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 RESPONSE

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TABLE OF AUTHORITIES

Page(s)

Cases

Apple Inc. v. Samsun Elecs. Co., Ltd.,
839 F.3d 1034 (Fed. Cir. 2016) (*en banc*) 54

Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino,
738 F.3d 1337 (Fed. Cir. 2013) 59

InTouch Techs., Inc. v. VGO Commc'ns, Inc.,
751 F.3d 1327 (Fed. Cir. 2014) 19

In re Lemay,
660 Fed. App'x 919 (Fed. Cir. 2016) 53

Leo Pharma. Products, Ltd. v. Rea,
726 F.3d 1346 (Fed. Cir. 2013) 45, 47

Liqwd, Inc. v. L'Oreal USA, Inc.,
941 F.3d 1133 (Fed. Cir. 2019) 62

Medtronic, Inc. v. Teleflex Innovations S.a.r.l.,
70 F.4th 1331 (Fed. Cir. 2023) 62

Millennium Pharmas., Inc. v. Sandoz Inc.,
862 F.3d 1356 (Fed. Cir. 2017) 54

Mintz v. Dietz & Watson, Inc.,
679 F.3d 1372 (Fed. Cir. 2012) 54

Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.,
97 F.4th 882 (Fed. Cir. 2024) 19

WBIP, LLC v. Kohler Co.,
829 F.3d 1317 (Fed. Cir. 2016) 54, 57

EXHIBIT LIST

Ex.	Short Name	Description
2001	Affymetrix SNP Array 6.0	*Affymetrix® Genome-Wide Human SNP Array 6.0*, Affymetrix, Inc. (2007).
2002	Introduction to Affymetrix Microarrays	*Introduction to Affymetrix Microarrays*, GENSTAT, https://genstat.kb.vsni.co.uk/knowledge-base/affymetrix-introduction/ (last visited February 19, 2025)
2003	Microarray Affymetrix Chips	*Microarray Affymetrix Chips*, GENSTAT, https://genstat.kb.vsni.co.uk/knowledge-base/affymetrix-chips/ (last visited February 19, 2025).
2004	Dalma-Weiszhausz 2006	Dennise D. Dalma-Weiszhausz et al., *The Affymetrix GeneChip® Platform: An Overview*, 410 METHODS IN ENZYMOLOGY 3 (2006).
2005	Evans 2009	Mark F. Evans, *The Polymerase Chain Reaction and Pathology Practice*, 15 DIAGNOSTIC HISTOPATHOLOGY 344 (2009).
2006	NHGRI 2021	*The Cost of Sequencing a Human Genome*, 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., *Coming of Age: Ten Years of Next-Generation Sequencing Technologies*, 17 NAT. REV. 333 (2016).
2008	Mardis 2017	Elaine R. Mardis, *DNA Sequencing Technologies: 2006-2016*, 12 NAT. PROTOC., 213 (2017).
2009	Ernani 2009	*Bringing Cost and Process Efficiency to Next Generation Sequencing*, DRUG DISCOVERY WORLD, https://www.ddw-online.com/bringing-cost-and-process-efficiency-to-next-generation-sequencing-731-200908/ (last visited February 19, 2025)
2010	Milbury 2009	Coren A. Milbery et al., *PCR-Based Methods for the Enrichment of Minority Alleles and Mutations*, 55 CLIN. CHEM.. 632 (2009).

Ex.	Short Name	Description
2011	Mamanova 2011	Lira Mamanova et al., *Target-Enrichment Strategies for Next-Generation Sequencing*, 7 NAT. METHODS 111 (2010).
2012	Treangen 2012	Todd J. Treangen et al., *Repetitive DNA and Next-Generation Sequencing: Computational Challenges and Solutions*, 13 NAT. REV. 36 (2012).
2013	Shokralla 2012	Shadi Shokralla et al., *Next-Generation Sequencing Technologies for Environmental DNA Research*, 21 MOL. ECOL. 1794 (2012).
2014	QIAGEN 2010	*QIAGEN® Multiplex PCR Handbook*, QIAGEN (2010).
2015	Han 2006	Sangjo Han et al., *AtRTPrimer: Database for Arabidopis Genome-Wide Homogeneous and Specific RT-PCR Primer-Pairs*, 7 BMC BIOINFORMATICS 179 (2006).
2016	Matz 1999	Mikhail V. Matz et al., *Amplification of cDNA Ends Based on Template-Switching Effect and Step-out PCR*, 27 NUCLEIC ACIDS RES. 1558 (1999).
2017	Bru 2008	D. Bru et al., *Quantification of the Detrimental Effect of a Single Primer-Template Mismatch by Real-Time PCR Using the 16S rRNA Gene as an Example,* 74 APPL. ENVIRON. MICROBIOL. 1660 (2008).
2018	Bustin 2005	Stephen A. Bustin et al., *Quantitative Real-time RT-PCR – A Perspective,* 34 J. MOL. ENDOCRINOL. 597 (2005).
2019	Duncavage 2011	Eric J. Duncavage et al., *Hybrid Capture and Next-Generation Sequencing Identify Viral Integration Sites from Formalin-Fixed, Paraffin-Embedded Tissue*, 13 J. MOL. DIAGNOSTICS. 325 (2011).
2020	Brownie 1997	Jannine Brownie et al., *The Elimination of Primer-Dimer Accumulation in PCR*, 25 J. NUCLEIC ACIDS. RES. 3235 (1997).
2021	Mertes 2011	Florian Mertes et al., *Targeted Enrichment of Genomic DNA Regions for Next-Generation Sequencing*, 10 BRIEF. FUNCT. GENOM. 374 (2011).
2022	Shen 2010	Zhiyong Shen et al., *MPrimer: A Program for Reliable Multiplex PCR Primer Design*, 11 BMC BIOINFORMATICS FUNCT. GENOM. 143 (2010).

Ex.	Short Name	Description
2023	Deutsche 2011	Ulla Deutsch et al., *Streamlining Multiplex PCR Analysis*, GENETIC ENGINEERING & BIOTECHNOLOGY, Dec. 1, 2011, https://www.genengnews.com/insights/streamlining-multiplex-pcr-analysis/.
2024	Tewhey 2009	Ryan Tewhey et al., *Microdroplet-based PCR Enrichment for Large-Scale Targeted Sequencing*, 27 NAT. BIOTECHNOL. 1025 (2009).
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. Bustamente, Ph.D.
2029	Garber 2008	Ken Garber, *Fixing the Front End*, 26 NAT. BIOTECHNOL. 1101 (2008).
2030	Illumina 2014	*TruSeq® DNA Library Prep Kits*, Illumina, Inc. (2014).
2031	Matsuzaki 2004	Hajime Matsuzaki et al., *Parallel Genotyping of Over 10,000 SNPs Using a One-Primer Assay on a High-Density Oligonucleotide Array*, 14 GENOME RES. 414 (2004).
2032	Risen 2021	Clay Risen, *Andrew Brooks, Who Developed a Rapid Covid Test, Dies at 51*, N.Y. TIMES, Jan. 31, 2021, https://www.nytimes.com/2021/01/31/science/andrew-brooks-dead.html.
2033	Affymetrix Assay Kit	*GeneChip® Human Mapping 10K Array and Assay Kit*, Affymetrix, Inc. (2003).
2034	Nature 2007	*Chipping out Our Differences*, 449 NATURE 629 (2007).
2035	Kennedy 2003	Giulia C. Kennedy et al., *Large-Scale Genotyping of Complex DNA*, 421 NAT. BIOTECHNOLOGY 1233 (2003).
2036		*Reserved*
2037		*Reserved*

Ex.	Short Name	Description
2038		*Reserved*
2039		*Reserved*
2040	Mullis 1986	K.Mullis et al., *Specific Enzymatic Amplification o fDNA In Vitro: The Polymerase Chain Reaction*, 51 COLDSPRING HARBOR SYMPOSIA QUANTITATIVE BIOL. 1(1986)
2041	Kanagawa 2003	Takahiro Kanagawa, *Bias and Artifacts in Multitemplate Polymerase Chain Reactions (PCR)*, 96 J. BIOSCI. & BIOENG 4 (2003)
2042	Aird 2011	Daniel Aird et al., *Analyzing and minimizing PCR amplifications bias in Illumina sequencing libraries*, 12 GENOME BIOL. (2011)
2043	Chenchik 1996	A. Chenchik et al., *Full-Length cDNA Cloning and Determination of mRNA 5' and 3' Ends by Amplification of Adaptor-Ligated cDNA*, 21 BIOTECHNIQUES 3 (1996)
2044	Devon 1995	Rebecca S. Devon et al., *Splinkerettes—improved vectorettes for greater efficiency in PCR walking*, 23 NUCLEIC ACIDS RES. 9 (1995)
2045	Padegimas 1998	Linas S. Padegimas & Nancy A. Reichert, *Adaptor Ligation-Based Polymerase Chain Reaction-Mediated Walking*, 260 ANALYTICAL BIOCHEMISTRY (1998)
2046	Arnold 1991	C. Arnold & I.J. Hodgson, *Vectorette PCR: A Novel Approach to Genomic Walking*, PCR METHODS & APPLICATIONS (1991)
2047	Miura 2005	Fumihito Miura et al., *A novel strategy to design highly specific PCR primers based on stability and uniqueness of 3'-end subsequences*, 21 BIOINFORMATICS 24 (2005)
2048	Tsoktouridis 2005	Georgios Tsoktouridis et al., *Adaptor Long-Range PCR Procedure for Clone-Specific Characterization and Chromosomal Localization*, 38 BIOTECHNIQUES 6 (2005)
2049	Bower 2010	Neil I. Bower & Ian A. Johnston, *Targeted rapid amplification of cDNA ends (T-RACE)—an improved RACE reaction through degradation of non-target sequences*, 38 NUCLEIC ACIDS RES. 21 (2010)
2050	Sohn 2011	Jung-Hoon Sohn, *A Novel Genome Walking Method for Cloning of Unknown DNA Sequences Adjacent to Known Sequence*, Application No. WO 2011/004994

Ex.	Short Name	Description
2051	Almomani 2011	Rowida Almomani et al., *Experiences with array-based sequence capture; toward clinical applications*, 19 EURO. J. HUMAN GENETICS (2011)
2052	Myllykangas 2011	Samuel Myllykangas et al., *Targeted sequencing library preparation by genomic DNA circularization*, 11 MCB BIOTECH. 122 (2011)
2053	Quail 2008	Michael A. Quail et al., *A large genome center's improvements to the Illumina sequencing system*, 5 NAT. METHODS 12 (2008)
2054	Kozarewa 2009	Iwanka Kozarewa et al., *Amplification-free Illumina sequencing-library preparation facilitates improved mapping and assembly of (G+C)-biased genomes*, 6 NAT. METHODS 4 (2009)
2055		*Reserved*
2056	Grunenwald 2010	Haiying Gruenwald et al., *Rapid, high-throughput library preparation for next-generation sequencing*, NAT. METHODS (2010)
2057	Glenn 2011	Travis C. Glenn, *Field guide to next-generation DNA sequencers*, MOLECULAR ECOLOGY RES. (2011)
2058		*Reserved*
2059		*Reserved*
2060	Niedringhaus 2011	Thomas P. Niedringhaus, *Landscape of Next-Generation Sequencing Technologies*, 83 ANALYTICAL CHEMISTRY (2011)
2061		*Reserved*
2062		*Reserved*
2063	Irwin 2011	Jodi Irwin et al., *Assessing the potential of next generation sequencing technologies for missing persons identification efforts*, 3 FORENSIC SCI. J. (2011)
2064	Lange 2010	Julia Lange, *Targeted resequencing for large-scale genomic studies: accelerating NGS throughput using molecular barcodes*, NAT. METHODS (2010)
2065	Barchi 2019	Lorenzo Barchi, *Single Primer Enrichment Technology (SPET) for High-Throughput Genotyping in Tomato and Eggplant Germplasm*, 10 FRONTIERS IN PLANT SCI. (2019)

Ex.	Short Name	Description
2066	Gnirke 2009	Andreas Gnirke et al., *Solution Hybrid Selection with Ultra-Long Oligonucleotides for Massively Parallel Targeted Sequencing*, 27 NAT. BIOTECH. 182 (2009)
2067	Smith 2021	Caitlin Smith, *Growing Options for Enriching Target DNA*, FUTURELABS, June 17, 2021, https://www.biocompare.com/Editorial-Articles/576645-Growing-Options-for-Enriching-Target-DNA/.
2068	Scaglione 2019	Davide Scaglione et al., *Single primer enrichment technology as a tool for massive genotyping: a benchmark on black poplar and maize*, 124 ANNALS OF BOTANY (2019)
2069	Benjamino 2021	Jacquelynn Benjamino et al., *Genome-Based Targeted Sequencing as a Reproducible Microbial Community Profiling Assay*, 6 MSPHERE 2 (2021)
2070		*Reserved*
2071	Quail 2011	Michael A. Quail et al., *Optimal enzymes for amplifying sequencing libraries*, 9 NAT. METHODS 1 (2012)
2072		*Reserved*
2073		*Reserved*
2074		*Reserved*
2075	Bielas 2013	International Publication No. WO 2013/123442 A1
2076		*Reserved*
2077		*Reserved*
2078		*Reserved*
2079		*Reserved*
2080		*Reserved*
2081		*Reserved*
2082	Nugen Nature	*Accelerating Genomics with Advanced Sample Preparation Solutions*, NATURE RESEARCH CUSTOM MEDIA
2083	Scolnick 2015	Jonathan A. Scolnick et al., *An Efficient Method for Identifying Gene Fusions by Targeted RNA Sequencing from Fresh Frozen and FFPE Samples*, PLOS ONE (2015)
2084	Nugen BioSpace	Priya Balachandran, *NuGEN Announces Issuance of U.S. Patent For Its Single Primer Target Enrichment Technology (SPET) For Next Generation Sequencing*

Ex.	Short Name	Description
		Applications, BIOSPACE, https://www.biospace.com/nugen-announces-issuance-of-u-s-patent-for-its-single-primer-target-enrichment-technology-spet-for-next-generation-sequencing-applications (last visited July 18, 2025)
2085	Allegro V2	*Allegro® Targeted Genotyping V2 Product Sheet*, TECAN GENOMICS, INC. (2019)
2086		*Reserved*
2087		*Reserved*
2088		*Reserved*
2089		*Reserved*
2090		*Reserved*
2091		*Reserved*
2092		*Reserved*
2093		*Reserved*
2094		*Reserved*
2095		*Reserved*
2096		*Reserved*
2097		*Reserved*
2098		*Reserved*
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2100		*Reserved*
2101		*Reserved*
2102		*Reserved*
2103		*Reserved*
2104		*Reserved*
2105		*Reserved*
2106		*Reserved*
2107	Bustamante Declaration	Declaration of Carlos D. Bustamante, Ph.D.
2108	Metzker Deposition 1	Transcript for the July 31, 2025 Deposition of Dr. Michael L. Metzker
2109	Metzker Deposition 2	Transcript for the August 1, 2025 Deposition of Dr. Michael L. Metzker

Ex.	Short Name	Description
2110	Glaszmann 2010	JC Glaszmann et al., *Accessing Genetic Diversity for Crop Development*, 13 CURRENT OPINION IN PLANT BIOLOGY 167 (2010)
2111	Wright 2005	Stephen I. Wright et al., *The Effects of Artificial Selection on the Maize Genome*, 308 SCIENCE 1310 (2005)
2112	Generational Challenge Program	CGAIR, *General Terms of Reference for the Final Review of the Generational Challenge Program 2004-2014*, https://www.genengnews.com/insights/streamlining-multiplex-pcr-analysis/ (last visited Aug. 20, 2025)
2113	Park 2009	Peter J. Park, *ChIP-seq: Advantages and Challenges of a Maturing Technology*, 10 NAT. REV. 669 (2009)
2114	Kaufmann 2009	Kerstin Kaufmann et al., *Target Genes of the MADS Transcription Factor SEPALLATA3: Integration of Developmental and Hormonal Pathways in the Arabidopsis Flower*, 7 PLOS BIOLOGY 854 (2009)
2115	Kaufmann 2010	Kerstin Kaufmann et al., *Orchestration of Floral Initiation by APETALA 1*, 328 PLOS SCIENCE 85 (2010)
2116	CBOL 2009	CBOL Plant Working Group, *A DNA Barcode for Land Plants*, 106 PNAS 12794 (2009)
2117	Han 2009	Xuehui Huang., *High-Throughput Genotyping by Whole-Genome Sequencing*, 328 GENOME RSCH. 1068 (2009)
2118	Meyer 2009	Eli Meyer et al., *Sequencing and De Novo Analysis of a Coral Larval Transcriptome Using 454 GSFlx*, 10 BMC GENOMICS 219 (2009)
2119	Barker 2005	Christopher S. Barker et al., *Increased DNA Microarray Hybridization Specificity Using sscDNA Targets*, 6 BMS GENOMICS 57 (2005)
2120	Nygaard 2006	Vigdis Nygaard et al., *Options Available for Profiling Small Samples: A Review of Sample Amplification Technology When Combined with Microarray Profiling*, 34 NUCLEIC ACID RSCH. 996 (2010)
2121	Matsuzaki 2004	Hajime Matsuzaki et al., *Genotyping Over 100,000 SNPs on a Pair of Oligonucleotide Arrays*, 1 NATURE METHODS 109 (2004)
2122	Affymetrix Data Sheet 2009	*Data Sheet Genome-Wide Human SNP Array 6.0*, Affymetrix, Inc. (2009).

Ex.	Short Name	Description
2123	Jiang 2008	Ning Jiang et al., *Methods for Evaluating Gene Expression from Affymetrix Microarray Datasets*, 410 BMS BIOINFORMATICS 284 (2008)
2124	Dalma-Weiszhausz 2006	Dennise D. Dalma-Weiszhausz al., *The Affymetrix Genechip® Platform: An Overview*, 9 METHODS IN ENZYMOLOGY 3 (2006)
2125	Affymetrix Data Sheet 2007	*GeneChip® Human Genome U133 Arrays*, Affymetrix, Inc. (2007).
2126	Dahl 2005	Fredrik Dahl et al., *Multiplex Amplification Enabled by Selective Circularization of Large Sets of Genomic DNA Fragments*, 33 NUCLEIC ACID RSCH. 1 (2005)
2127	Benjamin 2005	Ivor J. Benjamin et al., *Learning from Failure: Congestive Heart Failure in the Postgenomic Age*, 115 J. CLIN. INVEST. 495 (2005)
2128	Zhou 2005	Guo-Hua Zhou et al., *Multiplex SNP Typing by Bioluminometric Assay Coupled with Terminator Incorporation (BATI)*, 33 NUCLEIC ACID RSCH. 15 (2005)
2129	Ronaghi 2005	Mostafa Ronaghi et al., *Single Nucleotide Polymorphisms: Discovery, Detection, and Analysis*, 2 PERSONALIZED MED. 996 (2005)
2130	Howell 2006	W. Mathias Howell et al., *Detection and Techniques for Single Nucleotide Polymorphisms*, 6 NUCLEIC ACID TESTING FOR HUMAN DISEASE 139 (2006)
2131	Li 2006	Li Li et al., *SNP Genotyping by Multiplex Amplification and Microarrays Assay for Forensic Application*, 162 FORENSIC SCI. INTL. 74 (2006)
2132	Wang 2006	Wei-peng Wang et al., *Multiplex Single Nucleotide Polymorphism Genotyping by Adapter Ligation-Mediated Allele-Specific Amplification*, 355 ANALYTICAL BIOCHEMISTRY 240 (2006)
2133	Wang 2006b	Wei-peng Wang et al., *Association of IL1B Polymorphisms with Gastric Cancer in a Chinese Population*, 40 CLINICAL BIOCHEMISTRY 218 (2006)
2134	Loakes 2007	David Loakes, *Nucleotides and Nucleic Acids; Oligo- and Polynucleotides*, 36 ORGANOPHOSPHORUS CHEM. 232 (2007)

Ex.	Short Name	Description
2135	Morin 2007	Phillip A. Morin et al., *Highly Accurate SNP Genotyping from Historical and Low-Quality Samples*, 7 MOLECULAR ECOLOGY NOTES 937 (2007)
2136	Stromqvist Meuzelaar 2007	Linda Stromqvist Meuzelaar et al., *MegaPlex PCR: A Strategy for Multiplex Amplification*, 4 NATURE METHODS 835 (2007)
2137	Zakharova 2008	Natalia V Zakharova et al., *Simultaneous Qualitative and Quantitative Identification of Multiple Targets by Polymerase Chain Reaction on Microarray*, OLIGONUCLEOTIDE ARRAY SEQUENCE ANALYSIS Chapter 12 (2008)
2138	Bui 2009	Minh Bui et al., *Simple Allele-Discriminating PCR for Cost-Effective and Rapid Genotyping and Mapping*, 5 PLANT METHODS 1 (2009)
2139	Palka-Santini 2009	Maria Palka-Santini et al., *Large Scale Multiplex PCR Improves Pathogen Detection by DNA Microarrays*, 9 BMC MICROBIOLOGY 1 (2009)
2140	Jin 2011	Tao Jin et al., *Molecular Basis for Resistance to Tribenuron in Shepherd's Purse (Capsella Bursa-Pastoris (L.) Medik.)*, 100 PESTICIDE BIOCHEMISTRY AND PHYSIOLOGY 160 (2011)
2141	Liu 2012	Jing Liu et al., *An Improved Allele-Specific PCR Primer Design Method for SNP Marker Analysis and Its Application*, 8 PLANT METHODS 34 (2012)
2142	Liu 2024	Ying Liu et al., *Multiplex Asymmetric PCR by Combining the Amplification Refractory Mutation System with the Homo-Tag-Assisted Nondimer System*, 96 ANAL. CHEM. 9200 (2024)
2143	QIAseq Targeted DNA Panel	*QIAseq Targeted DNA Panels*, QIAGEN, https://www.qiagen.com/us/products/discovery-and-translational-research/next-generation-sequencing/dna-sequencing/somatic-panels/qiaseq-targeted-dna-panels (last visited Aug. 20, 2025)
2144	QIAseq Targeted RNAscan Panel	*QIAseq Targeted RNAscan Panels*, QIAGEN, https://www.qiagen.com/us/products/discovery-and-translational-research/next-generation-sequencing/rna-

Ex.	Short Name	Description
		sequencing/rna-fusions/qiaseq-targeted-rnascan-panel (last visited Aug. 20, 2025)
2145		*Reserved*
2146	QIAGEN 2016	*Exploring New Frontiers with Next-Generation Sequencing*, QIAGEN (2016)
2147	QIAGEN 2018	*QIAseq and Single Primer Extension Chesmistry: Redefining Aplicon-Based NGS*, QIAGEN (2018)
2148	QIAseq SPE 2018	*QIAseq™ SPE Technology for Illumina®: Redefining Amplicon Sequencing*, QIAGEN (2018)
2149	QIAGEN NGS 2018	*Issues with Primer Dropouts*, QIAGEN (2018)
2150	Lu 2008	Fei Lu et al., *Comparative Sequence Analysis of MONOCULM1-Orthologus Regions in 14 Oryza Genomes*, 106 PNAS 2071 (2009)
2151	Applied Biosystems 2005	*Applied Biosystems 3770/3730x/ DNA Analyzers and 3130/3130x/ Genetic Analyzers*, Applied Biosystems (2005)
2152	Ammiraju 2008	Jetty S.S. Ammiraju et al., *Dynamic Evolution of Oryza Genomes is Revealed by Comparative Genomic Analysis of a Genus-Wide Vertical Data Set*, 20 THE PLANT CELL 3191 (2008)
2153	Porreca 2007	Gregory J. Porreca et al., *Multiplex Amplification of Large Sets of Human Exons*, 4 NATURE METHODS 931 (2007)
2154		*Reserved*
2155	Bronner	Iraad F. Bronner et al., *Improved Protocols for Illumina Sequencing*, CURR PROTOC HUM GENET. 1 (2009)
2156		*Reserved*
2157		*Reserved*
2158		*Reserved*
2159		*Reserved*
2160		*Reserved*
2161		*Reserved*
2162		*Reserved*
2163		*Reserved*
2164		*Reserved*

Ex.	Short Name	Description
2165	Wright Supplement 2005	Supplemental Material to EX2111
2166	Willenbrock 2009	Hanni Willenbrock et al., *Quantitative miRNA Expression Analysis: Comparing Microarrays with Next-Generation Sequencing*, 15 RNA 2028 (2009)
2167	Matsuzaki Supplement 2004	Supplementary Methods to EX2121
2168	Boutrand 2001	L. Boutrand et al., *Variations in Primer Sequences are the Origin of the Allele Drop-Out at Loci D13S317 and CD4*, 114 INT. J. LEGAL. MED. 295 (2000)
2169	Moorthie 2011	Sowmiya Moorthie et al., *Review of Massively Parallel DNA Sequencing Technologies*, 5 HUGO J 1 (2011)
2170	QIAGEN Answer	QIAGEN Sciences, LLC et al., Answer and Defenses to Tecan Genomics, Inc.'s Complaint in a related proceeding (Case No. 23-1115-GBW, D. Del.)
2171	'628 Application	U.S. Patent Application Publication No. 2013/0231253
2172	QIAseq Targeted DNA Panels Wayback	QIAseq Targeted DNA Panels, QIAGEN, https://www.qiagen.com/us/products/next-generation-sequencing/dna-sequencing/somatic-panels/qiaseq-targeted-dna-panels/ (archived at https://web.archive.org/web/20200623202534/https://www.qiagen.com/us/products/next-generation-sequencing/dna-sequencing/somatic-panels/qiaseq-targeted-dna-panels/#orderinginformation) (June 23, 2020)
2173	Wolfgruber 2009	Thomas K. Wolfgruber et al., *Maize Centromere Structure and Evolution: Sequence Analysis of Centromeres 2 and 5 Reveal Dynamic Loci Shaped Primarily by Retrotransponsons*, 5 PLOS GENETICS 1 (2009)
2174	Lu Supplement 2008	Supporting Information for EX2150
2175	Bui 2009b	Minh Bui, *Leunig, Leunig Homolog, and Seuss are Transcriptional Co-Repressors that Regulate Flower*

Ex.	Short Name	Description
		Development, Mucilage Secretion, and Pathogen Resistance, UNIVERSITY OF MARYLAND (2009)
2176	Callow 2004	Matthew J. Callow et al., *Selective DNA Amplification from Complex Genomes Using Universal Double-Sided Adaptors*, 32 NUCLEIC ACIDS RSCH. 1 (2004)
2177	Stenberg 2006	Johan Stenberg, *Software Tools for Design of Reagents for Multiplex Genetic Analyses*, 4 NATURE METHODS 835 (2006)
2178	Kaur 2018	Rajdeep Kaur, *Allele Specific Primer Designing for SNPs of ACHE Gene Related to Oxidative Stress*, 5 J. OF EMERGING TECHS. AND INNOVATIVE RSCH. 291 (2018)
2179	Kelley 2011	Scott T. Kelley et al., *Comparative Analysis of Microbial Diversity in Longitarsus Flea Beetles (Coleoptera: Chrysomeidae)*, 139 GENETICA 541 (2011)
2180	Shapero References	List of publications referencing EX1006

Patent Owner Tecan Genomics, Inc. ("Tecan") submits this Patent Owner's Response ("POR") to respond to the Petition (Paper 2) for *inter partes* review ("IPR") of claims 1-15 and 17-22 (the "challenged claims") of U.S. Patent No. 10,036,012 ("the '012 patent," EX1001) filed by QIAGEN Sciences, LLC ("Petitioner"), and the Board's institution decision, Paper 7.

I. INTRODUCTION

Based solely on impermissible hindsight, Petitioner argues that the claims of the '012 patent are obvious based on the combination of a specific pre-NGS library preparation method designed for use with microarrays (Shapero) and a general review of the Next Generation Sequencing ("NGS") technologies in use at the time (Delseny). Prior to this proceeding, however, Petitioner spent years proclaiming that the very same claimed method was "a revolutionary approach that redefines amplicon-based enrichment and sequencing." *See infra*, 64-66. Petitioner's new, litigation-driven arguments do not withstand scrutiny.

Shapero was published in 2004 by Affymetrix to highlight the capabilities of Affymetrix's microarrays. Shapero used a library preparation method (MARA) that, even under optimized conditions, could not perform better than whole genome amplification methods in use before 2004. While Petitioner attempts to draw unsupported inferences from the data reported in Shapero, a skilled person

considering the entirety of the reference would have held deep reservations about adapting MARA for use with NGS, especially as claimed by the '012 patent.

Those reservations were, in fact, echoed throughout the prior art. Prior to 2012, scientists working with NGS, including Petitioner's own expert, Dr. Metzker, taught that library preparation methods that employed polymerase chain reaction ("PCR") should be avoided. Petitioner fails to overcome the decades of articles that teach away from combining the PCR-based MARA method of Shapero with an NGS platform. The record shows that the prior art, including the Syvänen publication on which Petitioner relies, instead suggested that such an attempt would have been futile.

Petitioner relies on an overbroad interpretation of a few statements in Delseny to suggest that a scientist would have used Shapero's method for genotyping with NGS. Petitioner asks the Board to essentially conclude that a POSA would have understood, based on a few statements in a review article, that NGS could be automatically substituted for any and all genotyping methods. Such a conclusion does not reflect the complexities of the genetics field as of 2012. A POSA reading Delseny would have understood that, at best, Delseny discloses that NGS platforms could potentially be used for genotyping where the whole genome is sequenced. Delseny does not provide any suggestion that a PCR-based targeted enrichment method using a single, target-specific primer could be combined with NGS nor that

target capture could be used with NGS for genotyping. As such, Petitioner fails to show that a POSA would have been motivated to combine Shapero and Delseny with a reasonable expectation of success.

Further, real world evidence confirms that no scientists in the field as of 2012 would have been motivated to combine Shapero and Delseny to arrive at the challenged claims. The art reflects that the claimed method satisfied long-felt, but unmet needs and was widely praised for doing so. Petitioner itself also copied the claimed method and touted its unexpected results. For these reasons and the further reasons herein, Tecan requests that the Board reject Petitioner's claims and affirm the nonobviousness of the '012 patent.

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. EX2107.¶¶35-42. One way in which researchers have sought to study genetic information is through genotyping. EX2107.¶¶43-44. 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 microarrays and sequencing technologies (such as Sanger sequencers and NGS). EX2107.¶¶45-46.

A. Hybridization Microarrays ("Microarrays")[1]

Predating NGS, microarrays (also known as DNA density arrays) are silica chips where hundreds of billions of target-specific probes are affixed to the array's surface. EX2107.¶65. These probes bind to the complementary sequences of targets as samples are washed over the arrays. EX2107.¶¶70, 111-12. Where there is no complementary probe, the sequence is filtered from the array. EX2107.¶¶111-12. Typically, these probes are used to screen for single nucleotide polymorphisms ("SNPs"). EX2107.¶70. SNPs are variations in a single nucleotide in a genetic sequence. EX2107.¶43. Researchers are interested in SNPs in the human genome because these variations can result in profound downstream implications, such as driving certain diseases. EX2107.¶¶43-45.

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. EX2107.¶¶45-46. 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-

[1] Hybridization describes the process by which complementary single strands of DNA bind together. EX2107.¶65. This concept is utilized by various genotyping and sequencing technologies, including microarrays and NGS.

next-generation sequencing" ("Pre-NGS") technologies. EX2107.¶¶75-80. The gold standard of these Pre-NGS technologies was Sanger Sequencing, developed in 1977. EX2107.¶76. Sanger Sequencing was the first method that allowed for a DNA sequence to be determined. *Id.* 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* EX2107.¶¶75-79. 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. *Id.* 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. *See id.* Although revolutionary, Sanger Sequencing was expensive and ill-suited for large-scale applications. EX2107.¶¶77, 80.

C. Next-Generation Technologies

Starting in the early 2000s, the field of genetics was revolutionized by the invention of NGS. EX2107.¶81. 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. EX2107.¶¶81-82. Instead, NGS now allowed for hundreds of thousands of original template strands to

be sequenced in the same reaction. *Id*. With NGS, a user could perform massively parallel sequencing, allowing for elements of the genome to be sequenced in a fast, scalable manner. *Id.* 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. EX2107.¶86. Additionally, NGS platforms exhibited a higher error rate than Sanger Sequencing. *Id.*

D. Targeted Enrichment

By 2012, 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. EX2107.¶¶87-88. 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. EX2107.¶88. 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, PCR-based target enrichment, and capture-by-circularization. EX2107.¶89; EX1001.0016 (1:39-47).

Like microarrays, hybrid capture methods relied on hybridization to target samples. The difference was that microarrays targeted sequences as part of the analytical step, not during sample preparation. Hybrid capture instead sought to target sequences during sample preparation so that the targeted sequences could be isolated and enriched. EX2107.¶¶100-01. As the '012 patent explains, hybrid capture methods relied on the selective hybridization of a target genomic region to a custom designed oligonucleotide. EX2107.¶100; EX1001.0016 (1:64-66). The oligonucleotide could be immobilized to a surface or contain a ligand that could be immobilized (such as biotin). EX2107.¶100; EX1001.0016 (1:64-2:04). 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. EX2107.¶101; EX1001.0016 (2:04-10). 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. EX2107.¶90; EX1001.0016 (1:48-50). The need for numerous primer pairs made multiplex PCR impractical due to high levels of non-specific amplification and

primer-primer interactions. EX2107.¶90; EX1001.0016 (1:51-53). One attempt at addressing these issues was through microdroplet PCR where each amplification reaction is physically separated into an individual droplet. EX2107.¶¶96-97; 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. EX2107.¶97; EX1001.0016 (1:58-63).

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. EX2107.¶102; EX1001.0016 (2:11-16). Once the probe annealed to a target sequence, the gap region was filled by polymerization and ligation, resulting in a circularized probe. *Id.* These probes were then amplified using primers specific to the common linker region. EX2107.¶102; EX1001.0016 (2:16-18). These methods, however, exhibited high variability in sequence coverage across target regions and required a large number of target-specific oligonucleotides, driving up costs. EX2107.¶103; EX1001.0016 (2:18-24).

By 2012, 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 (2:25-28). There was

"also a need for high efficiency nucleic acid library generation." *Id.* (2:28-29). The claimed methods of the '012 patent fulfilled these needs.

III. THE '012 PATENT

A. Overview

The '012 patent is directed to methods for sequencing an enriched nucleic acid sequence of interest. EX1001.0033. The '012 patent discloses that the claimed methods "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 (6:12-16). The claimed methods, therefore, improve on the then-existing methods by targeting a sequence of interest using a single target-specific primer as opposed to two target-specific primers. The single target-specific primer is used to select for target sequences of interest, and common primer pairs are used to selectively amplify only those sequences containing the target sequence of interest, thus enriching for the target sequence. The claimed methods avoid the time and expense associated with generating multiple sets of 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.* (6:25-27).

B. Independent Claim 1

The sole independent claim of the '012 patent, claim 1, is reproduced below. *See also* EX2107.¶¶122-32 (discussing how a POSA would have understood the claimed limitations).

Claim Element	Claim Language
1[pre]	A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
1[a]	obtaining a nucleic acid fragment ligated to a partial duplex adaptor, wherein the nucleic acid fragment comprises a nucleic acid sequence of interest, wherein the partial duplex adaptor comprises a first adaptor sequence, and wherein the partial duplex adaptor comprises a first strand and a second strand, wherein the first strand is longer than the second strand;
1[b]	annealing one or more oligonucleotides in solution to the nucleic acid sequence of interest in the nucleic acid fragment ligated to the partial duplex adaptor, wherein the one or more oligonucleotides comprise a 3′ portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and

Claim Element	Claim Language
	a 5′ tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;
1[c]	extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment ligated to the partial duplex adaptor with a polymerase, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;
1[d]	amplifying the one or more oligonucleotide extension products using a first primer that anneals to a complement of the first adaptor sequence and a second primer that anneals at its 3′ end to a complement of the second adaptor sequence to enrich for the nucleic acid sequence of interest, wherein products of the amplifying comprise a 3′ end with sequence complementary to a sequence on a surface;
1[e]	annealing a strand of the products of the amplifying to the sequence on the surface using the 3′ end with sequence complementary to the sequence on the surface; and
1[f]	sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

C. Level of Ordinary Skill in the Art

The Board adopted the following definition in its Institution Decision:

> [A] POSA would have had a Ph.D. in molecular biology, molecular genetics, bioinformatics, biochemistry, or a related field. Alternatively, a POSA would have had a B.S. or M.S. degree with three to five years of experience working in any of those fields. Additionally, the POSA would have had experience with NGS sequencing methods and a working knowledge of how those methods functioned.

Paper 7, 18-19. While Tecan contends that a POSA may have experience with DNA sequencing methods more broadly than NGS (*see id.*, 17-19), Tecan adopts the Board's definition of a POSA for purposes of this Response.

D. Relevant Prosecution History

The '012 patent issued from U.S. Patent Application No. 15/471,785 ("the '785 application"), which was filed on March 28, 2017. EX1001.0001. The '785 application ultimately claims priority to Provisional Application No. 61/591,241, which was filed on January 26, 2012. EX1001.0001. 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. EX1001.0001.

During the prosecution of the parent '768 application, the Examiner issued a series of anticipation and obviousness objections based on two patent applications that named Keith W. Jones and Michael H. Shapero as co-inventors, including U.S.

Patent Publication No. 2005/0142577 ("Jones") (EX1011). EX2107.¶137. Jones and Shapero are two of the authors of the Shapero reference cited in the Petition, which describes the same technology. In traversing the rejections, Applicants submitted an affidavit from Dr. Andrew I. Brooks in support of its arguments for patentability. EX2107.¶138. 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. EX2107.¶139. Dr. Brooks would have been considered at least a POSA. EX2107.¶140. In his declaration, Dr. Brooks explained how the microarrays 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. December 21, 2016 Declaration of Andrew Brooks ("Brooks Declaration"), EX2025.0004.[2] Thereafter, the Examiner issued a notice of allowance for the application.

[2] Patent Owner cites to the native page numbers of all Exhibits that have native page numbers. *See* Paper 7, 8 n.6.

The ’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. August 10, 2017 Non-Final Rejection, EX2026.0004-11. Upon resubmission of the Applicant’s positions and the Brooks Declaration, the Examiner withdrew the rejections and issued a notice of allowance. April 10, 2018 Notice of Allowability, EX2026.0004.

E. Claim Construction

The Petition does not ask the Board to explicitly construe any terms of the challenged claims. Although Petitioner incorrectly asserts that the nucleic acid sequence of interest to which the oligonucleotide is annealed in the ’012 patent must be double-stranded, Petitioner adopts the correct construction, which recognizes that the nucleic acid sequence of interest may be single- or double-stranded. *See* Paper 2, 14-15.

In IPR2025-00015, Tecan requested that the Board construe “amplify the one or more oligonucleotide extension products . . . to enrich for the nucleic acid sequence of interest” to mean “increase the proportion of the nucleic acid sequence of interest relative to the nucleic acid fragments in the solution not containing the sequence of interest by amplifying the oligonucleotide extension product and its complement.” IPR2025-00015, Paper 23, 21. Tecan also requested that the Board

construe "RNA fragment" to mean "an RNA polynucleotide product generated through fragmentation." *Id.*, 25. These terms do not seem to be at issue in this proceeding.

However, for clarity in this proceeding, Tecan proposes that the Board construe a "massively parallel platform" to mean a "platform developed after Sanger sequencing, commonly referred to as a next generation sequencing ('NGS') platform." This construction does not appear to be contested in the Petition. *See, e.g.*, Paper 2, 34 n.4 ("The '012 patent makes clear that NGS is synonymous with massively parallel sequencing"), 35 ("After Shapero was published, NGS sequencing became commercially available and had a profound effect in the field"). Yet during his deposition, Dr. Metzker seemed to change his definition of this term, suggesting that "it depends on the context of whether you think of [hybridization platforms] as NGS." EX2109.0020 (80:1-18). In an abundance of caution, Tecan asks the Board to adopt its construction of this term.

The '012 patent supports Tecan's proposal, distinguishing between next generation sequencing and earlier sequencing technologies, like hybridization arrays. EX1001.0028 (26:64-67) ("massively parallel sequencing (i.e. next generation sequencing methods)"), 29 (28:7-12). During prosecution, Applicants argued that NGS was different than hybridization platforms. *See, e.g.*, Brooks Declaration, EX2026.0003-04. As Dr. Bustamante explains, a POSA would have

understood this distinction. EX2107.¶¶141-42. Dr. Metzker also seemed to agree with this definition at certain points in his deposition. *See* EX2108.0007 (26:7-27:8) ("Q. What is your understanding of what next generation sequencing is? A. It is a broad field of different technologies that replaced what I called first generation sequencing or commonly known as Sanger sequencing. … they don't require the use of electrophoresis, which was one of the main limitations of Sanger sequencing. Most of them start with a single molecule, some of them end up amplifying those molecules, some of them continue to use single molecules."); EX2109.0009 (36:-10-16) ("Q. And you contrast the NGS-based approaches versus traditional microarrays, right? Am I reading that sentence correct? A. That's correct."), .0011 (41:12-17) ("They make a microarray product and they make an NGS product. … They're very different technologies"), .0011 (41:20-42:1) ("Q. So for clarification, just so we're on the same page; the Illumina NGS product is not a traditional microarray? A. That's correct. It's an NGS platform."). Thus, the intrinsic and extrinsic records support Tecan's proposed construction.

IV. PETITIONER FAILS TO DEMONSTRATE THAT ANY CLAIM IS UNPATENTABLE

Petitioner asserts that the sole independent claim of the patent is rendered obvious by the combination of Shapero and Delseny. Petitioner argues that a POSA would have combined certain teachings of Shapero—a library preparation method

for use with microarrays—and Delseny—a review article discussing NGS technology that had been around for years before Delseny was published, and long before the priority date. Petitioner admits that Shapero is not a method for "sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform," as required by the claims. *See* Paper 7, 19-20. Petitioner relies on Delseny for a POSA's motivation to use Shapero's method with NGS, but as described further below, Delseny would not have motivated a POSA to develop the claimed method. Delseny provides a general overview of NGS platforms and suggests that some NGS techniques may be usable for genotyping a whole genome. Delseny's disclosure, however, is not as sweeping as Petitioner contends and is critical of the use of NGS for genotyping with target capture methods, such as MARA.

Importantly, the Petition entirely ignores the body of prior art that discouraged a POSA from combining a PCR-based library preparation method like Shapero with the NGS platforms disclosed in Delseny. Along these lines, real world evidence confirms that a POSA in 2012 would not have been motivated to make the claimed combination. As such, the Petition's hindsight-driven arguments should be rejected.

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

Petitioner's argument that it would have been obvious to combine Shapero's MARA library preparation method for use with NGS based on the teachings of Shapero and Delseny (Paper 2, 24) is misplaced because it overlooks the context of the disclosures in these references and ignores contemporaneous publications reflecting that a POSA would have avoided this combination. Shapero's MARA method was developed to be used with the authors' proprietary microarrays, and there was no suggestion that it could be used in other contexts with success. EX2107.¶¶149-50, 271-74. Additionally, the prior art, including Delseny and Syvänen, taught away from the claimed methods. EX2107.¶¶170-73, 186-98, 234-59. A POSA would similarly not have had a reasonable expectation of success in combining and modifying Shapero and Delseny at least because of the unfavorable data reported in Shapero and the prior art that was full of doubts that the claimed inventions would work. EX2107.¶¶261-70.

1. A POSA Would Not Have Had a Motivation to Combine MARA 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." Paper 2, 34. For support, Petitioner advances three arguments: (1) Shapero's limited experimental data demonstrates that MARA would work with any NGS platform;

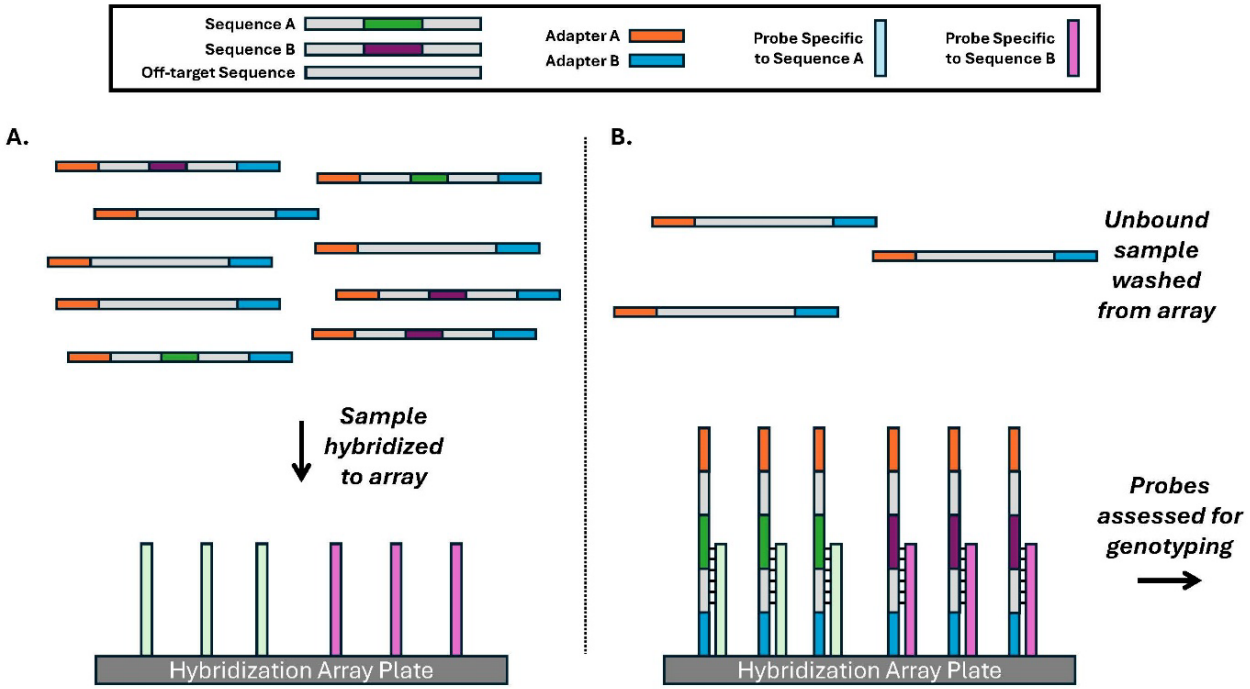
(2) Delseny teaches that any NGS technology can be used for any genotyping project; and (3) Syvänen's pre-NGS experiments show that Shapero's genotyping methods were compatible with NGS. *See* Paper 2, 34-37. As explained below, each of these arguments is fundamentally flawed. Petitioner's arguments are, at best, that a POSA ***could have tried*** to combine Shapero and Delseny, but such an argument is insufficient to prove obviousness. "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." *See Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 886-87 (Fed. Cir. 2024) (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 ignores critical concerns raised by the prior art, including Delseny and Syvänen, that would have discouraged a POSA from combining and modifying Shapero and Delseny to practice the claimed methods. Petitioner's arguments are predicated on impermissible hindsight, as evident from

the fact they are contrary to the actual teachings of the references and state of the art at the time.

a) The array method in Shapero is fundamentally different from massively parallel sequencing (NGS)

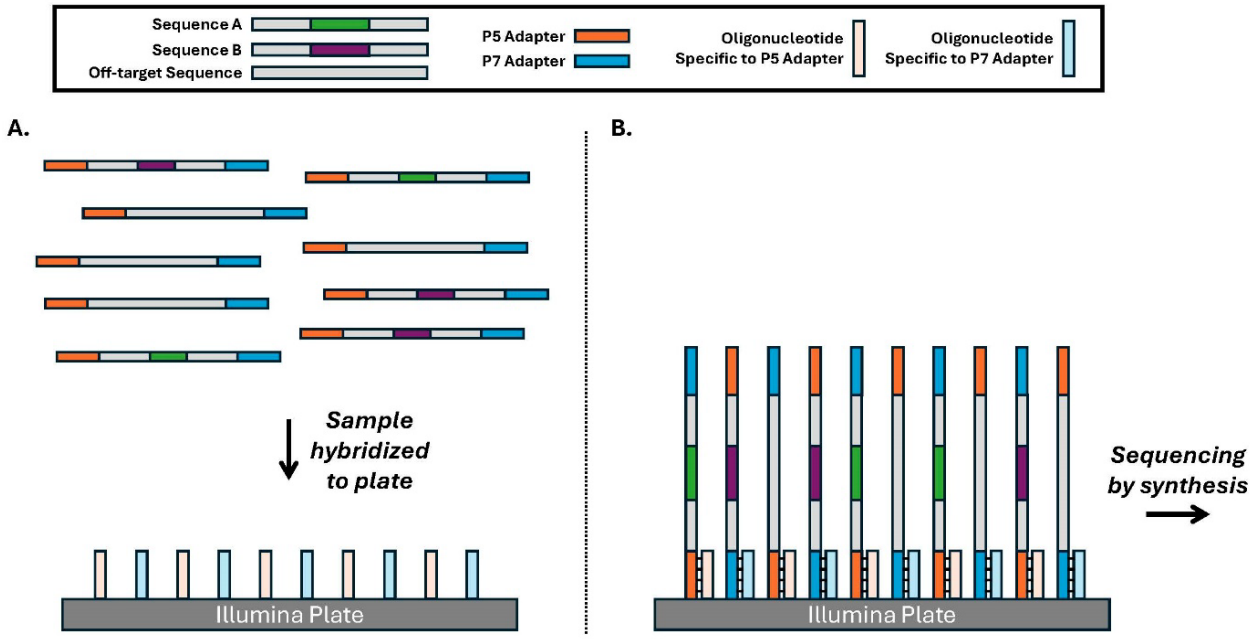
Shapero reflects the use of the MARA method with microarrays, which function differently than the surfaces used with NGS platforms. With a microarray, probes complementary to target sequences are bound to the surface of the array. EX2107.¶¶111, 208-09. Researchers can target a sequence of interest through the use of many target-specific probes on a single microarray. *Id.*

In the figure below, the target specific probes are depicted in light blue (Sequence A) and light purple (Sequence B).



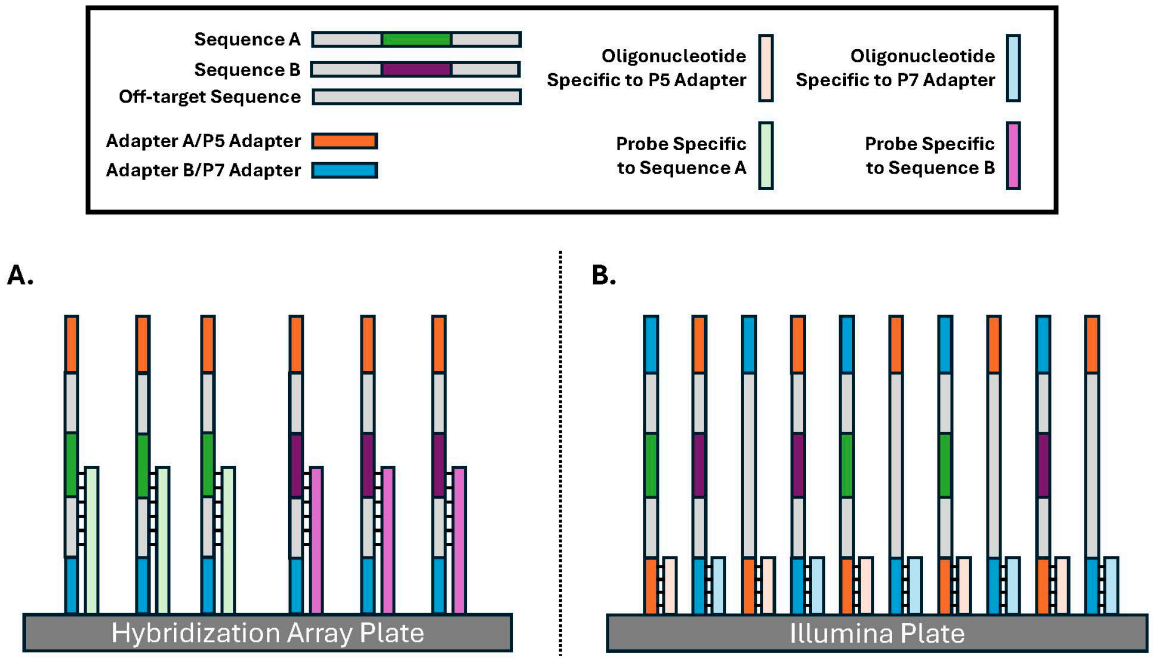
EX2107.¶¶111-12. The sample is exposed to the microarray, allowing complimentary sequences to hybridize with the probes on the surface of the array. *Id.* In the figure above, the illustrated sample includes three sequence types: two target sequences that are complimentary to the probes, A (green) and B (purple), and sequence that is not targeted and thus not complimentary to a probe on the surface (gray). *Id.* Those fragments in the sample containing sequences complementary to the probes will hybridize to the probes. *Id.* The sequences that do not have a corresponding probe on the array plate do not attach and are instead washed from the array (depicted in part B of the figure above). *Id.* As a result, only the sequences that are bound to the surface via hybridization to the target-specific probes are analyzed. *Id.* While adapters may be ligated to the nucleic fragments, as shown in the above figure, these adapters are not used to bind the fragments to the arrays. *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. EX2107.¶¶106-09, 211-12. To accomplish this, universal adaptors are appended to the ends of the fragments in the sample during library preparation. EX2107.¶¶106-09. For the Illumina platform, for example, the adaptors are referred to as P5 and P7. *Id.* The NGS platform surfaces are covered with probes with sequences complimentary to the universal adaptors (for Illumina, complementary to P5 and P7), as shown in part A of the figure below.



As the fragments are washed over the plate, all fragments with the universal adapters—regardless of their sequences—bind to the complementary probes and are sequenced, as shown in part B, above. *Id.*

Unlike the microarrays, the surface binding step of NGS is not target specific, i.e., all fragments in the sample can bind to the surface. EX2107.¶¶110, 211-13.



That is intentional. NGS platforms are designed to be able to sequence an entire genome. *See* EX2107.¶¶109, 211. Dr. Metzker acknowledged this distinction at his deposition where, in comparing traditional microarrays to NGS, Dr. Metzker explained that "microarrays were built where a chip, a microarray chip, may have a million different SNPs or SNVs, that can be typed all in a single experiment, but you know what you were looking for. Contrast that with NGS, NGS discovers things." EX2109.0010 (37:11-18).

Also unlike with microarrays, a researcher must use one or more additional sample preparation methods to filter out unwanted products prior to sequencing

samples on an NGS platform if that researcher is seeking to sequence target sequences of interest. EX2107.¶¶110, 212. The ability of these sample preparation methods to accurately target a sequence of interest is paramount for NGS library preparation, given the platform's inability to filter off-target sequences. EX2107.¶¶109-12, 212-15. Such precision is not necessary for microarrays, where the target-specific probes can correct for inaccuracies caused by library preparation methods. *Id.* A POSA, therefore, would not have relied on Shapero to determine whether MARA could be decoupled from the microarray and used accurately with NGS. EX2107.¶¶207-15.

This is made clear by Shapero's acknowledgement that MARA is intended to be used with microarrays because the microarrays will confer target-specificity. EX2107.¶¶216-19. For example, Shapero discloses that "[i]n order to leverage the power of SNPs in genetic studies, novel target preparation methods need to be developed that, ***when combined with methods for allele discrimination***, allow rapid and accurate genotypic information at a fraction of the cost of current approaches." EX1006.0002 (emphasis added). Shapero's reference to "methods for allele discrimination," means "[h]igh-density arrays." *Id.* A POSA would have understood that an NGS platform cannot replace high-density arrays as a method for allele discrimination given the lack of target specificity with NGS platforms. EX2107.¶¶220, 230-232.

A POSA would have also understood that accuracy would be the primary concern for any modified use of MARA. EX2107.¶151. While speed and cost are also important variables, potential savings are worthless if the data generated cannot be trusted. *Id.* At no point does Shapero discuss the balancing of accuracy with speed and cost nor that optimizing a balance between speed and cost was the goal. *Id.* A POSA would have understood that any library preparation method used with NGS would have to provide the desired target specificity and accuracy that would allow the data gathered from an NGS analysis to be usable (i.e., data that can be processed with confidence and without considerable background noise). *Id.* It is only through hindsight, with the challenged claims in hand, that one can claim that Shapero's MARA method would provide sufficient target specificity and accuracy for an NGS platform, given Shapero's heavy reliance on the specificity of the microarray for its success. EX1006.0007 ("allele discrimination is achieved by hybridization to arrays containing SNP-specific complementary sequences rather than a universal array.").

b) Shapero's call rates and discrimination scores do not support using MARA with NGS

Petitioner relies on the data in Shapero to argue that "a POSA reading Shapero would understand that its enrichment methods generate N specificity and that there is significant enrichment over a situation where no target specific primer is used."

Paper 2, 37. But this data says nothing about whether the same results would occur in the absence of the target specificity provided by the microarray used in Shapero. A POSA would not have been able to reliably make those inferences based on the data to which Petitioner points. EX2107.¶¶220-29. And as explained further below, several results reported by Shapero would have discouraged a POSA from using MARA with NGS. *See infra*, 50-52.

Petitioner relies on the call rates and the discrimination score ("DS") reported in Shapero. Paper 2, 36-37. The call rates reflect the "percentage of successful genotype calls [made by the microarray probes] within a DNA sample" EX1006.0006. The DS "serves as a measure of detection of DNA target sequences" within the sample. *Id.* These data points are specific to the purpose of Shapero's experiments, showing that the MARA method could improve the genotyping analysis on the microarrays. EX2107.¶¶162-64, 220. A POSA, however, would not have relied on the call rates or the DS to infer whether the MARA method sufficiently enriched for the target sequence such that the sample could successfully run on an NGS platform. EX2107.¶¶220. A POSA would have no way of knowing whether the MARA method would provide similar effects when used without the

additional step of eliminating off-target sequences that is built into the microarray procedures. *Id.*

Petitioner further relies on Shapero's disclosure that for the 250- and 750-plex reactions, Shapero saw improvement in call rates when using locus-specific primers. Paper 2, 37, citing EX1006.0005 (reporting that for the 250-plex reactions, 99.4% of the SNPs had a mean DS > 0.08 when locus-specific (i.e. target-specific) primers were used but only 6.6% had a mean DS > 0.08 when the primers were not used); *see also id.* A POSA would have understood these disclosures to mean that more SNPs could be identified when the target-specific primers were used. EX2107.¶¶221-25. But that outcome would not have motivated a POSA to combine Shapero and Delseny because a POSA would not have understood that the improved outcome would translate to an NGS platform, especially given that the data is not indicative of off-target binding. EX2107.¶¶224-26.

A POSA would have understood that the improved values could be a result of the difference in volume of genetic material used in both instances. *Id.* As Dr. Bustamante explains, where target-specific primers are used, the sample is exponentially duplicated; where target-specific primers are omitted, no extension products are generated and no duplication occurs. EX2107.¶¶223-24. Thus, the volume of genetic material applied to the microarray would be substantially different

between the samples generated with target-specific primers versus those generated without. EX2107.¶¶223-25.

It was well known in the art at the time that microarrays, like the ones created by Shapero, required large volumes of genetic material. *Id.* A POSA would have expected that the accuracy of the microarray would dramatically decline (leading to fewer SNP calls with strong DS values) because an insufficient amount of genetic material was likely used with the microarray. *Id.* A POSA would have understood that the improvement in call rates when using the target-specific primers established that the target-specific primers functioned as expected to amplify genetic material. The data says nothing about potential off-target effects. EX2107.¶¶223-26. As such, this data reflecting the ability to generate sufficient material for a microarray ***would not*** have provided any information to a POSA about the efficacy of using MARA with an NGS platform. *Id.*

Additionally, a POSA would not have been motivated to adapt MARA for use with NGS based on the reported outcome given that a POSA would have no understanding as to the specific contents of the amplified genetic material, including the quantity of off-target products. EX2107.¶226. For example, a POSA could not make reliable inferences as to the specific proportions of sequences in the mixture. *Id.* A POSA would not have understood to what extent off-target binding and primer dimers occurred as a result of the MARA method. *Id.* As such, a POSA would not

have interpreted Shapero's MARA method to "generate high on-target specificity" on its own and would not have understood that the MARA method resulted in the alleged "significant enrichment over a situation where no target specific primer is used." *Id.* Thus, this data would not have motivated a POSA to use the MARA method with an NGS platform. *Id.*

Shapero confirms this interpretation of the data, noting that the use of the microarray alleviates the need for absolute target specificity during MARA. EX1006.0007 ("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 acknowledges the role the microarray 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.* A POSA would have understood that to mean that the microarray is capable of handling the volume of sample that was used in the experiments reported and would filter high levels of unwanted sample—unlike NGS, which cannot filter for off-target products. EX2107.¶219. And in fact, Shapero only discloses examples or data that rely on a microarray—not MARA—for target specificity and to filter off-target products. EX2107.¶¶162-69, 216. As such, the array hybridization data reported in Shapero would not have motivated a POSA to

combine Shapero's MARA library preparation method with the NGS platforms reviewed in Delseny to practice the challenged claims. EX2107.¶¶216-26.

Further, Petitioner fails to reconcile its claims that Shapero's experimental data "show[s] high on-target specificity" with its argument that a POSA would have discarded the very instrument that provided that specificity. *See* Paper 2, 17. Shapero discloses that this specificity is "achieved through hybridization to high-density arrays." EX1006.0003-04. Petitioner fails to explain why a POSA would decouple the MARA method from the microarrays that allow for this alleged "high on-target specificity" and instead use MARA with an NGS platform that does not confer target specificity. Especially where the prior art taught that array-based techniques would be the future for accomplishing the form of genotyping performed in Shapero. EX1006.0001; EX2129.0123. And where the authors of Shapero focused their future efforts on continuously improving these microarrays. EX2107.¶¶230-32. Petitioner also fails to explain why a POSA would not have instead been motivated to adapt Shapero for hybrid capture or use with molecular inversion probes ("MIPs"), especially considering that Dr. Metzker referred to MIPs as "an example of how technology evolves from microarrays to NGS very fluidly just because of the power of NGS." EX2109.0012-13 (47:18-51:3); EX2107.¶260. Petitioner's discordant claims smack of hindsight bias.

c) Delseny would not have motivated a POSA to modify Shapero to arrive at the claimed methods

Petitioner's obviousness argument is essentially that a POSA would swap Shapero's microarrays for an NGS platform because Delseny suggests generally that NGS ***could*** be used for genotyping, without providing any specifics on how. Such a conclusion is impossibly overbroad and assumes that a POSA would ignore the complexities of sequencing methods at the time. Petitioner has not identified anything in the prior art that suggests Shapero's MARA method could be used with NGS or that addresses the accuracy concerns that a method like MARA would raise in the context of genotyping. *See, e.g.*, EX2107.¶¶271-74.

(1) Petitioner overstates Delseny's teachings

Petitioner's overbroad statement that "Delseny recognizes that NGS is a replacement for genotyping described in Shapero" conflates two separate issues. Paper 2, 36. While Delseny recognizes that NGS "can substitute for the genotyping microarray strategy because of its higher resolution," it does not mean that NGS could be seamlessly substituted into every pre-NGS sequencing protocol with success. As explained above, the limitations of NGS platforms are different than those of the microarray used in Shapero, and a POSA would have understood that the library preparation methods for these sequencing platforms would need to adjust to those differences. There is nothing in Delseny that would have encouraged a

POSA to practice Shapero by replacing the microarrays with NGS. EX2107.¶¶174-91, 237-45.

As the Board noted, Petitioner relied on Delseny's disclosure that "[t]he ultimate resolution is at the base-pair level and NGSTs now open the possibility to genotype a line by sequencing it." *See* Paper 7, 22. A POSA, however, would not have understood that statement as encouraging NGS for every genotyping application or ***use of the MARA method*** specifically with NGS for genotyping. EX2107.¶¶238-43. Instead, a POSA would have considered Delseny's suggestion that NGS may allow for genotyping by sequencing in the context of the disclosure. *Id.* Delseny's discussion of genotyping with NGS is entirely based on the Han publication (EX2117), which describes the sequencing of entire rice genomes with NGS. EX2107.¶¶191-96, 238-43. Han explains that the entire genome must be sequenced to overcome the accuracy issues of NGS. EX2107.¶¶192-96. In fact, Han warns against focusing on target sequences given accuracy concerns. *Id.* A POSA reading Delseny in the proper context would have understood Delseny to suggest that NGS could potentially be used for genotyping where the entire genome is sequenced, not for every genotyping application as Petitioner erroneously suggests. EX2107.¶¶239-43. This more limited understanding of Delseny is in line with later teachings in the prior art, which taught away from the use of target capture and towards sequencing the entire genome with NGS. EX2169.0007.

As the Board also noted, Petitioner relied on Delseny's disclosure that NGS "can substitute for the genotyping microarray strategy because of its higher resolution." Paper 7, 22. Here again, this is based on hindsight as a POSA would not have understood this statement to apply as broadly as Petitioner alleges. EX2107.¶¶239-43. Delseny's statement is again based on the same study of entire rice genomes discussed above. *Id.* Delseny does not teach the use of the MARA method, or any method that targeted a sequence of interest, in combination with NGS for genotyping. *Id.* A POSA would have understood that at most, Delseny is teaching that NGS could be used for whole genome sequencing instead of microarrays because whole genome sequencing captures all sequences in the sample. *Id.* That teaching, however, would not have led a POSA to use the MARA method with NGS to target, enrich, and sequence enriched target sequences of interest. EX2107.¶245.

(2) Delseny expresses concerns with using NGS with target capture for genotyping

Delseny describes several accuracy issues suffered by NGS that would have raised concerns with using target capture methods with NGS for genotyping. Specifically, Delseny points to errors in base-calling, sequencing read artifacts, and higher false discovery rates. EX1007.0411-17; EX2107.¶¶189, 244. Base-calling refers to the process of the sequencer determining the specific nucleotide in a

polynucleotide sequence. EX2107.¶244. 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." *Id.* These concerns are echoed in Han, which teaches whole genome genotyping with NGS where a reference genome is available to verify accuracy. EX2107.¶¶191-96, 238-43. Because of these concerns with accuracy, Delseny recognizes the pre-NGS Sanger method as the "gold standard" due to it having the "highest accuracy," i.e., "high fidelity." EX1007.0411. In fact, prior art publications like Meyer (EX2118) disclosed the use of Sanger sequencing to verify the presence of SNPs that were predicted from whole transcriptome NGS sequencing where a reference transcriptome did not exist. EX2107.¶¶197-98. These concerns and endorsement of pre-NGS Sanger sequencers taught away from using target capture methods, like MARA, with NGS for the genotyping performed in Shapero, especially given the heightened need for accuracy. EX2107.¶245.

Notably, Delseny briefly discusses how certain targeted capture methods work, but none of the referenced methods use a single target-specific primer. EX2107.¶¶178-85. Two of the methods use target-specific primer pairs, and the remaining references discuss entirely different technology, like precipitating certain proteins to isolate DNA or circularizing captured regions into a plasmid for amplification. *Id.* One method relies on padlock probes, which as discussed further below, do not rely on PCR amplification. *Id.*; *see infra*, 36-37. Delseny entirely

fails to suggest the use of a single target-specific primer for target capture with NGS or any form of target capture with NGS for genotyping.

d) The prior art taught away from Petitioner's proposed combination

Not only does Petitioner fail to show a motivation to combine Shapero and Delseny to arrive at the claimed methods, the prior art actively taught away from such a combination.

(1) Syvänen discourages a POSA from using MARA with 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* Paper 2, 35. Shapero references Syvänen for the general proposition that "[t]here are a multitude of genotyping methodologies for SNPs that have been described over the years." EX1006.0001. 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. EX2107.¶¶170-73, 234-36; EX2109.0019 (76:9-13). 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 cover narrow applications of pre-NGS Sanger sequencing. EX2107.¶¶234-36.

First, Syvänen teaches away from library preparation methods that use allele-specific primers for PCR and enrich for 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." EX1012.0939. The platforms used to genotype SNPs at the time Syvänen published demanded large amounts of sample material, requiring researchers to amplify sequences to generate sufficient sample. *See* EX2107.¶225. Syvänen notes that "***[t]he next generation technology for SNP analysis should avoid the PCR amplification step***." EX1012.0940 (emphasis added). A POSA would have understood that Syvänen was referring to the various accuracy issues that can be caused by PCR amplification—such as off-target binding and nucleotide misincorporation, which would be detrimental to reliably identifying a single nucleotide polymorphism. EX2107.¶236.

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. EX1012.0934; EX2107.¶¶170, 236, 253. For one technology,

referred to as "padlock probes," Syvänen identifies a "special feature" as that it "avoids target amplification." *Id.* As Syvänen explains, "[p]adlock probes are linear oligonucleotides" with ends that "are complementary to the target." EX1012.0939. Where those ends perfectly hybridize to the target, the oligonucleotide circularizes, and a subsequent, non-PCR amplification occurs for the circularized probes. EX1012.0934. For another technology, Syvänen describes the "most significant advantage" as that "PCR amplification [is] avoided." *Id.* As Syvänen explains, that technology uses two target-specific hybridization oligonucleotides to target and cleave sequences that are then amplified by "a serial, isothermal Invader assay." EX1012.0939.

Syvänen further specifically highlights the limitations 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." EX1012.0935. Syvänen cautions that 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). A POSA would have understood that to mean that without additional safeguards, allele-specific PCR amplification would

lead to unintended off-target products. EX2107.¶¶236, 252. Syvänen also explains that target specific PCR amplification can be burdensome, noting 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." EX1012.0935. Syvänen suggests that "the homogenous allele-specific PCR methods are best suited for the analysis of a limited number of SNPs in large sample collections." *Id.* A POSA would have understood Syvänen to be referring to the labor-intensive work involved with ensuring that the targeted alleles are amplified enough for detection, especially where the risks of low on-target amplification and high off-target amplification increase with higher multiplex reactions. EX2107.¶¶235-36. 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. EX2107.¶¶235-36, 252.

Second, Petitioner incorrectly argues that Syvänen's "minisequencing" methods demonstrate the use of enrichment methods with sequencing technology. *See* Paper 2, 35. Syvänen's "minisequencing" is neither a method of enrichment nor next generation sequencing. EX2109.0019 (76:9-11). 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). EX2107.¶¶171-72, 235. The minisequencing techniques described in Syvänen, therefore, would not have provided any information to a POSA attempting to design a library preparation method for an NGS platform, especially for the sequencing of polynucleotides. *Id.*

Nevertheless, Petitioner overstates Syvänen's disclosure that "DNA-sequencing instruments might also be used as platforms for genotyping SNPs using fluorescently labelled dideoxynucleotides in the minisequencing reactions." *See* Paper 2, 35. Petitioner 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. EX1012.0937; EX2107.¶¶171-72, 235. 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 suggesting using these techniques for sequencing but instead the incorporation of aspects of the DNA sequencing methods for other purposes, such as using electrophoresis for size-separation of different SNPs. Syvänen concludes that paragraph by saying that "this assay can be automated for high-throughput genotyping." *Id.* A POSA would have understood "this assay" to be referring to Applied Biosystems' SNaPshot Assay, which uses capillary electrophoresis in conjunction with a minisequencing reaction to detect

SNPs. EX2107.¶¶172, 235. That disclosure does not allude to sequencing the SNPs, let alone by NGS. *Id.* Even more, Petitioner's claim directly contradicts Syvänen expressed warning against 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." EX1012.0940. 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.

Syvänen's teaching away from the use of PCR amplification with NGS is echoed by Dr. Metzker's own work. In 2010, Dr. Metzker explained that "PCR coupled with Sanger sequencing is suitably matched for analysing a handful of candidate genes, ***but coupling PCR with high-throughput NGS platforms for targeting strategies is not practical***, as sample preparation would require handling tens of thousands of primers individually or in large multiplex groups to meet the needs of a single instrument run." EX1025.0041 (emphasis added). Despite Dr. Metzker attempting to limit this statement to only "traditional PCR" where "two

target-specific primers amplify[] a single region of interest," EX2109.0017-18 (68:6-69:16), no such distinction is reflected in Dr. Metzker's paper, or anywhere else in the literature. EX2107.¶¶255-59. At no point in his 2010 publication did Dr. Metzker suggest using MARA or any single target-specific primer. *See* EX1025.0041. Instead, Dr. Metzker highlighted microdroplet PCR, hybrid capture with microarrays, and MIPs—all methods that minimize the importance of PCR amplification. *Id.*; EX2107.¶¶255-59.

(2) The prior art discouraged the use of methods that heavily relied on PCR with NGS, including the claimed methods

The rest of the prior art confirms that a POSA would not have been motivated to combine a library preparation method that is heavily reliant on PCR, like Shapero's MARA method, with NGS platforms. EX2107.¶¶57-64, 246-54. As Dr. Bustamante explains, a POSA would have been aware of nearly two decades worth of literature by 2012 that demonstrated concerns with the amplification process on which the claimed methods rely, such as target specificity and off-target binding. EX2107.¶¶57-64 (compiling prior art disclosures). Publications concerning how to improve NGS library preparation methods emphasized the need for accurate target specificity. EX2107.¶¶57-64, 246-54. Additionally, publications concerning microarrays and the library preparation methods used with those microarrays

emphasized that the arrays themselves promote target specificity and can be used as a means to address the concerns in the art. EX2107.¶¶230-233.

The literature as of 2012 was replete with statements cautioning against the use of a single target-specific primer for amplification, given concerns about specificity and off-target binding. EX2107.¶¶57-64, 246-54. For example, Miura (EX2047) discloses that PCR amplification "uses a pair of unique primers to selectively amplify the target sequence" and that specificity is achieved "by a synergistic effect between the specificities of the two primers." EX2047.4363. In 2005, Miura explained that pre-NGS, there were genome walking methods that departed from this convention by instead using only "a single unique primer in combination with a common primer." *Id.* Miura teaches that these pre-NGS methods were understood to "often [be] plagued with non-specific amplification products derived from so-called 'off-targets.'" *Id.* In 2011, Sohn (EX2050) reiterated that while "many studies have been made to improve the genome walking method," "it is still in need of improvement." EX2050.0002. Sohn explained that the "most serious problems of the PCR-based genome walking methods are low amplification efficiency and non-specific amplification." *Id.* Sohn noted that to "improve this problem, complicated multi-step methods were developed, including secondary PCR, purification of desired PCR products using biotinylated primers, or

improvement of PCR cycle conditions." *Id.* Even then, "satisfactory performance [had] not yet been achieved" as of 2011. *Id.*

Additionally, a POSA would have been aware of other publications attempting to resolve various problems with primer design for multiplex PCR for NGS (such as problems with off-target binding and primer dimers). EX2107.¶¶91-94. These publications would have discouraged a POSA from using a single target-specific primer given that they reflected a basic understanding in the art that target-specific ***primer pairs*** were necessary for PCR enrichment for NGS. *See id.* For example, researchers in the field hypothesized on various ways to improve off-target binding and dimerization, such as through "careful primer design and reaction optimization" so that "***several dozen primer pairs*** can be used together effectively in a multiplexing reaction." EX2021.0380 (emphasis added); EX2107.¶¶91-99. Software designers similarly focused on how to optimize target-specific primer sets for NGS analysis. EX2107.¶99. At the time, the expectation was that pairs of target-specific primers were needed, especially as researchers sought to enrich for complex genomic DNA. EX2107.¶¶91-99. Researchers focused on how to optimize primer pairs—not on using a single target-specific primer. *Id.* The words "single primer enrichment" were not even in the lexicography of the art. EX2107.¶¶90-99. In fact, researchers outright dismissed the use of a single target-specific primer for enrichment. *See* EX2018.0598 ("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."); EX2107.¶94.

In fact, Dr. Metzker wrote in 2010 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." EX1025.0041 (emphasis added). The "improvements" to which Dr. Metzker referred concerned the use of primer pairs. *See, e.g.*, EX2029.1101-1102 (noting that "[a]ll 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).

Even more broadly, the art taught away from and expressed skepticism at PCR amplification methods generally. Tsoktouridis 2005 (EX2048) compared various PCR amplification methods and found "no simplicity, low reproducibility, high backgrounds of nonspecific PCR products, insufficient homopolymer tailing, small

PCR product amplification, and laborious time-consuming procedures." EX2048.0885; EX2107.¶¶61, 252. Prior art publications recognized that "the best way to avoid bias during PCR is to avoid library amplification by PCR altogether." Aird 2011, EX2042.0011. Along these lines, Quail 2008 (EX2053) and Kozarewa 2009 (EX2054) taught methods of adapter ligation that bypassed PCR amplification. EX2107.¶253. Bronner and Quail (EX2155) taught that "[u]necessary PCR amplification steps will exacerbate amplification biases, and so they should be avoided wherever possible" and that it was possible to perform NGS without PCR amplification. EX2155.0018-19. In 2011, Quail reported that "[l]ibraries prepared without PCR amplification performed best." EX2071.0010; EX2107.¶253.

e) Real world evidence shows that Shapero's data did not overcome concerns in the art

Petitioner's claim that the data reported in Shapero would be convincing to a POSA is misplaced. As an initial matter, Shapero, including all of the data on which Petitioner relies, was published in 2004. NGS platforms were commercially available at least as early as 2007. NGS "rapidly changed the field of DNA sequencing," Paper 2, 35 (citing EX1007.0407), with technology evolving "very fluidly just because of the power of NGS." EX2109.0013 (51:1-3). Yet between 2007 and January 26, 2012, there were ***zero*** publications disclosing or suggesting the use of Shapero's MARA method with NGS. EX2107.¶¶271-74; *Leo Pharma.*

Products, Ltd. v. Rea, 726 F.3d 1346, 1356 (Fed. Cir. 2013) ("The elapsed time between the prior art and the [priority date] evinces that the [] claimed invention was not obvious to try."). Dr. Bustamante reviewed the 21 publications that have discussed Shapero. EX2107.¶¶271-74. Not only do these references fail to disclose or suggest the use of MARA with NGS, many of these references criticize or disregard MARA. *Id.* For example, Liu (published shortly after the priority date) describes Shapero's method as "expensive and requir[ing] specialized equipments [sic], which cost more [than] standard primers and are not practical for assaying low- to moderate-throughput SNPs." EX2141.0002. Howell explains that Shapero fails to "achieve[] the ideal goal of amplifying a large set of arbitrary sequences without the production of undesired amplification products." EX2130.0160. Palka-Santini teaches away from the "replacement of target-specific primers with universal ones" and explains that methods like MARA "are time consuming and prone to contamination." EX2139.0010. Bui explains that Shapero is "impractical for assaying a selected set of SNPs in specific genomic regions" and "usually beyond the reach of small to medium sized laboratories with limited resources." EX2138.0002.

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

EX2126.0001. Dahl rejects Shapero and goes on to propose a method using circularization instead. *Id.*, .0001-02. While many of these references considered MARA in conjunction with using microarrays, none suggested its use with NGS. EX2107.¶274 The lack of evidence that researchers in the field considered the claimed combination in this quickly evolving field confirms that a POSA would not have been motivated to use a method such as MARA with NGS. *See Leo Pharma.*, 726 F.3d at 1356. The commentary on MARA further reinforces that a POSA would not have been motivated to use Shapero's method with an NGS platform. EX2107.¶¶271-74.

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

There is nothing in the prior art that would have given a POSA a reasonable expectation of success. As explained above, the prior art shows that a POSA would have been faced with numerous articles explaining the limitations of such a combination. *See supra*, 35-47. Despite this clear teaching to the contrary, 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." Paper 2, 37-38. That argument, however, ignores the limitations of the data reported in Shapero. First, the data would not have allowed a POSA to draw reasonable inferences regarding the

enrichment, target specificity, and off-target binding that are attributable to MARA, as opposed to the microarray. Shapero's experimental design would have made this data unattainable for a POSA given Shapero's required use of a microarray. Second, Shapero noted that the microarrays, when used with the MARA method, proved less reliable for reasons that Shapero could not explain, calling into question the reliability of the methods. Shapero's data, therefore, would not have demonstrated to a POSA that the claimed combination would be successful. Delseny's disclosure that NGS may be used for the genotyping of an entire genome does not address the concerns raised by the art, including by Shapero. *See* EX2107.¶¶261-263.

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

Petitioner misapplies the data reported in Shapero to argue that it "shows a high on-target specificity that a POSA would understand would likely work for NGS applications." *See* Paper 2, 37. In order to be able to predict that the MARA method could be successfully combined with NGS, a POSA would need information relating to the efficacy of MARA in enriching for the target sequence. EX2107.¶¶219-26, 264-65. A POSA would have understood that attempting to apply the experimental data in Shapero to NGS would be comparing apples to oranges. EX2107.¶220.

As explained above, the call rates and DS are ways to assess the efficacy of the microarray probes binding to targeted SNPs. *See supra*, 26-27. Neither metric

in isolation reflects the efficacy or impact of the MARA method. EX2107.¶220. As such, this data is insufficient to teach a POSA that the combination would be successful. *Id.* As also explained above, there were other explanations for the differing results when using and omitting the target-specific primers—none of which supported claims that the results reflect enrichment. *See supra*, 27-28. For example, omitting the target-specific primers would have greatly impacted genetic sample volume given that it would have prevented multiple rounds of oligonucleotide extension and subsequent exponential amplification. *Id.* Shapero failed to provide any data about the relative proportions of specific sequences before and after amplification, which would have made it impossible for a POSA to reliably infer the specific impact of the MARA amplification scheme on the sample, including MARA's generation of off-target products. EX2107.¶226.

Further, the use of a hybridization array makes drawing inferences from Shapero's data even more difficult 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). EX2107.¶¶217-20. The target-specific nature of the microarray precludes a POSA from knowing to what degree the target-specific primers enriched any specific sequence as compared to the rest of the sample population. *Id.* As such, a POSA could not infer what degree of target specificity is driven by MARA as compared to the microarray. *Id.*; EX1006.0007 (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." EX1006.0007. In other words, if there were off-target binding issues introduced due to MARA, those issues would be addressed by the microarray. EX2107.¶219. As disclosed in Shapero, there is no way a POSA can ascertain from the publication what level of off-target binding would have occurred using MARA in the absence of the target-specific microarray. EX2107.¶¶216-26.

Given these limitations, a POSA could not have reliably inferred from the reported hybridization data how effective MARA would be with an NGS platform. EX2107.¶¶216-26.

b) The data confirms a POSA would not have been motivated to adapt 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 would have taught a POSA that MARA suffered from undeterminable deficiencies that would be fatal to use with NGS. For example, Shapero discloses a series of concordance rates. EX2107.¶¶162-69, 227-28, 266. These rates demonstrated how accurate the

microarray was in identifying SNPs compared to an established reference. *Id.* As Shapero explained, the concordance rates were lower when using the microarray with MARA than when used without target-specific primers. *Id.*; EX1006.0007. 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 microarray. EX2107.¶¶164-69, 227-28, 266. The increased error rate would have contributed to why a POSA would not have had a reasonable 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. EX2107.¶¶227-29, 266.

Additionally, when applying MARA in higher multiplex reactions, Shapero reports that only 75% of the input primers can function with a multiplex above 1,000 bps. EX1006.0007. Therefore, a POSA would have concerns with whether this method could be reliably used with a high-throughput method like NGS. EX2107.¶¶168-69, 267, 273; EX2129.0121. For a quarter of the primers used, Shapero could not offer an explanation for the poor results. EX1006.0007; EX2107.¶¶168-69, 267. Rather, Shapero could only state that "non-specific primer-primer interactions at the higher multiplex level may not solely be responsible for failed target generation." *Id.* A POSA would have understood this to mean that in addition to primer dimer issues, Shapero believed other problems were occurring

with MARA. EX2107.¶267. 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 microarrays could determine what issues confounded the analysis. EX2107.¶¶168-69, 266-67. That uncertainty would further contribute to why a POSA would not have had a reasonable expectation of adapting MARA for use with NGS. *Id.*

c) Delseny Does Not Address the Issues Raised in Shapero

Petitioner argues that a POSA "would have had a reasonable expectation of success utilizing Shapero's enrichment methods with the NGS technologies described in Delseny" because "Delseny expressly teaches that NGS can be a replacement for array-based genotyping, as used in Shapero." Paper 2, 37-38. However, as explained above, Delseny discloses the potential use of NGS instead of microarrays for genotyping where the entire genome is sequenced and where a reference genome is available for comparison. *See supra*, 32-33. That is the opposite of enriching for and sequencing a target sequence as required by the claims. EX2107.¶268. Delseny offers no insights into how NGS may be used with a single target-specific primer to genotype a SNP of interest. EX2107.¶269. If anything, Delseny lends credence to Shapero's disclosure that whole genome sequencing is a better method for genotyping than targeted capture. EX2107.¶¶268-70. Which

aligned with the other prior art teachings. *See, e.g.*, Han, EX2117. As such, a POSA could not draw any reliable inferences as to how MARA might work with NGS based on Delseny. EX2107.¶¶268-70.

3. Dependent Claims

For the reasons that Shapero and Delseny fail to render obvious claim 1 of the '012 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: Petitioner Has Failed To Show that Claims 7-10 are Obvious

Petitioner argues that Shapero could be adapted in view of Delseny and in further view of Hamady to practice dependent claims 7-10. Paper 2, 51-53. As explained above, Shapero and Delseny fail to render obvious claim 1 of the '012 patent. Ground 2 fails to address the deficiencies in Ground 1 with respect to the only independent claim of the '012 patent. As such, Ground 2 necessarily fails for at least the same reasons.

C. Ground 3: Petitioner Has Failed to Show that Claims 3-4 and 21 are Obvious

Petitioner argues that Shapero could be adapted in view of Delseny and in further view of Jones to practice dependent claims 3-4 and 21. Paper 2, 54-55. As explained above, Shapero and Delseny fail to render obvious claim 1 of the '012

patent. Ground 3 fails to address the deficiencies in Ground 1 with respect to the only independent claim of the '012 patent. As such, Ground 3 necessarily fails for at least the same reasons.

D. Secondary Considerations Support a Finding of Nonobviousness

Objective indicia constitute independent evidence of nonobviousness and are often considered to "be the most probative and cogent evidence of nonobviousness." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012). Because of how probative this evidence is to the inquiry, objective indicia "must be considered in every case where present." *Apple Inc. v. Samsun Elecs. Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016) (*en banc*).

1. The Prior Art Taught Away from and Expressed Skepticism for the Claimed Methods

"A reference may be said to teach away when a person of ordinary skill, upon reading the reference, … would be led in a direction divergent from the path that was taken by the applicant." *Millennium Pharmas., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017). Additionally, "[i]f industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317 (Fed. Cir. 2016). As discussed above and in further detail by Dr. Bustamante, the weight of the prior art taught against the use of a single target-

specific primer, especially with PCR amplification, to enrich for and sequence those enriched target sequences. *See supra*, 41-45; EX2107.¶¶285-87. For example:

- Miura (EX2047.0001) explained that genome walking methods using a single target-specific primer were "often plagued with non-specific amplification products derived from so-called 'off-targets'";
- Sohn (EX2050.0002) noted that even in 2011, the "most serious problems of the PCR-based genome walking methods are low amplification efficiency and non-specific amplification";
- Metzker (EX1025.0041) disclosed that "coupling PCR with high-throughput NGS platforms for targeting strategies is not practical";
- Tsoktouridis (EX2048.0885) compared PCR amplification methods and found "no simplicity, low reproducibility, high backgrounds of nonspecific PCR products, insufficient homopolymer tailing, small PCR product amplification, and laborious time-consuming procedures";
- Aird (EX2042.0011) disclosed that "the best way to avoid bias during PCR is to avoid library amplification by PCR altogether";
- Syvänen (EX1012.0940) taught that "[t]he next generation technology for SNP analysis should avoid the PCR amplification step"; and

- Bronner (EX2155.0018) disclosed that "[u]nnecessary PCR amplification steps will exacerbate amplification biases, and so they should be avoided wherever possible."

Prior art discussions of Shapero also taught away from its use with NGS. *See supra*, 45-47; EX2107.¶286; Howell (EX2130.0160) (explaining that Shapero fails to "achieve[] the ideal goal of amplifying a large set of arbitrary sequences without the production of undesired amplification products"); Palka-Santini (EX2139.0010) (describing methods like MARA as "time consuming and prone to contamination"); Dahl (EX2126.0001) (rejecting MARA and stating that "[c]urrently, the only way to amplify many defined sequences in the same reaction is by combining several different PCR primer pairs.").

This skepticism is also reflected in the Brooks Declaration, submitted during prosecution. Dr. Brooks explained that "[b]ased on [his] experience in the field, [he] was skeptical that the claimed methods would provide efficient sequencing data." Brooks Declaration (submitted February 15, 2018), EX2026.0003. He expressed concerns that "the target-specific primers [of the claimed inventions] 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.* Dr. Brooks contrasted the claimed methods with the invention of Jones (and Shapero) to emphasize why prior art microarrays did not address the concern. With

Jones' microarrays, 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." *Id.* 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.*, .0004. 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.*

2. There Were Long-Felt, Unmet Needs to Develop Accurate Target Capture Techniques for NGS that Were Cost-Effective and Efficient

"Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious." *WBIP*, 829 F.3d at 1332. In the mid- and late-2000s, practitioners recognized that the technology suffered from "the inability to easily target specific regions of a genome." EX2107.¶288; EX2009.0003. Scientists acknowledged that new "sequence capture [(target specific)] methodologies [were] required for time- and cost-effective sequence analysis in high-throughput genomic projects." EX2107.¶288; EX2064.0001 (disclosing a microarray-based sequence

capture strategy). But any viable method of targeting sequences would require accuracy and efficiency, including addressing off-target binding. EX2107.¶288.

The targeted library preparation methods at the time relied on complex, specialized instrumentation. EX2107.¶289; EX2009.0002-07; EX2064.0001-02. Practitioners viewed PCR-based methods as "laborious, time-consuming and costly" and where multiplexed, "difficult to check successful amplification per fragment," increasing the "chance of obtaining artifacts." EX2107.¶289; EX2051.0052. The lack of target-specific methods not requiring specialized instrumentation resulted in cost-conscious researchers re-using instruments, like microarrays, despite risks of sample contamination. EX2107.¶289. Grunenwald (EX2056) recognized at the time that "there is greater demand for cost-effective, streamlined library preparation methods." EX2056.0001. Grunenwald's solution (Nextera) attempted to improve efficiency by sacrificing target specificity—Nextera uses transposition to randomly fragment and tag DNA fragments. *Id.* While that solution was viable for certain applications, it failed to address target capture concerns. EX2107.¶289.

Despite considerable work in the field to address these needs, the solutions developed fell short of resolving the problems. EX2107.¶¶289-91. One review of the prior art as of 2011, just before the priority date of the '012 patent, determined that the three categories of targeting methods (PCR, circularization, and hybrid capture) all suffered from varying degrees of "uniformity, efficiency of coverage and

off-target capture." EX2169.0007. Given the problems, Moorthie taught that "it may ultimately be more cost-effective to sequence a whole genome" rather than use target capture. *Id.* That sentiment was echoed by Delseny, who disclosed using whole genome sequencing for genotyping. *See supra*, 32-33.

These needs remained unmet until the claimed inventions. EX2107.¶¶291-92. One month before the priority date, researchers noted that current target enrichment and sequencing library preparation methods were "laborious, time-consuming, prone to experimental errors and difficult to automate." EX2052.0002; EX2107.¶291. These researchers complained that the methods had "complex protocols which require large amounts of starting genomic DNA" and that they were "susceptible to coverage biases secondary to amplification and molecular artifacts." *Id.* The researchers proposed a form of capture by circularization that failed to address the high number of custom oligonucleotides required. EX2038.¶291. Before the claimed methods, the field did not have an efficient solution for targeting portions of the genome for sequencing.

3. Industry Praised the Claimed Inventions

Industry praise "provides probative and cogent evidence that one of ordinary skill in the art would not have reasonably expected" the claimed invention to succeed. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013). As reflected by praise from the industry, the claimed

inventions, as embodied in NuGEN and Tecan's SPET products, addressed the long-felt, unmet needs in the art. As Dr. Bustamante explains, NuGEN and Tecan's SPET products were designed to perform the claimed methods. EX2107.¶¶276-84 (demonstrating nexus between the claimed inventions and commercial embodiments). Tecan's Ovation and Allegro products are coextensive with the claimed methods. *Id.* The products also embody the unique SPET covered by the claimed methods. *Id.*

After release of these products, the field praised the convenience and efficiency that the products provided. One study conducted by Italian and Spanish research institutions and funded by the European Union described the claimed technology as "a new, robust, customizable solution for targeted genotyping." EX2107.¶294; EX2065.0001. It also described the technology as "a customizable solution for targeted sequencing at an affordable price." EX2065.0002. As explained by Barchi, the claimed technology's "reliance on single primers, rather than on primer pairs, greatly simplifies panel design, and allows higher levels of multiplexing than PCR-based genotyping." *Id.* Barchi concluded that the technology "performed well with DNA samples prepared by different laboratories using different DNA mini-preparation protocols," that it provided "the ability of multiplexing thousands of samples in a single sequencing run," and that it "allow[ed]

the discovery of thousands of novel SNPs not originally included in the panel." *Id.*, .0013.

These findings are echoed in other industry publications. An editorial in Biocompare's Future Lab extolled a Tecan commercial embodiment of the claimed inventions, explaining that "[u]sing single primers instead of primer pairs greatly simplifies the design of primer panels, and allows higher levels of multiplexing compared to amplicon-based enrichment." EX2107.¶295; EX2067.0003. In a study performed by Italian and British research institutions, the researchers explained that "[u]nlike other methods, [the claimed] technique allows for the execution of cost-effective genotyping experiments while providing full control on target sites," which it attributed in part to the "high efficiency enrichment system" and "the scalability to tens of thousands of probes in a single reaction." EX2107.¶295; EX2068.0548. It reported that the study "results suggest that [the claimed] SPET genotyping is a very effective approach for genotyping a large number of loci," and "suggest[ed] that it might be a valuable tool for large-scale genotyping studies in virtually all species." EX2068.0550. Another study conducted by the famed Jackson Laboratory for Genomic Medicine and Baylor College of Medicine described a commercial embodiment of the claimed inventions as "widely used for genotyping" and an adaptation "as a quantitative, straightforward, and cost-effective method for profiling mouse microbial communities." EX2107.¶297; EX2069.0002.

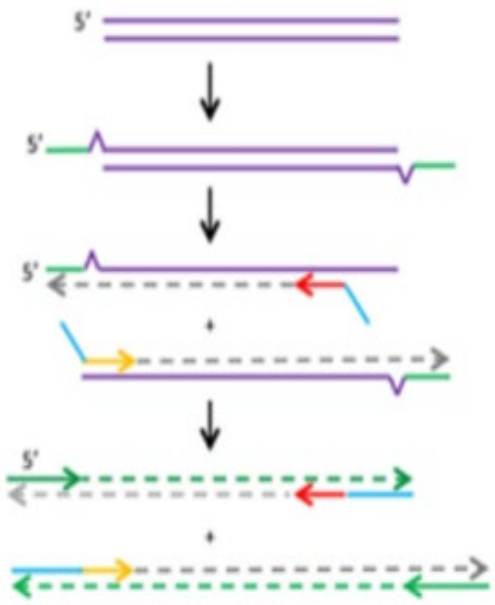
4. QIAGEN Copied Tecan's Claimed Inventions

"It is well established that copying by a competitor is a relevant consideration in the objective indicia analysis." *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1137 (Fed. Cir. 2019). Access to an embodiment of the claimed invention "in combination with similarity can create a strong inference of copying." *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 70 F.4th 1331, 1340 (Fed. Cir. 2023) (cleaned up). QIAGEN was aware of the claimed inventions for years before it copied them. For example, in 2013, NuGEN and QIAGEN entered into discussions related to QIAGEN's potential acquisition of NuGEN. EX2170.0031-32. QIAGEN met with NuGEN employees and reviewed various technical documents concerning the claimed inventions, including underlying research and development documents and pending patent applications. *See id.* As another example, the claimed inventions were marked by NuGEN under the Ovation trade name as early as September 2013. *See, e.g.*, EX2171.0016. In July 2015, NuGEN reported on the use of the claimed SPET technology with NuGEN's Ovation Target Enrichment System. EX2107.¶300. NuGEN illustrated how the commercial embodiment practiced the claimed limitations in the publication. *Id.* This publication has been accessible to the public, including QIAGEN, since 2015. *Id.*

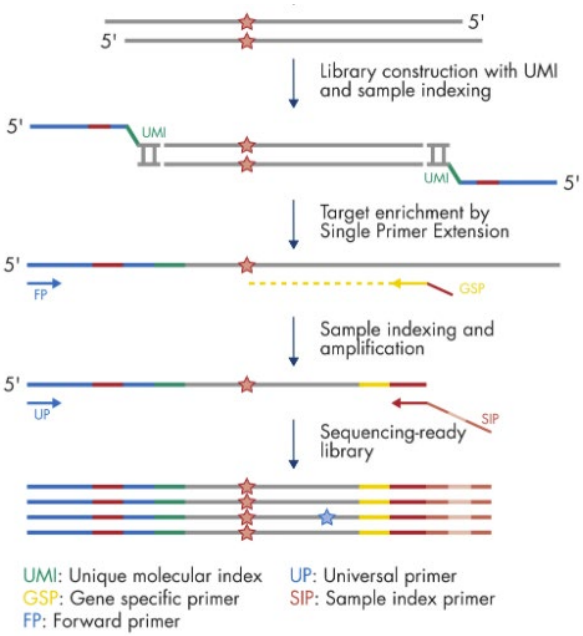
After QIAGEN's discussions with NuGEN and NuGEN's publications on SPET, QIAGEN copied Tecan's SPET methods, releasing its Single Primer

Extension ("SPE") commercial products. EX2107.¶¶299-304. As Dr. Bustamante explains, QIAGEN's SPE products copy the claimed features that are embodied in NuGEN's Ovation Target Enrichment System, as evidenced by the below comparison of product workflows. *Id.*

Ovation Target Enrichment



QIAseq Targeted DNA Panel



Both workflows begin with nucleic acid fragments. *Id.* Partial duplex adapters are ligated to the ends of the fragments. *Id.* These adapters contain the first adapter sequence. *Id.* Oligonucleotides with target-specific primer sequences are annealed to the target sequence and extended to generate oligonucleotide extension products. *Id.* The oligonucleotide extension products are amplified using primers specific to the first and second adapter sequences. *Id.* The amplified libraries are prepared for NGS. *Id.*

QIAGEN's QIAseq Targeted DNA Panel is just one of its numerous SPE products that were copied from and that are substantially similar, if not identical, to Tecan's patented technology. EX2107.¶303.

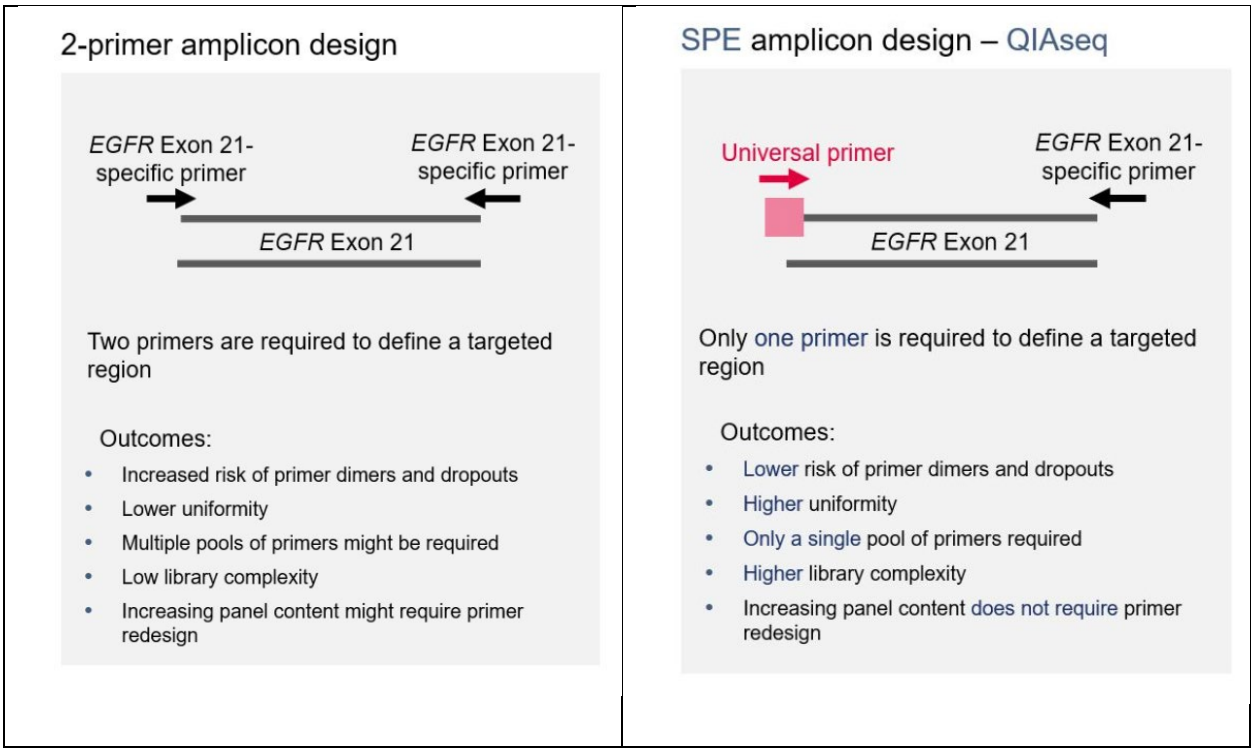
5. QIAGEN's Prior Statements Support the Nonobviousness of the Claimed Inventions

After QIAGEN copied Tecan's patented technology and released its own SPE products, QIAGEN published several articles on its website in which it made numerous statements that contradict the litigation-driven statements in its Petition. *See* EX2107.¶¶305-09. In those publications, QIAGEN described the "revolutionary" nature of using a single target-specific primer for NGS target capture. EX2148.0002. For example, QIAGEN recognized that "[m]ultiplex PCR and nested PCR-based library preparation approaches present primer design and specificity challenges inherent to these methods." EX2147.0002. While "[a]mplicon-based next-generation sequencing (NGS) assays offer[ed] many advantages for targeted enrichment," QIAGEN explained that the "typical approaches [had] suffered due to restraints in multiplexing capacity and introduction of additional bias." *Id.* According to QIAGEN, "[a]s primer multiplexing and PCR cycle numbers are increased, so does the potential for bias and error." *Id.* As a result, QIAGEN explained in February 2018 that the "current amplicon-based enrichment and sequencing methods that rely on either two-primer designs or nested PCR

approaches suffer from" numerous inefficiencies, including "[l]ow uniformity and lack of coverage due to primer dropouts," "[r]equirement for multiple primer pools resulting in increased DNA input per sample," and "[l]ow library complexity as both start and stop positions are defined by primers." EX2148.0001.

Despite QIAGEN's current claims, QIAGEN described single primer extension in 2018 as a "***revolutionary approach*** that redefines amplicon-based enrichment and sequencing." EX2148.0002 (emphasis added). QIAGEN explained that "SPE overcomes the challenges of traditional amplicon-based approaches of two-primer and nested PCR designs to deliver [numerous] advantages." EX2148.0002-04. QIAGEN also noted that "PCR enrichment efficiency using one primer is also better than [the] conventional two primer approach, due to the absence of an efficiency constraint from a second primer." EX2147.0005. According to QIAGEN, using a single target-specific primer "help[ed] to increase the efficiency of capturing rare mutations in the sample" and "permit[ted] discovery of unknown structural variants, such as gene fusions." *Id.*

In 2018, QIAGEN provided the below comparison of a two-primer amplicon design with the SPE amplicon design:



EX2149.0003-05. Around the time, QIAGEN also explained that its QIAseq Targeted DNA Panels feature a "[p]rimer design [that] is based on single primer extension, in which each genomic target is enriched by one target-specific primer and one universal primer – a strategy that removes conventional two target-specific primer design restriction and reduces the amount of required primers." EX2172.0001.

QIAGEN spent years touting the "revolutionary" nature of its copied products. QIAGEN's prior statements reflect how the prior art did not consider using the claimed single primer enrichment methods with NGS and how the claimed methods addressed numerous long-felt, unmet needs in the art. EX2107.¶309.

QIAGEN's praise of its copied products is directly attributable to Tecan's claimed inventions. *Id.*

6. Tecan's Patented Inventions Led to Unexpected Results

During prosecution, Dr. Brooks explained that he "observed unexpected results when enriched nucleic acid sequences generated using the claimed methods were sequenced by massively parallel sequencing." Brooks Declaration, EX2026.0004. He "expected to observe about fifty percent of sequences of interest in the sequencing results." *Id.* Instead, by using the claimed methods, he "observed greater than ninety percent of on-target sequences of interest in the sequencing results." *Id.* He explained that "[b]ased on my knowledge and experience in this field, I did not expect and would not have predicted this level of specificity." *Id.*

Petitioner seeks to discredit Dr. Brooks' insights by arguing that Dr. Brooks failed to compare the results to Shapero, which Petitioner argues is the closest prior art. Paper 2, 41. As explained above, Shapero's results were not obtained through NGS. *See supra*, 26-30. A POSA would not have been able to compare the results obtained through Shapero's microarrays to that of an NGS platform like Illumina in the way that Petitioner attempts to do. *Id.* Additionally, Shapero would not have been considered the closest prior art given that it is not a library preparation method for use with NGS. *Id.* Instead, the closest prior art would have been NGS library preparation methods using target-specific primer pairs. EX2107.¶¶310-11.

Dr. Brook's conclusions likewise align with QIAGEN's own publications and data concerning the claimed methods. In June 2018, QIAGEN published an article (EX2149) comparing the sequencing coverage obtained for specific genes through NGS when using target-specific primer pairs and single target-specific primers. EX2107.¶¶313-14. As Dr. Bustamante explains, a POSA would have expected greater coverage where target-specific primer pairs are used instead of single target-specific primers. EX2107.¶¶312-19. QIAGEN, however, highlighted an unexpected result. Through the use of single target-specific primers, QIAGEN demonstrated that sequencing coverage substantially increased for the target genes. *Id.* Despite the teachings of the art that single primers suffered from greater targeting issues (*see supra*, 41-45), QIAGEN's results reflected "enhanced coverage." EX2107.¶316. These results are reproduced below.

	2-primer amplicon		SPE in QIAseq		
Gene	Region	Coverage	Region	Coverage	LOD
Akt1	Chr14: 105246446–105246583	0	Chr14: 105246245–105246553 NM_001014431	5734	0.4%
FGFR3	Chr4: 1806082–1806187	0	Chr4: 1806057–1806247 NM_000142	4406	0.5%
NOTCH1	Chr9: 139399338-139399447	0	Chr9: 139399125–139399556 NM_017617	5406	0.4%
STK11	Chr19: 1220481–1220603	0	Chr19: 1220372–1220504 NM_000455	5286	0.4%
TP53	Chr17: 7579351–7579485	0	Chr17: 7579312–7579590 NM_001276761	5740	0.4%
	Primer dropout		No primer dropout		

Id. QIAGEN's unexpected results for its copied and infringing products support the nonobviousness of the claimed methods. EX2107.¶¶310-19.

V. CONCLUSION

For the foregoing reasons, Tecan respectfully requests that Board reject Petitioner's arguments and affirm the patentability of the challenged claims.

Dated: August 20, 2025

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

The undersigned hereby certifies that the foregoing **Patent Owner's 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 13,905 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.

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that, on August 20, 2025, a copy of the foregoing **Patent Owner's 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:

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