (“Tucker”, EX1013). The Examiner relied on Tucker to fill in the missing limitations, explaining that “Tucker describes methods of obtaining sequence information about a region of interest in a nucleic acid, and specifically describes a number of massively parallel sequencing methods.” EX2025.0045.

The Applicant again traversed the rejections, arguing that the claimed inventions were nonobvious over the prior art combination. The Applicant also submitted an affidavit from Dr. Andrew I. Brooks in support of its arguments. At the time, Dr. Brooks was the Chief Operating Officer at Rutgers University Cell and DNA Repository (“RUCDR”) Infinite Biologics, which was the largest university-based biorepository and one of the largest genomics research facilities in the United States, placing it at the forefront of using NGS for various genomic research. EX2028.¶103. Dr. Brooks held a Ph.D. in Molecular Medicine and Gene Therapy and had decades of applied research and industry experience in nucleic acid library preparation and high-throughput sequencing technologies. *Id.*; EX2025.0127-28. Under either parties’ proposed definition, Dr. Brooks would have been considered at least a POSA.

In his declaration, Dr. Brooks explained how the hybridization arrays disclosed in Jones were different than the claimed inventions, how Dr. Brooks did not expect that an enrichment method for NGS using a single target-specific primer would work, and why Jones would not have changed his opinion. EX2025.0130. Thereafter, the Examiner issued a notice of allowance for the application.

The parent ’785 application was filed as a continuation application two months after the notice of allowance for the ’768 application. The same examiner considered the application and issued a set of rejections based on Jones and Tucker

for the same reasons as was the case for the parent application. EX2026.0005-12. Upon resubmission of the Applicant's positions and the Brooks Declaration, *Id.*, .0020-39, the Examiner withdrew the rejections and issued a notice of allowance. *Id.*, .0058.

The '340 application was filed as a continuation application two months after the '012 patent after the notice of allowance for the '785 application. The same examiner considered the application and issued a set of rejections based on Jones and Tucker for the same reasons that were asserted against the claims of the '785 and '768 applications. EX2027.0006-12. In response, the Applicant explained that "Jones report[ed] methods for preparing nucleic acids for microarray analysis" and that "[a]mplified products are hybridized to a microarray for analysis." *Id.*, .0028. The Applicant noted that "because Jones does not disclose sequencing, the disclosure is not relevant to the claimed methods" and that a "person of skill in the art would not find Jones' disclosure applicable to sequencing because sequencing demands less off-target enrichment than microarray hybridization. Consequently, one would not have a reasonable expectation of success in applying Jones' enrichment method to massively parallel sequencing." *Id.*, .0029. In support, the Applicant resubmitted the Brooks Declaration. *Id.*, .0033-37. The Examiner subsequently withdrew the rejections and issued a notice of allowance. *Id.*, .0061-62.

IV. THE BOARD SHOULD DENY THE PETITION UNDER 35 U.S.C. § 325(D)

In determining whether to institute *Inter Partes* Review, the Board may “reject the petition [where] the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d). The Board has articulated several nonexclusive factors that guide its application of § 325(d). *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, at 17-18 (PTAB Dec. 15, 2017) (precedential). These factors have been consolidated into two questions: (1) whether “the same or substantially the same art [or arguments] previously [were] presented to the Office”; and if so, (2) whether the “petitioner has demonstrated that the Office erred in a manner material to the patentability of the challenged claims.” *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 8 (PTAB Feb. 13, 2020) (precedential). Petitioner argues that § 325(d) does not support denial because: (1) Shapero contains data not included in Jones that alters the analysis of the prior art; and (2) the Examiner erred by considering the Brooks Declaration but not the Shapero data. Neither point is availing, as explained below.

A. Substantially the same art and the same arguments were previously before the Office

Petitioner relies on art that discloses the *same information* as what was considered during prosecution and makes the *same obviousness arguments* raised

by the Examiner. Shapero (asserted here) is co-authored by two of the inventors listed on the face of Jones (asserted during prosecution). Petition, 17. The Petitioner concedes that Shapero discloses the same methodology as Jones. *Id.* Petitioner relies on Delseny for nothing more than the proposition that NGS could be used to sequence nucleic acid sequences—the same manner in which the Examiner relied on Tucker. *Id.*, at 20-22. Petitioner argues that the data reported in Shapero distinguishes it from Jones, but as explained further below, the data merely shows that the methodology disclosed in both Jones and Shapero works with a hybridization array, as expected. Thus, the art asserted in the Petition is cumulative to that considered during prosecution. *Roku, Inc. v. Universal Elecs., Inc.*, IPR2019-01619, Paper 11, at 16 (PTAB Apr. 2, 2020); *Dropworks, Inc. v. The Univ. of Chicago*, IPR2021-00100, Paper 9, at 13-14 (PTAB May 14, 2021) (The “analysis under § 325(d) does not require that the teachings be identical or entirely cumulative, only that they are substantially the same.”).

1. Shapero’s data is cumulative of the disclosures of Jones

There is no dispute that Shapero discloses the same methodology as Jones—the primary reference that the Examiner considered and relied upon during prosecution. *See supra*, Section III.E; Petition, 17 (“Shapero and Jones both disclose the same enrichment methodology”), 55 (“Shapero and Jones both teach the same MARA technology”). Petitioner’s only argument to distinguish Shapero from Jones

is that certain data published in Shapero—and not included in Jones—is material and warrants reopening the Office’s previous consideration into the patentability of the ’108 patent. But this additional data does not alter the teachings of Jones because, contrary to Petitioner’s arguments, it merely confirms the conclusions of Jones and does not suggest the use of NGS.

The data to which Petitioner points is Shapero’s comparison of various array call rates (instances in which an array probe registered a SNP during analysis), arguing that this data would have provided a POSA with a motivation to use Shapero’s methods with NGS with a reasonable expectation of success. *See* Petition, 34-36, 39-40. The call rates reported by Shapero, however, demonstrate nothing more than confirming that the Multiplexed Anchored Runoff Amplification (“MARA”) method could be used with a specific hybridization array to achieve acceptable call rates—a concept that was already contemplated by Jones. *See* EX2028.¶¶109-110.

For example, Jones discloses the MARA method as a preferred embodiment for a set of claimed methods of “genotyping a plurality of polymorphisms in an organism” using hybridization arrays. EX1011.0022, cl. 1. As explained by Jones, the amplification product generated through methods such as MARA “may be hybridized to an array of probes designed to discriminate between different alleles of a polymorphic allele so that the base or bases present at the polymorphic positions

may be determined.” *Id.*, .0008 at [0006]. Shapero disclosed using the MARA method for the same purpose. EX1006.0006, .0008-0009. Neither Jones nor Shapero teach methods related to NGS. *See* EX2028.¶¶121-125, 153-56.

During prosecution, the Examiner concluded that Jones “teaches that nucleic acids amplified by the disclosed method *may be analyzed by array hybridization* or any other method known in the art to obtain sequence information about a region of interest (paragraph 79-80), but *massively parallel sequencing [(NGS)] is not disclosed.*” EX2026.0008. (emphases added); *see also* EX2028.¶¶109-110. The data disclosed in Shapero does nothing more than reinforce the disclosure of Jones and is therefore cumulative to the information before the Examiner.

Petitioner argues that the “experimental data provides a strong motivation to combine Shapero with Delseny, and it directly rebuts the alleged skepticism and unexpected results set forth in the Brooks declaration.” Petition, 55. In doing so, Petitioner compares apples to oranges. To be clear, the data in Shapero does not reflect the use of the MARA method *with an NGS platform*. Instead, MARA was used with a hybridization array, the same technology claimed in Jones. *See, e.g.*, EX1006.0009 (“robust SNPs that genotype accurately by allele-specific hybridization” were pre-selected and used with the “p502” array—a predecessor *genotyping array* to Affymetrix’s Gene Chip® 10K Mapping Xba 131 Array).

Petitioner is also incorrect that the data in Shapero would alter how a POSA would have viewed Jones. EX2028.¶153-63. The question during prosecution was not whether MARA could have worked with a hybridization array. Indeed, even QIAGEN's expert, Dr. Metzker admits that MARA "worked exactly as [it was] always known to work." See EX1003.¶179. Instead, the question was whether a POSA would have been motivated to adapt MARA for use with an NGS platform and would have had a reasonable expectation of success in doing so. Shapero's data using the hybridization assay does not speak to whether the method would work with NGS. EX2028.¶¶153-63. As Dr. Bustamante explains, these methods utilize different techniques and require attention to different factors to achieve reliable, usable data. *Id.*, ¶¶81-87. Concerns with target specificity and off-target binding are pronounced with NGS because binding to the sequencer is not target specific. *Id.* These concerns are minimized with hybridization arrays because the method is designed to filter off-target binding from the results. *Id.* The data reported in Shapero does nothing to address the issues with NGS because it is not based on the use of an NGS platform. See, e.g., *Id.*, ¶¶119-21. Nor can a POSA infer how the MARA method would work with NGS based on the data from Shapero. *Id.*, ¶¶158-63. The data in Shapero, therefore, is cumulative of the disclosures of Jones.

2. Delseny is used for the same reason as Tucker

Petitioner relies on Delseny, but this reference simply discloses sequencing on a massively parallel sequencing platform, just as Tucker does. During prosecution, the Examiner recognized that Jones did not teach the use of the disclosed MARA method with an NGS platform. EX2026.0008. The Examiner instead relied on Tucker to fill that gap. The Examiner explained that “Tucker describes methods of obtaining sequence information about a region of interest in a nucleic acid, and specifically describes a number of massively parallel sequencing methods.” *Id.* Specifically, Tucker taught the use of the Illumina sequencing platform. *Id.*, .0008-09. The Examiner argued that a POSA would have been motivated to combine Jones and Tucker “since Tucker taught that such methods offered very high-throughput sequencing,” “as well as the ability to accurately detect minor alleles,” and “that massively parallel sequencing methods may replace array methods.” *Id.*, 0009. The Examiner also argued that a POSA would have had a reasonable expectation of success “in view of the guidance provided by Tucker concerning the use of massively parallel sequencing methods and also since Jones taught that the amplification products could be analyzed using any desired method.” *Id.*

Here, Petitioner’s arguments mirror the Examiner’s. The Petition relies on Delseny for disclosure of the same elements of the claims as was asserted in the Examiner’s rejection. Petitioner argues that “Delseny describes a number of

commercially available NGS platforms, including the massively parallel sequencing method developed by Illumina.” Petition, 47-48. Petitioner also argues that a POSA would have been motivated to combine Shapero with Delseny since Delseny describes that “NGS allows for many more samples to be analyzed at the same time” and that “NGS is a replacement for genotyping described in Shapero.” *Id.*, 34 (cleaned up). And like the Examiner, Petitioner argues that a POSA would have had a reasonable expectation of success because “Delseny expressly teaches that NGS can be a replacement for array-based genotyping.” *Id.*, 36. Nothing about Delseny or how Petitioner uses this reference materially differs from how the Examiner relied on Tucker during prosecution.

As such, the prior art and arguments advanced in the Petition are substantially the same as the prior art and arguments raised by the Examiner during prosecution, and the first *Advanced Bionics* factor favors denial.

B. Petitioner fails to demonstrate a material error by the Office

Petitioner argues that the Examiner materially erred by “exclusively” relying on the Brooks Declaration to overcome the combination of Jones and Tucker. Petition, 56-57. Petitioner’s arguments, however, fail as both a matter of law and

fact at least because the Examiner appropriately considered the testimony from Dr. Brooks and the Applicant's arguments in assessing obviousness.

During prosecution, Dr. Brooks explained how the hybridization arrays disclosed in Jones were different than the claimed inventions, drawing on his expectations as to how the claimed inventions would work. Dr. Brooks explained that “[b]ased on [his] experience in the field, [he] was skeptical that the claimed methods would provide efficient sequencing data.” EX2026.0037. According to Dr. Brooks, he thought “the technology would provide poor target specificity that is not consistent with enrichment worthy of high quality sequencing data” because “the claimed methods involve annealing and extending a target-specific primer to enrich a sequence of interest (rather than, for example, annealing a forward target-specific and reverse target-specific primer pair at a sequence of interest).” *Id.* He expressed concerns that “the target-specific primers would bind to off-target sites at a relatively high rate, leading to non-specific enriched nucleic acid sequences that would flood the sequencing system and confound sequence analysis.” *Id.* According to Dr. Brooks, “in order to generate enriched sequences that would provide highly specific sequencing results, one would want to amplify a sequence of interest with, for example, a primer pair including a forward target-specific primer and reverse target-specific primer . . . for each sequence of interest.” *Id.* These are concerns that were shared across the art at the time. *See* EX2028.¶¶66-70.

Comparing the claimed methods to Jones, Dr. Brooks noted that “[i]f a target-specific primer anneals to the target sequence, the resulting on-target amplified product will hybridize to the unique complementary probe on the microarray.” EX2026.0038. But “if the target-specific primer anneals to off-target sequences, there would be no equivalent complementary probe on the microarray to hybridize to the resulting off-target amplified product.” *Id.* As Dr. Brooks explained, it was this difference in technology that rendered Jones inapplicable to addressing the concerns in the art with NGS: “unlike on a massively parallel sequencing platform, the off-target product that may be produced would not confound analysis since the noise from off-target sequences would be minimal or absent.” *Id.* Given Dr. Brooks’ expectation that a single target-specific primer would not work for NGS, especially where no hybridization arrays were used to otherwise target the sequence, Dr. Brooks reported “unexpected results when enriched nucleic acid sequences generated using the claimed methods were sequenced by massively parallel sequencing.” *Id.* He was surprised to see “greater than ninety percent of on-target sequences of interest in the sequencing results,” which exceeded his expectations on what he knew of the art. *Id.*

Petitioner incorrectly argues that “the Brooks declaration is legally deficient with respect to both skepticism and unexpected results, and therefore, the Office erred in a manner material to the patentability of Challenged Claims.” Petition, 56.

Notably, the Examiner did not state that the allowance was based on skepticism and unexpected results, nor were the Brooks statements so limited. First, in the Notice of Allowance, the Examiner acknowledged that the Brooks Declaration was “sufficient to overcome the rejections,” and that the Examiner found persuasive the Applicant’s argument “that the rejections should be withdrawn in view of the declaration of Dr. Andrew Brooks.” EX2026.0066. Second, although Dr. Brooks also provided an explanation of his skepticism and the unexpected results of the claimed methods, the Brooks Declaration discussed a POSA’s fundamental concerns regarding using a single target-specific primer enrichment method with NGS and a POSA’s expectations regarding using the methods of Jones. *See id.* at .0038 Dr. Brooks’ testimony, when considered with the totality of evidence before the Examiner, demonstrated that a POSA would have lacked the motivation to modify Jones and would not have had a reasonable expectation of success in doing so—each deficiency fatal to an obviousness determination. The Applicant made that same point by singling out the Examiner’s arguments with respect to motivation to combine and reasonable expectation of success, and noting how the Brooks Declaration rebutted those points: “Declarant’s insights about the specificity of the claimed methods and the generation of unexpected results render the claimed methods nonobvious.” *Id.*, .0032. Therefore, there is no basis to assume that the Examiner’s allowance was based solely on skepticism and unexpected results.

Even if that were the case, however, it would not have been legal error for the Examiner to consider a POSA's testimony on unexpected results or skepticism in considering the overall obviousness inquiry—to the contrary, such considerations are required. *Leo Pharma. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (“Whether before the Board or a court, this court has emphasized that consideration of the objective indicia is *part of* the whole obviousness analysis, not just an afterthought.”) (emphasis original). As explained further below, it was proper for the Examiner to consider Dr. Brooks' testimony through the lens of skepticism and unexpected results.

1. Skepticism

With respect to skepticism, Petitioner argues that “[s]kepticism requires a showing that third parties were skeptical of the claimed invention” and that it was legal error for the Examiner to rely on Dr. Brooks who was a member of the Board of Directors of NuGEN Technologies at the time. Petition, 38. Petitioner, however, misstates the law. Evidence of skepticism is not restricted to just third parties. *See, e.g., Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1352-53 (Fed. Cir. 2012). Nor does either of the two cases cited by Petitioner address the propriety of considering the skepticism of an interested party.

See Neptune Generics, LLC v. Eli Lilly & Co., 921 F.3d 1372, 1378 (Fed. Cir. 2019); *Circuit Check Inc. v. QXQ Inc.*, 795 F.3d 1331, 1337 (Fed. Cir. 2015).

In fact, the Federal Circuit has relied on inventor testimony of skepticism in overturning findings of obviousness, without any concerns about the inventors being “interested parties.” In *Transocean*, the Federal Circuit rejected similar arguments as advanced by Petitioner. *Transocean*, 699 F.3d at 1352-53. There, the patentee only “proffered testimony regarding skepticism by two named inventors of the patents-in-suit.” *Id.* The district court concluded that the patentee “presented insufficient evidence of industry skepticism to support the jury’s finding.” *Id.* On appeal, the Federal Circuit concluded that the district court had erred in finding the inventors’ testimony insufficient. *Id.* The Federal Circuit raised no concerns with the evidence of skepticism being exclusively proffered by the named inventors of the patents.

Contrary to Petitioner’s claims, interested experts may provide testimony on these issues. As explained by the MPEP, “[e]xpressions of disbelief by experts constitute strong evidence of nonobviousness.” MPEP § 716.05 (citing *Environmental Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698 (Fed. Cir.

1983)).³ This simply requires that the individual be an expert. Dr. Brooks was undisputedly an expert in the field. EX2026.0035. In fact, Dr. Brooks ran the world's largest university-based biorepository and one of the largest sequencing centers in the United States, making him an expert in the field. *Id.*; EX2028.¶103. Petitioner's only criticism of Dr. Brooks is that he allegedly was not a "disinterested third party," but that does not make his opinions irrelevant. Petition, 38.

In any case, Dr. Brooks disclosed his affiliations with NuGEN in his declaration. EX2026.0036. The Examiner, aware of these affiliations, was able to weigh Dr. Brooks' interests in assessing his testimony. Petitioner's request to exclude any non-third-party testimony on skepticism flies in the face of Federal Circuit precedent and should be rejected as such. *See Transocean*, 699 F.3d at 1352-53. The Examiner, therefore, did not err in relying on Dr. Brooks' testimony of skepticism in considering whether the inventions were obvious over Jones and Tucker.

³ *Environmental Designs* is another example of how it is permissible for courts to weigh the testimony of skepticism by interested parties. There, the Federal Circuit noted that "highly probative evidence of nonobviousness resides in the expressions of disbelief by the chemical experts for both sides," who were interested parties to the litigation. 713 F.2d at 697-98.

2. Unexpected Results

With respect to unexpected results, Petitioner argues that the data in Shapero “directly rebuts the alleged . . . unexpected results set forth in the Brooks declaration.” Petition, 55-56. As explained above, Shapero and Jones concern the same methodology, with Shapero testing a preferred embodiment disclosed in Jones. *See supra*, Section IV.A.1. Petitioner cannot identify any claim element missing from Jones that is found in Shapero. A POSA would have perceived the disclosures in Shapero and Jones to be cumulative and the data in Shapero to be inapplicable for addressing whether the MARA method could be successfully used with an NGS platform. EX2028.¶¶153-63. As such, it was not legal error for the Applicant to compare the results obtained from the claimed inventions with the expected results from Jones. MPEP § 716.02(a)(III) (“Presence of a property not possessed by the prior art is evidence of nonobviousness.”)

Petitioner argues that the Examiner committed factual errors because “the experimental data in Shapero demonstrates that Dr. Brooks’ opinions on unexpected results are factually incorrect.” Petition, 39. However, as Dr. Bustamante explains and as explained above, the experimental data in Shapero no more proves or disproves Dr. Brooks’ opinions. EX2028.¶¶153-63. Shapero reported the hybridization specificity achieved with the MARA method and a specific hybridization array. *Id.*, ¶¶120-25. Shapero fails to demonstrate the target

specificity or off-target binding rate of the MARA method with an NGS platform. *Id.*, ¶158-63. Because of the experimental design used by Shapero to generate its data, a POSA could not have reliably made assumptions as to how the MARA method may impact NGS. *Id.*

As such, Petitioner fails to show that the Office committed a material error. The Board should deny the Petition under 35 U.S.C. § 325(d).

V. THE PETITION DOES NOT ESTABLISH THAT THE CHALLENGED CLAIMS ARE OBVIOUS

A. Ground 1 Fails Because Shapero and Delseny Do Not Render Obvious the Challenged Claims

Petitioner argues that the sole independent claim of the '108 patent would have been obvious over Shapero in view of Delseny. Petition, 24. Petitioner's argument essentially asks the Board to find that different technologies are interchangeable without regard for their fundamental differences. Petitioner argues that a POSA would have readily used the methods of an older technology (the hybridization arrays disclosed in Shapero) for use with the entirely different NGS platforms. Petitioner ignores that the prior art cautioned against the very combination that Petitioner asserts would have been obvious. Petitioner's arguments are predicated on impermissible hindsight and should be rejected.

Petitioner does not assert that Shapero discloses any of the claim elements specific to sequencing the enriched sequences of interest with NGS platforms,

including “sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.” Petition, 31. Petitioner instead relies on Delseny’s disclosures of various NGS platforms, arguing that these disclosures would have made it obvious for a POSA to modify Shapero to use with NGS platforms. *Id.*, 32-36.

As such, the dispute is centered on one issue: would a POSA have been motivated to modify Shapero’s MARA method to be used with an NGS platform in view of Delseny with a reasonable expectation of success in doing so. Only with the benefit of hindsight is Petitioner able to argue that a POSA would have used data unrelated to NGS to arrive at the Challenged Claims. The Federal Circuit has repeatedly cautioned that “we must guard against hindsight bias and ex post reasoning.” *See, e.g., St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) (cleaned up). The Petition lacks evidence, other than unsupported testimony of an expert, to show a POSA would have modified Shapero in the way Petitioner claims and would have reasonably expected to succeed, and thus the Petition should be denied.

1. A POSA Would Not Have Had a Motivation to Combine a Hybridization Array Method with NGS Technology

Petitioner argues that a POSA “would have been motivated to combine the enrichment methods of Shapero with the NGS technologies described in Delseny.”

Petition, 32. For support, Petitioner advances three arguments: (1) Delseny teaches that NGS can be used as a substitute for the genotyping performed in Shapero; (2) Syvänen shows that Shapero's genotyping methods were compatible with sequencing; and (3) Shapero's experimental data demonstrates that MARA would work with NGS. Petition, 32-36. Each argument is unavailing at least because each fails to address the concerns at the time with using a single, target-specific primer to enrich sequences for NGS. Petitioner's arguments are, at best, that a POSA *could have* combined Shapero and Delseny, but such an argument is insufficient to prove obviousness. The Federal Circuit has held that just because a POSA *could have* combined the prior art does not mean that a POSA *would have been motivated* to do so. See *Virtek Vision*, 97 F.4th at 886 ("Obviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention.") (cleaned up); *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014) (reversing finding of obviousness and criticizing expert's testimony as "primarily consist[ing] of conclusory references to her belief that one of ordinary skill in the art could combine these references, not that they would have been motivated to do so."). Petitioner instead ignores critical concerns raised by Delseny

and Syvänen that would have discouraged a POSA from combining Shapero and Delseny to practice the claimed methods.

a) Delseny teaches away from the claimed methods

Petitioner incorrectly argues that “Delseny recognizes that NGS is a replacement for genotyping described in Shapero.” Petition, 34. Petitioner overstates what Delseny teaches. While Delseny may teach that NGS can be used for genotyping, Delseny cautions against using NGS for the exact genotyping described in Shapero, high-throughput genotyping of known SNPs.

Delseny expresses concerns with the use of NGS for genotyping SNPs due, in part, to errors in base-calling, sequencing read artifacts, and higher false discovery rates. EX1007.0005, 08. Base-calling essentially refers to whether the sequencer is accurately determining the specific nucleotide in a sequence of nucleotides. EX2028.¶170. As an example of base-calling errors, Delseny describes how “[m]istakes occur with short homopolymers”—stretches of the same repeating nucleotide—“with the 454 technology because multiple incorporation of the same nucleotide instead of single incorporation can occur at each round.” EX1007.0005, 08. Base-calling errors can lead to issues with the output, such as read artifacts, that lead to incorrect results, which is referred to by Delseny as “false discovery rates.” EX2028.¶170. Because the genotyping of SNPs depends entirely on identifying a single nucleotide, base-calling errors and sequencing misreads can lead researchers

to mistake an error for a SNP (and vice versa), creating uncertainty as to the validity of results. *Id.* While Delseny recognizes that NGS provides higher resolutions than genotyping microarrays (including hybridization arrays), Delseny's suggestion is related to the resolution of NGS for mapping SNPs across broad swathes of genetic material. *Id.* Delseny does not teach that NGS is a replacement for the array hybridization disclosed in Shapero, where Shapero is engaging in high-throughput genotyping to screen for the presence of already identified SNPs, which requires both rapidity and accuracy. EX2028.¶¶168-71; EX1006.0007.

Because of Delseny's concerns with read fidelity, Delseny instead recognizes the pre-NGS Sanger method as the "gold standard" due to it having the "highest accuracy" because of its "high fidelity." EX1007.0005. Delseny's concerns and endorsement of pre-NGS Sanger sequencers would have taught away from using MARA with NGS given the heightened need for read fidelity for the SNP genotyping performed in Shapero. EX2028.¶¶168-71. These concerns would also have taught away from reducing the number of target-specific primers used in preparing samples for NGS due to concerns that using only one target-specific primer would reduce target specificity, increase off-target binding, and lead to even higher base-calling errors, read artifacts, and false discovery rates. EX2028.¶¶59-62, 131, 168-71. Contrary to Petitioner's arguments, Delseny would not have taught a POSA toward the challenged claims but would have deterred a POSA from making such a

combination. *AstraZeneca AB v. Mylan Pharmas. Inc.*, 19 F.4th 1325, 1337 (Fed. Cir. 2021) (A “reference that properly teaches away can preclude a determination that the reference renders a claim obvious.”).

b) Syvänen discourages a POSA from modifying MARA for NGS

Petitioner misapplies the Syvänen article to argue that “Shapero teaches that its enrichment methods can be used with the sequencing technologies that existed.” *See* Petition, 35. Shapero references Syvänen only for the general proposition that “[t]here are a multitude of genotyping methodologies for SNPs that have been described over the years.” EX1006.0006. Syvänen does not discuss or address the use of MARA with sequencers, let alone with NGS, where the platforms were not even commercially available at the time Syvänen and Shapero were published. EX2028.¶¶59-62, 127-29, 165-67. Moreover, Syvänen would not have motivated a POSA to use MARA with sequencing technology at least because (1) Syvänen teaches away from using the PCR amplification required by the Challenged Claims; and (2) Syvänen’s limited disclosures concerning the use of sequencing technology for genotyping only covers narrow applications of pre-NGS Sanger sequencing.

First, Syvänen teaches away from the claimed methods, especially using allele-specific primers for PCR and enriching sequences of interest through amplification. In discussing strategies for SNP genotyping, Syvänen explains that

“[i]n practice, the requirement of a PCR amplification step to achieve sensitive and specific SNP genotyping is the principal factor that limits the throughput of assays today.” EX1012.0010. The platforms used to genotype SNPs at the time Syvänen published required large amounts of sample material, requiring researchers to amplify sequences to generate sufficient material. EX2028.¶146. Syvänen notes that “[t]he next generation technology for SNP analysis should avoid the PCR amplification step.” EX1012.0011 (emphasis added). This hostility towards the use of PCR amplification is also reflected in an earlier section of Syvänen, where Syvänen discloses a table summarizing the “most significant advantage,” “disadvantage,” and “special feature” of various “SNP-genotyping methods.” See *id.* at 1012.0005. For one technology, referred to as “padlock probes,” Syvänen identifies a “special feature” as that it “avoids target amplification.” *Id.* For another technology, Syvänen describes the “most significant advantage” as that “PCR amplification [is] avoided.” *Id.*

Syvänen further describes a series of genotyping assays that rely on the same amplification strategy as the MARA method: “PCR primers with the 3’-end complementary to either of the nucleotides of a SNP can be used in combination with a common reverse PCR primer to selectively amplify the SNP alleles.” EX1012.0006. Syvänen identifies several limitations with this method. According to Syvänen, when using “allele-specific PCR primers 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.*” *Id.* (emphasis added). Syvänen also discloses that a “limitation of all variants of allele-specific PCR is that the reaction conditions or primer design for selective allele amplification must be optimized empirically for each SNP.” *Id.* Syvänen notes that “the homogenous allele-specific PCR methods are best suited for the analysis of a limited number of SNPs in large sample collections.” *Id.* As such, Syvänen would have discouraged a POSA from incorporating enrichment methods using PCR amplification—such as the MARA method and embodiments of the claimed methods—with NGS genotyping technology that requires amplification. EX2028.¶¶165-67.

Second, Petitioner incorrectly argues that Syvänen’s “minisequencing” methods demonstrate the use of enrichment methods with sequencing technology. Petition, 35. Syvänen’s “minisequencing” is not a method of enrichment. Syvänen and other researchers use this term to describe a process of using DNA-polymerases to extend a single nucleotide for purposes of creating an extension product (a library preparation step). Bustamente Decl., ¶¶127-29, 165-67. No enrichment occurs.

Nevertheless, Petitioner relies on Syvänen’s disclosure that “DNA-sequencing instruments might also be used as platforms for genotyping SNPs using

fluorescently labelled dideoxynucleotides in the minisequencing reactions.”

Petition, 35. Petitioner, however, disregards the rest of the paragraph, which makes clear that Syvänen was proposing a way to filter and identify genotype samples, not to sequence them. EX1012.0008; EX2028.¶¶127-29, 165-67. The rest of the paragraph discusses using certain assays (not DNA sequencers) as “indirect detection procedure[s]” through the generation of various color-coded outputs to identify SNPs and how DNA-sequencing instruments could be used. *Id.* Contrary to Petitioner’s representations, Syvänen is not advocating for DNA sequencing but instead the incorporation of aspects of the DNA sequencing methods. Syvänen concludes that paragraph by saying that “*this assay* can be automated for high-throughput genotyping.” *Id.* (emphasis added). That disclosure does not even allude to sequencing the SNPs, let alone by NGS. *Id.* Even more, Petitioner’s claim directly contradicts the hostility that Syvänen expressed towards adapting sequencing technologies for genotyping: “Hopefully, future SNP-genotyping technology will be more elegant than the incremental and brute-force expansion of existing technologies in the way that the Sanger sequencing method has been exploited for genome sequencing.” *Id.* at 11. Petitioner, therefore, points to nothing in Syvänen that would have motivated a POSA to expand the existing methods in Shapero to arrive at the Challenged Claims. And, in fact, to the extent Petitioner contends that Shapero incorporates the disclosures of Syvänen, then Shapero teaches

away from using the MARA method with NGS for genotyping given Syvänen's express teachings against allele-specific PCR and PCR amplification.

c) Shapero's Data Is Inapplicable and Would Not Have Motivated a POSA to Combine Shapero and Delseny

Petitioner also incorrectly claims that a "POSA would have been further motivated to utilize the enrichment methods of Shapero in connection with NGS technologies described in Delseny given the experimental data in Shapero." Petition, 34. Essentially, Petitioner is arguing that the data in Shapero overcomes the flaws of Jones discussed in the Brooks Declaration. But, as discussed above, the data in Shapero does not address the use of the disclosed MARA method with NGS. Nor does it concern the use of the MARA method with any sequencing technology available in the art at the time.

The experimental data reported by Shapero reflects the use of MARA with hybridization arrays, which function differently than NGS platforms. Unlike NGS, a hybridization array allows researchers to target a sequence of interest during the analysis by using hundreds of billions of probes across the surface of the array that can bind to specific target sequences. EX2028.¶¶42-51, 80-87. Untargeted sequences are washed from the array and not included in its analysis. EX2028.*Id.*

NGS platforms, on the other hand, are specifically designed to allow for the sequencing of many samples at once without the need for target-specific probes.

EX2028.¶¶58-62, 80-87. Instead, NGS platform surfaces are covered by sets of common probes that bind to common primer sequences specific to a given NGS platform (e.g., Illumina's p5/p7 primers). *Id.*, ¶¶58-62, 80-87. Any fragment containing the common primer sequences will be bound to the platform and sequenced. *Id.*, ¶¶80-87. As such, researchers often use additional sample preparation methods to filter out unwanted products prior to sequencing samples. *Id.* Because of this key difference between hybridization arrays and NGS platforms, a POSA would not have considered data obtained from a hybridization array to be indicative of how any given method might perform with NGS. *Id.*, ¶¶80, 152-63, 175-76.

Petitioner, nonetheless, argues that “a POSA reading Shapero would understand that its enrichment methods generate high on-target specificity and that there is significant enrichment over a situation where no target specific primer is used.” Petition, 35. In doing so, Petitioner erroneously blurs the lines between Shapero's use of hybridization arrays and the use of library preparation techniques in connection with NGS methods. For example, Petitioner relies on the data in Shapero showing the percentage of hybridization array probes that detected a particular SNP and argues that data shows how MARA would function with NGS. *Id.*, 35-36. Petitioner's position, however, is misplaced because this data does not show what the target specificity would be for an NGS platform nor how many off-

target sequences would also be amplified in the process. EX2028.¶¶117-18, 144-52, 154-56, 162-63. Shapero even recognizes this same limitation, noting that the use of the hybridization array alleviates the requirement for absolute target specificity during MARA. EX1006.0012 (“With MARA, allele discrimination is achieved by hybridization to arrays containing SNP-specific complementary sequences,” thus, ***“the requirement for absolute specificity of primer annealing to target sequences in genomic DNA is alleviated.”***) (emphasis added). Shapero recognizes the role the hybridization array plays in preventing off-target binding, stating that “even if the primers contribute to non-specific amplification products, the complexity should not reach a level that would affect array hybridization.” *Id.* Shapero only discloses examples or data relying on a hybridization array for target specificity and to filter off-target products. As such, the array hybridization data reported in Shapero would not have motivated a POSA to combine Shapero with Delseny to practice the Challenged Claims.

d) Petitioner’s Proposed Combination Destroys the Purpose of Shapero

Petitioner’s argument suggests that a POSA would have been motivated to use Shapero’s MARA method with an analytical method that was known to lack the target specificity and reduced off-target binding that hybridization assays enjoy. Doing so, however, would impermissibly destroy the specific purpose of Shapero’s

methods. *See Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 69 F.4th 1341, 1349 (Fed. Cir. 2023) (“we have held it was error for the Board to ignore evidence that a proposed modification would interfere with a reference’s stated purpose.”). Shapero states that the purpose of developing MARA is “for highly multiplexed single nucleotide polymorphism (SNP) genotyping.” EX1006.0001, 06. As Shapero explains, “[i]n order to leverage the power of SNPs in genetic studies, novel target preparation methods need to be developed that, when combined with methods for allele discrimination, allow rapid and *accurate* genotypic information at a fraction of the cost of current approaches.” *Id.*, .0007.

Decoupling MARA from the array hybridization assays works against the purpose of Shapero. EX2028.¶¶162-63. As explained above, Shapero discloses that it is the hybridization array that promotes target recognition and specificity. *See supra*, Section V.A. The hybridization array also ensures that any off-target binding is filtered out of the results. *Id.* As such, the hybridization array ensures that the results are accurate, not Shapero’s MARA method. *See* EX2028.¶¶42, 153-63.

On the other hand, by 2012, the art was clear that NGS platforms suffered accuracy issues that made the technology less reliable than predecessor technology, such as Sanger sequencing. EX2028.¶¶61, 131, 170. As Delseny discloses, “identifying high-confident SNPs” with early NGS technologies was “a major challenge” given inaccurate base-calling and high false discovery rates.

EX1007.0008. These issues with read fidelity were only compounded by issues with target specificity and off-target binding that occurred during sample preparation. EX2028.¶¶61, 68-75, 131, 170. Taking a preparation method that was designed to be used with hybridization arrays to ensure accurate genotypic information and instead using it with a technology known to have different types of accuracy issues—higher than other sequencing technologies at the time—destroys the very purpose of Shapero. Such a combination cannot have been obvious. “In this case, such an intended-purpose-destroying modification counsels strongly against an obviousness determination.” *Medtronic, Inc. v. Teleflex Innovations S.a.r.L.*, IPR2020-00129, Paper 127, at 16 (PTAB June 17, 2021) *affirmed* 69 F.4th 1341 (Fed. Cir. 2023) (“The Board reasonably recognized that modifying a device in a manner that would undermine a purpose it shares with the challenged claims counsels against a motivation to make such modifications”).

2. A POSA Would Not Have Had a Reasonable Expectation of Success in Combining Shapero and Delseny to Practice the Claimed Inventions

Petitioner relies on the hybridization results of Shapero to argue that a “POSA also would have had a reasonable expectation of success utilizing Shapero’s enrichment methods with the NGS technologies described in Delseny.” Petition, 36. According to Petitioner, a POSA would have had a reasonable expectation of success because “the experimental data in Shapero shows a high on-target specificity that a

POSA would understand would likely work for NGS applications.” *Id.* That argument, however, disregards the limitations of the data reported in Shapero. Shapero would not provide a POSA with a reasonable expectation of success in combining Shapero with Delseny for at least two reasons: (1) the enrichment, target specificity, and off-target binding attributable to MARA cannot be determined from Shapero’s disclosure; and (2) the hybridization arrays, when used with the MARA method, proved less reliable for reasons that Shapero could not explain.

a) A POSA cannot make inferences about enrichment, target specificity, and off-target binding from Shapero

Petitioner cites to Shapero’s comparison of the call rates in the 250- and 750-plex reactions to argue that “a POSA reading Shapero would understand that its enrichment methods generate high on-target specificity and that there is significant enrichment over a situation where no target specific primer is used.” Petition, 37. The data, however, supports none of Petitioner’s argument.

At the heart of the disagreement is Petitioner’s overreach as to what can be inferred from the data about enrichment. Shapero discloses two sets of tests where Shapero compared the call rates (how often the array probe captured a SNP) for two different methodologies. EX1006.0009-10. The first method is MARA where a locus-specific primer is used to introduce one of two universal primer sequences used for PCR amplification. *Id.* The second method is a modified version of MARA

where the locus-specific primer is not used and the universal primer sequence is not present for amplification. *Id.* As such, the comparison of the call rates reflects the efficacy of the hybridization array when using *amplified* nucleic acid samples compared to *non-amplified* nucleic acid samples. *See id.* at 10 (“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.”); EX2028.¶¶120-22, 158-63.

While Petitioner argues that the difference in call rates between the methods is the result of enrichment, there is nowhere in Shapero that makes that conclusion. In fact, the tests conducted by Shapero make it difficult to know whether the improved results was due to enrichment of the targets or due to increased quantity of the sample. A POSA cannot know for certain whether the lower call rates attributed to the method that excluded the locus-specific primers is because the arrays needed more sample material (i.e., less material led to less coverage across the array) or because the locus-specific primers facilitated enrichment. *See* EX2028.¶¶158-63. The use of a hybridization array only makes it harder to make an inference because it masks any potential issues with target specificity and off-target binding (due to the array’s ability to target specific sequences during analysis). The target-specific nature of the hybridization array precludes a POSA from knowing to what degree the locus-specific primers enriched any specific sequence

as compared to the rest of the sample population. *See id.*, ¶¶153-63. A POSA could not infer what degree of target specificity is driven by MARA as compared to the array. *See id.*, ¶¶153-63; EX1006.0012 (the need for “absolute specificity of primer annealing to target sequences in genomic DNA is alleviated” due to “allele discrimination [being] achieved by hybridization to arrays containing SNP-specific complementary sequences.”).

Similarly, with respect to off-target binding, Shapero explains that “even if the primers contribute to non-specific amplification products, the complexity should not reach a level that would affect array hybridization.” EX1006.0012. In other words, if there were off-target binding issues with MARA, those issues would also be obscured by the use of the hybridization array. *See* EX2028.¶¶153-63. As disclosed in Shapero, there is no way a POSA can ascertain from the publication what level of off-target binding occurred using MARA. *See id.*, ¶¶153-63.

Given these limitations, a POSA could not have reliably inferred from the reported hybridization data how effective MARA would be with an NGS platform. *Id.*, ¶¶153-63.

b) The data confirms a POSA’s hesitation with adapting MARA beyond its disclosed purpose

Even looking past the inability for a POSA to draw any inferences as to how MARA would work with NGS, the data reported by Shapero demonstrates that

MARA suffered from undeterminable deficiencies that could have been fatal to use with NGS. For example, the concordance rates reported by Shapero—which are meant to demonstrate how accurate the hybridization array was in identifying SNPs compared to an established reference—were lower than the public rates reported by Affymetrix for the same type of hybridization array. *See* EX2028, ¶¶122, 125, 162, 176. In most instances, the data reported in Shapero reflected an approximately four-to-five times greater error rate than the standard rates reported for the hybridization array. *See Id.*, ¶¶122, 125, 162, 176. The increased error rate would have led a POSA to have an even lower expectation of success in being able to adapt the methodology of Shapero for use with another genotyping technology, and especially for NGS, where a POSA would have expected even greater error rates due to the lack of target specificity. *See Id.*, ¶¶122, 125, 162, 176.

Additionally, when applying MARA in 1,100- and 4,365-plex reactions, using arrays designed to target SNPs specifically found in human chromosome 21, Shapero reports that only 75% of the input primers can function with a multiplex above 1,000 bps. EX1006.0012. Therefore, a POSA would have questions with whether this method could be reliably used with a high-throughput method like NGS. Shapero was not able to determine the reason for the failure with the larger reactions, explaining that “the overall primer conversion rates do not differ significantly between 1100 primer-plex (x4) and 4365 primer-plex, *suggesting that*

*non-specific primer-primer interactions at the higher multiple level may not solely be responsible for failed target generation.” See id. at .10-12 (emphasis added). A POSA reviewing this data would have had a diminished expectation of being able to use MARA with high-throughput techniques, let alone with NGS, given that not even the inventors of both MARA and the hybridization arrays could determine what issues confounded the analysis. EX2028.¶¶175-76. That uncertainty would only further contribute to why a POSA would not have had a reasonable expectation of taking MARA and using it with NGS. *Id.**

c) Petitioner ignores the concerns in the art in 2012

Ignoring these issues with the Shapero data, Petitioner instead dismisses the concerns in the art regarding target specificity and off-target binding, claiming that such concerns are directly contradicted by the teachings of Shapero. *See* Petition, 39-40. This misinterpretation of the data disclosed in Shapero—which was published in 2004—ignores the state of the art by 2012. In 2012, a POSA would have been aware of numerous publications discussing various problems concerning primer design for multiplex PCR for NGS. EX2028.¶¶66-75. Those problems included mis-priming due to nonspecific binding to non-target DNA templates and primer dimerization. *See Id.*, ¶¶66-75.

The solutions in the prior art all reflected a basic understanding that target-specific *primer pairs* were necessary for PCR enrichment for NGS. *Id.* For

example, researchers in the field hypothesized on various ways to improve these problems, such as through “careful primer design and reaction optimization” so that “*several dozen primer pairs* can be used together effectively in a multiplexing reaction.” EX2021.0007. (emphasis added); *Id.*, ¶¶72-75. Software designers similarly focused on how to optimize target-specific primer sets for NGS analysis. *Id.*, ¶¶72-75. At the time, the expectation was that pairs of target-specific primers were needed, especially as researchers sought to enrich for complex genomic DNA. *Id.*, ¶¶66-75. Researchers focused on how to optimize primer pairs—not on using a single target-specific primer. *Id.*, ¶¶70-75. The words “single primer enrichment” were not even in the lexicography of the art. *Id.*, ¶¶66-75. In fact, researchers outright dismissed the use of a single target-specific primer for enrichment. *See* EX2018.0002. (“While the specificity of individual primers may be tested using BLAST, no further consideration may be given to the influence of non-target sites that can result in suboptimal binding of the primers. Accurate quantification requires primer sets that facilitate maximum amplification efficiency.”); EX2028.¶70.

Nonetheless, Petitioner’s expert witness, Dr. Metzker, claims that the methods of the ’108 patent “had been in use and were well proven to work” by 2012. *See* EX1003.¶99. But the only instance that Dr. Metzker identifies is the MARA method. *Id.*, ¶106. Indeed, Dr. Metzker concedes that prior art single-plex and multiplex PCR required target specific primer pairs. *See id.*, ¶57. Dr. Metzker identifies no prior

art references considering the use of a single target-specific primer with NGS. Dr. Metzker similarly fails to point to any prior art (beyond his misplaced reliance on the Shapero data) to argue how concerns over off-target binding through the use of a single target-specific primer with NGS were addressed before August 2012. Instead, Dr. Metzker couches the prior art solution as part of using multiple primer pairs: “researchers had already employed various strategies, such as the use of adaptors, to achieve high levels of enrichment and minimize off-target, non-specific amplification that typically resulted from the use of multiple primer pairs.” *Id.*, ¶ 99. In fact, in a 2010 publication co-authored by Dr. Metzker, Dr. Metzker wrote that “[i]nitial reports [of NGS] raised concerns as to the readiness of targeted capture for routine use owing to the high degree of variability in coverage and representation, ***the capturing of off-target fragments***, the requirement for microgram quantities of starting material and the high cost for microarrays, but improvements are being made to address these limitations.” EX1025.0011 (emphasis added). Those “improvements” concerned the use of primer pairs. *See, e.g.*, EX2029.0001 (noting that “all the new methods work, in principle, the same way. A ***set of oligonucleotide probes*** is used to capture the desired sequences from total human genomic DNA” and recognizing that the “biggest problem is that some DNA sequences are far harder to capture than others, for reasons that remain unclear. Although the numbers aren’t directly comparable, one group reported 53% coverage of their targets, another just

20%.”) (emphasis added). Petitioner’s silence on prior art solutions that rely on single primer enrichment to solve problems specific to NGS speaks volumes as to why a POSA would not have had a reasonable expectation of success.

Petitioner also argues that a POSA would have had a reasonable expectation of success in adapting Shapero for NGS because “Delseny expressly teaches that NGS can be a replacement for array-based genotyping, as used in Shapero.” Petition, 36. Petitioner misstates what Delseny teaches. *See supra*, V.A. Delseny expresses concerns with using NGS to genotype SNPs due to lower read fidelity. EX2007.0005. As such, Delseny encourages the use of pre-NGS Sanger sequencing methods (describing them as the “gold standard.”). *Id.* Nothing in Delseny would ease the concerns in the art at the time—let alone provide a POSA with a reasonable expectation of success in adapting a method to genotype SNPs so that it can be used with NGS platforms. EX2028.¶¶175-76.

As a result, the Petition has failed to establish that a POSA would have been motivated to combine Shapero with Delseny to arrive at claim 1 with a reasonable expectation of success.

3. Dependent Claims

For the reasons that Shapero and Delseny fail to render obvious claim 1 of the ’108 patent, Shapero and Delseny fail to render obvious any of the remaining dependent claims. *See In re Lemay*, 660 Fed. App’x 919, 927 (Fed. Cir. 2016)

(“dependent claims are nonobvious if the independent claims from which they depend are nonobvious”) (cleaned up).

B. Ground 2 (Claims 3-4 were obvious over Shapero and Delseny and further in view of Jones)

Petitioner argues that Shapero could be adapted in view of Delseny and in further view of Jones to practice dependent claims 3-4. Petition, 50. As explained above, Shapero and Delseny fail to render obvious claim 1 of the '108 patent. Ground 2 fails to address the deficiencies in Ground 1 with respect to the only independent claim of the '108 patent. As such, Ground 2 necessarily fails for at least the same reasons.

C. Ground 2 (Claim 8 was obvious over Shapero and Delseny and further in view of Hamady)

Petitioner argues that Shapero could be adapted in view of Delseny and in further view of Hamady to practice dependent claim 8. Petition, 51-53. As explained above, Shapero and Delseny fail to render obvious claim 1 of the '108 patent. Ground 3 fails to address the deficiencies in Ground 1 with respect to the only independent claim of the '108 patent. As such, Ground 3 necessarily fails for at least the same reasons.

VI. CONCLUSION

For the foregoing reasons, Tecan respectfully requests that the Board deny institution of an *Inter Partes* Review.

Dated: February 19, 2025

Respectfully submitted,

By: /Linnea P. Cipriano/
Linnea P. Cipriano
(Reg. No. 67,729)
Goodwin Procter LLP
620 Eighth Avenue
New York, NY 10018
Phone: (212) 813-8800
Cell: (443) 235-1739
Fax: (212) 937-2204
lcipriano@goodwinlaw.com

*Counsel for Patent Owner
Tecan Genomics, Inc.*

CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's Preliminary Response** complies with the type-volume limitation of 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(b)(1). The Response contains 11,431 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1), as measured by the word-processing system use to prepare the Response.

Dated: February 19, 2025

/Linnea P. Cipriano/
Linnea P. Cipriano (Reg. No. 67,729)
GOODWIN PROCTER LLP
620 Eighth Avenue
New York, NY 10018
lcipriano@goodwinlaw.com
Tel: (212) 813-8800
Fax: (212) 937-2204

CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on February 19, 2025, a copy of the foregoing **Patent Owner's Preliminary Response** 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:

David L. Bilsker (Reg. No. 39,611)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
50 California Street, 22nd Fl.
San Francisco, CA 94111
Tel: (415) 875-6432
Fax: (415) 875-6700
davidbilsker@quinnemanuel.com
Qe-qiagen-tecan@quinnemanuel.com

Matthew A. Traupman (Reg. No.
50,832)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
51 Madison Ave., 22nd Floor
New York, NY 10010
Tel: (212) 849-7322
Fax: (212) 849-7100
matthewtraupman@quinnemanuel.com

Tara Srinivasan (Reg. No. 77,091)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
50 California Street, 22nd Fl.
San Francisco, CA 94111
Tel: (415) 875-6600
Fax: (415) 875-6700
tarasrinivasan@quinnemanuel.com

Landon A. Smith (Reg. No. 79,248)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
300 W. 6th Street
Austin, TX 78701
Tel: (737) 667-6116
Fax: (737) 667-6110
landonsmith@quinnemanuel.com

Andrew E. Naravage (*pro hac vice* to
be applied for)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
50 California Street, 22nd Fl.
San Francisco, CA 94111
Tel: (415) 875-6432
Fax: (415) 875-6700

John Yang (*pro hac vice* to be applied
for)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
3100 McKinnon St, Suite 1125
Dallas, TX 75201
Tel: (469) 902-3600
Fax: (469) 902-3610

andrewnaravage@quinnemanuel.com

johnyang@quinnemanuel.com

/Linnea P. Cipriano/

Linnea P. Cipriano (Reg. No. 67,729)

GOODWIN PROCTER LLP

620 Eighth Avenue

New York, NY 10018

lcipriano@goodwinlaw.com

Tel: (212) 813-8800

Fax: (212) 937-2204