

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
Case IPR2025-00029
U.S. Patent Nos. 10,036,012 and 10,876,108

DECLARATION OF CARLOS D. BUSTAMANTE, PH.D.

TABLE OF CONTENTS

I.	BACKGROUND AND QUALIFICATIONS	6
II.	MATERIALS CONSIDERED	14
III.	LEGAL STANDARDS	14
IV.	TECHNICAL BACKGROUND	16
A.	Genetic Information	16
B.	Nucleic Acid Genotyping	19
C.	Hybridization Arrays	21
D.	Nucleic Acid Sequencing	29
1.	Pre-NGS Technologies for Sequencing.....	29
2.	Next Generation Sequencing.....	32
E.	Target Enrichment	34
1.	PCR-based Target Enrichment Methods	36
2.	Capture-by-Hybridization	42
3.	Capture-by-Circularization.....	43
F.	DNA Hybridization Microarrays and NGS Platforms Rely on Different Technology.....	44
V.	THE PERSON OF ORDINARY SKILL IN THE ART	52
VI.	THE PATENTED INVENTIONS	53
A.	The Claims of the '012 Patent.....	54
B.	The Claims of the '108 Patent.....	58
C.	Relevant Prosecution History	61
VII.	RELEVANT PRIOR ART	64
A.	Jones (EX1011)	64
B.	Shapero (EX1006).....	66
1.	The MARA Method.....	68
2.	Shapero Validates MARA Using Genotyping Array Results	72
C.	Syvänen (EX1012)	79
D.	Delseny (EX1007).....	82
VIII.	Neither Shapero Nor Delseny Disclose All Elements of the Independent Claims	84

IX. A POSA Would Not Have Been Motivated to Combine Shapero with Delseny With a Reasonable Expectation of Success	89
A. A POSA Would Not Have Been Motivated to Adapt a Method Used with Hybridization Arrays for Use With NGS.....	89
B. Shapero Fails to Resolve the Concerns with Target Specificity and Off-Target Binding.....	94
C. A POSA Reviewing Shapero Would Not Have Discerned a Need to Switch from Hybridization Arrays to NGS.....	100
D. A POSA Would Not Have Understood Shapero’s Reference to Syvänen to Teach that the MARA Method Could be Used with Sequencing Technologies.	101
E. A POSA Would Not Have Been Motivated by Delseny to Adapt the MARA Method for NGS	105
F. A POSA Would Not Have Had a Reasonable Expectation of Success in Modifying the MARA Method to Practice NGS	108
X. CONCLUSION	112

I, Carlos D. Bustamante, declare as follows:

1. I have been retained by Patent Owner, Tecan Genomics, Inc. (“Tecan”) as an expert witness in this *inter partes* review.

2. As part of my assignment, I have been asked to review Petitioner QIAGEN Sciences, LLC (“QIAGEN”)’s petitions for *inter partes* review and to provide my opinions regarding positions taken by QIAGEN.¹

3. For this assessment, I have considered QIAGEN’s allegations that a person of ordinary skill in the art would consider claim 1 of U.S. Patent No. 10,036,012 (“the ’012 patent”) and claim 1 of U.S. Patent No 10,876,108 (“the ’108 patent”) to be obvious over Shapero (EX1006) in view of Delseny (EX1007).

¹ In reviewing the petitions and the accompanying declarations from Dr. Metzker, I have concluded that the documents do not substantively differ with respect to their discussions of the independent claims of the challenged patents. For simplicity, when I refer to the “Petition,” I am referring to the petition filed in IPR2025-00028. Similarly, when I cite to the declaration of Dr. Metzker (EX1003), I am referring to his petition submitted in IPR2025-00028. In both instances, my references refer equally to the analogous (and near identical) documents submitted in IPR2025-00029, which do not materially differ with respect to the disclosures identified herein.

Based on my review of the prior art and my experience in this field, it is my opinion that a POSA would not have considered the independent claims to be obvious over Shapero in view of Delseny. I understand that dependent claims include all elements of the independent claims from which they depend. As such, I have also concluded that the challenged dependent claims of the '012 and '108 patents would not have been obvious for at least the same reasons. As such, I will not address the nonobviousness of the dependent claims of the challenged patents.

4. In assessing obviousness, I have considered the contents of the '012 and '108 patents, the file histories of the patents and related patents, prior art publications, the two petitions for *inter partes* review, and the Declaration of Michael L. Metzker, Ph.D. (EX1003)—a declaration that QIAGEN relies on to support its claims. I have considered the prior art relied on by QIAGEN in its Petition: Shapero (EX1006), Delseny (EX1007), Hamady (EX1033), and Jones (EX1011). I have also relied on my own experiences as a person of ordinary skill in the art as of the effective filing date of the '012 and '108 patents (January 26, 2012).

5. As explained further below, I disagree with QIAGEN's assertions. Shapero and Delseny do not render obvious the challenged claims of the '012 and '108 patents. In large part, QIAGEN's petitions are biased by hindsight, arguing that a POSA would have been motivated to adapt a preparation method for hybridization arrays to instead be used with Next Generation Sequencing ("NGS") even though

NGS suffered particular sensitivities that were not of the same concern for hybridization arrays. In fact, in 2012 there was broad agreement that hybridization arrays were generally highly accurate and reproducible for large scale genetic analysis of SNPs. In contrast, there was a lack of standardization for other methods, especially NGS sequencing where target specificity and off-target binding posed particular challenges. QIAGEN, however, dismisses the concerns in the art as of 2012 and asserts that Shapero's results—which are based on the use of hybridization arrays and not NGS—somehow disprove the conventional wisdom of the time. To the contrary, these concerns would have discouraged a POSA from modifying the MARA method disclosed in Jones and Shapero. A POSA would have still lacked a reasonable expectation of success given the concerns in the art and the constraints of Shapero. If anything, Shapero and Delseny would have only exacerbated a POSA's discouragement and expectations of failure.

I. BACKGROUND AND QUALIFICATIONS

6. In this section, I summarize my educational background, career history, publications, and other relevant qualifications.

7. I have extensive experience in the interface of computational and biological sciences, as well as its application in medicine, agriculture, and evolutionary biology, spanning a career of over 25 years in the field. In 1997, I graduated magna cum laude, highest honors, with a Bachelor of Arts in Biology from

Harvard University. Then, in 2001, I earned both my M.S. in Statistics and Ph.D. in Biology from Harvard University. From 2001 to 2002, I served as a postdoctoral researcher in mathematical genetics at the University of Oxford funded by a Marshall-Sherfield Scholarship.

8. Pertinent to the issues raised by QIAGEN, I have devoted my career to studying human genomic diversity and pioneering new methodologies for both microarray and next-generation sequencing (NGS) studies. I applied high-density SNP microarrays to explore population structure, admixture, and disease susceptibility, which allowed me to refine analytical pipelines for large-scale genotyping. Over time, my focus evolved in parallel with technological advances, and I was actively involved in the transition from array-based methods to NGS, contributing to key consortium-driven projects that required optimizing pipelines for alignment, variant calling, and quality control on unprecedented volumes of genomic data. Through these efforts, I developed a deep appreciation for the strengths and limitations of both arrays and NGS at different stages of their development. My publications detail novel computational approaches to assess data accuracy, precision, and reproducibility, including methods to detect and correct for systemic errors inherent in each platform. Having witnessed firsthand how early NGS pipelines struggled with alignment biases and false-positive calls, I also led comparative studies that used array-based validation, bridging the gap between

established microarray benchmarks and emerging NGS pipelines. As a result, I bring a broad perspective on historical and current best practices in genomic variant detection, along with practical insight into how and why the field has evolved in its reliance on arrays versus next-generation sequencing. Specifically, I am familiar with the Affymetrix hybridization arrays disclosed in Shapero and the software relied on by Shapero to interpret the results of the hybridization arrays as I have used and studied these same arrays in my career.

9. I am currently an adjunct professor of Biomedical Data Science, Genetics, and (by courtesy) Biology at Stanford University where I have served since 2010. I was a tenured full professor at Stanford University from 2010 until 2023. I also served as the Inaugural Chair of the Department of Biomedical Data Sciences and co-Director of the Center for Computational, Evolutionary, and Human Genomics from 2015-2019. I have also been an Entrepreneur-in-Residence at the University of Miami Herbert School of Business since 2024.

10. I am a named inventor on numerous relevant patents and patent publications, including: U.S. Publication No. 2015/0360194 (“*Enrichment of DNA Sequencing Libraries from Samples Containing Small Amounts of Target DNA*”); U.S. Publication No. 2015/0232834 (“*Partitioning of DNA Sequencing Libraries into Host and Microbial Components*”); and U.S. Publication No. 2014/0045705 (“*Techniques for Determining Haplotype by Population Genotype and Sequence*”).

Data’’)—all of which are now issued patents. I have also completed numerous projects with the NIH, such as: *Inferring Multiple-SNP Disease Association with DNA Resequencing Data* (NIH/NIMH, 2008-2012); *Population Genetic Inferences from Dense Genotype Data* (NIH/NHGRI, 2010-2013); and *Methods for High-Resolution Analysis of Genetic Effects on Gene Expression* (NIH, 2013-2016).

11. In 2002, I joined Cornell University as an Assistant Professor in the Department of Biological Statistics and Computational Biology and Department of Statistical Sciences. I later became an Associate and Full tenured Professor at Cornell University, and also served as the Associate Director of the Cornell Center for Comparative and Population Genomics. At Cornell, my work primarily focused on population genetics and agricultural genomics.

12. I am the founder of Galatea Bio, Inc. and serve as President, CEO, and Board Member of the company. I served as a venture partner at Fidelity’s early stage biotechnology group, F-Prime Capital, where the company was incubated during my tenure, and retain a venture partner title while serving as an operator of Galatea Bio. I am also the Principal and Chairman of CDB Consulting Group, Inc., an internationally recognized consulting firm, providing data science and genomics expertise in the areas of medicine, agriculture, and biology. I serve as a Board observer at Embark Veterinary, a company I advised at CDB Consulting and where F-Prime Capital is an investor.

13. I am also the founder of Arc-Bio (formerly IdentifyGenomics and BigData Bio) and now part of Cantata Bio. I served as chair of its Scientific Advisory Board and board member until the company was merged into Cantata Bio. Further, I was on the Board of Directors of Etalon Diagnostics and Eden Roc Sciences, two companies I co-founded.

14. I have served on the advisory boards of various other corporations, non-profit entities, and government organizations. For example, I am currently a member of the scientific advisory boards at the following companies: Fauna Bio and Cantata Bio. I was also a member of the National Advisory Council to the National Human Genome Research Institute at the National Institutes of Health and remain on the Scientific Advisory Board of NHGRI Center for Research on Genomics and Global Health. I was also the Co-Chair of the PAGE Analysis Working Group, the ClinGen Ancestry and Diversity Working Group, and the ClinGen Complex Disease/Polygenic Risk Score working group.

15. I have served on the Editorial Boards of numerous publications in the field, including PLoS-Genetics, American Journal of Human Genetics, Human Biology, Genome Research, Molecular Biology and Evolution, and Bioinformatics.

16. I have authored or co-authored over 250 articles and publications, including: including the following highly relevant to the topic of microarray and/or Next-Generation Sequencing (NGS) data analysis and interpretation: Polygenic risk

score portability for common diseases across genetically diverse populations *Hum Genomics*. 2024, 18: 93, Bayesian model comparison for rare-variant association studies *Am J Hum Genet*. 2021 Dec 2; 108(12): 2354–2367, Paths and timings of the peopling of Polynesia inferred from genomic networks *Nature*. 2021 Sep; 597(7877): 522–526, Native American gene flow into Polynesia predating Easter Island settlement *Nature*. 2020 Jul; 583(7817): 572–577, Development of a small panel of SNPs to infer ancestry in Chileans that distinguishes Aymara and Mapuche components *Biol Res*. 2020; 53: 15, Genetic analyses of diverse populations improves discovery for complex traits *Nature*. 2019 Jun; 570(7762): 514–518, Imputation-Aware Tag SNP Selection To Improve Power for Large-Scale, Multi-ethnic Association Studies *G3 (Bethesda)* 2018 Oct; 8(10): 3255–3267, An Unexpectedly Complex Architecture for Skin Pigmentation in Africans *Cell*. 2017 Nov 30; 171(6): 1340–1353.e14, Using genotype array data to compare multi- and single-sample variant calls and improve variant call sets from deep coverage whole-genome sequencing data *Bioinformatics*. 2017 Apr 15; 33(8): 1147–1153, Strategies for Enriching Variant Coverage in Candidate Disease Loci on a Multiethnic Genotyping Array *PLoS One*. 2016; 11(12): e0167758, GBStools: A Statistical Method for Estimating Allelic Dropout in Reduced Representation Sequencing Data *PLoS Genet*. 2016 Feb; 12(2): e1005631, Inexpensive and Highly Reproducible Cloud-Based Variant Calling of 2,535 Human Genomes *PLoS One*. 2015; 10(6):

e0129277, Exome capture from saliva produces high quality genomic and metagenomic data *BMC Genomics*. 2014; 15: 262, Imputation-Based Assessment Of Next Generation Rare Exome Variant Arrays *Pac Symp Biocomput*. 2014 : 241–252; Analysis of the Genetic Basis of Disease in the Context of Worldwide Human Relationships and Migration PLoS Genet. 2013 May; 9(5): e1003447, The genetic prehistory of southern Africa *Nat Commun*. 2012 Oct 16; 3: 1143, Population Genetic Inference from Personal Genome Data: Impact of Ancestry and Admixture on Human Genomic Variation *Am J Hum Genet*. 2012 Oct 5; 91(4): 660–671, Detecting and annotating genetic variations using the HugeSeq pipeline *Nat Biotechnol*. 2012 Mar; 30(3): 226–229, Demographic history and rare allele sharing among human populations *Proc Natl Acad Sci U S A*. 2011 Jul 19; 108(29): 11983–11988, ALCHEMY: a reliable method for automated SNP genotype calling for small batch sizes and highly homozygous populations *Bioinformatics*. 2010 Dec 1; 26(23): 2952–2960, Fine-scale population structure and the era of next-generation sequencing *Hum Mol Genet*. 2010 Oct 15; 19(R2): R221–R226, A Simple Genetic Architecture Underlies Morphological Variation in Dogs *PLoS Biol*. 2010 Aug; 8(8): e1000451, Genome-wide patterns of population structure and admixture among Hispanic/Latino populations *Proc Natl Acad Sci U S A*. 2010 May 11; 107(Suppl 2): 8954–8961, Genome-wide patterns of population structure and admixture in West Africans and African Americans *Proc Natl Acad Sci U S A*. 2010 Jan 12; 107(2):

786–791, The Population Reference Sample, POPRES: A Resource for Population, Disease, and Pharmacological Genetics Research *Am J Hum Genet.* 2008 Sep 12; 83(3): 347–358, Genes mirror geography within Europe *Nature.* 2008 Nov 6; 456(7218): 98–101.

17. For my work in the field, I have received several honors and fellowships. These honors and fellowships include: the MacArthur “Genius” Award (2010), a Marshall-Sherfield Scholarship to Oxford (2001-2002), the Stanford Prize in Population Genetics and Society (2016); the Cornell Provost Award for Distinguished Research (2008); a Sloan Research Fellowship in Molecular Biology (2007-2009); and a Howard Hughes Medical Institute Graduate Research Fellowship (1999-2001).

18. A copy of my curriculum vitae, attached as **Exhibit A**, contains further details on my education, experience, publications, and the other qualifications allowing me to render an expert opinion in this matter.

19. I am being compensated my standard rate of \$800 per hour, plus expenses. My compensation is in no way dependent on the content of my testimony or upon the outcome of this proceeding.

20. In the past five years, I have testified as an expert witness in four matters: (1) *Foundation Medicine Inc v. Guardant Health, Inc.*, IPR2019-00634 (P.T.A.B.); (2) *TwinStrand Biosciences, Inc. v. Guardant Health, Inc.*, C. A. 21-1126-

GBW-SRF (D. Del.); (3) *State v Pease*, 88-10 (D. Mont.); and (4) *Integrated DNA Technologies, Inc. v. Tecan Genomics, Inc.*, IPR2025-00015, IPR2025-00016 (P.T.A.B.).

II. MATERIALS CONSIDERED

21. In formulating the opinions in this declaration, I have relied on over 25 years of work experience and knowledge regarding bioinformatics, genomics, nucleic acid sequencing, and hybridization array design and associated analysis/interpretation. I also considered the documents cited in this declaration.

III. LEGAL STANDARDS

22. I have been informed by counsel for Tecan of certain legal standards, and I have applied these standards in rendering my opinions.

23. When I say in this Declaration “I understand,” I mean that “I understand from counsel for Tecan in this IPR.”

24. I understand that to prove obviousness in an *inter partes* review, it is the petitioner’s ultimate burden to prove obviousness by a preponderance of the evidence.

25. I understand that the question of whether the claims of a patent are obvious is considered from the perspective of a person of ordinary skill in the art (the “POSA”).

26. I understand that the POSA is a legal construct representing a hypothetical individual with the same level of skill as the typical practitioner of the art at issue. I understand that courts consider a non-exhaustive list of factors, including (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field. I understand that it is not appropriate to consider the level of skill possessed by the inventor in defining the POSA.

27. I understand that whether a patent claim is obvious is ascertained at the relevant time period, which in this proceeding I understand to mean before January 26, 2012.

28. I understand that an obviousness analysis involves ascertaining the scope and content of the prior art, the background and experience of a POSA, the differences between the claimed invention and the prior art, and whether there are additional factors present that may nevertheless weigh against obviousness, such as unexpected results attributable to the invention actually claimed. I also understand that the obviousness analysis is based on the knowledge possessed by one of ordinary skill in the art at the time when the invention was made and that the use of hindsight is impermissible.

29. I understand that for a prior art reference, or a combination of references, to render a claimed invention obvious, the POSA must have had a motivation to modify or combine the references to arrive at the claimed invention. I also understand that separate from having a motivation to modify or combine, the POSA must have also had a reasonable expectation of success in modifying or combining the references to arrive at the claimed invention.

30. I understand that for a dependent claim to be obvious, the independent claim from which that claim properly depends must be anticipated or obvious as well.

IV. TECHNICAL BACKGROUND

A. Genetic Information

31. All living organisms possess a genetic code, a chemical information system that contains the biological instructions required for an organism's development and function. Because an organism's genetic code dictates its biological functions, such as which proteins are produced, when they are produced, and where they are produced, understanding the composition and regulation of an organism's genetic information is essential to understanding biological function generally.

32. An organism's genetic information is contained in deoxyribonucleic acids ("DNA") and ribonucleic acids ("RNA"). These nucleic acids are made of a

chemically defined subunit termed a “base,” which defines the identity of the nucleic acid. For example, canonical DNA is composed of four bases: adenine (A), cytosine (C), guanine (G) and thymine (T). By organizing these bases into discrete linear sequences, nucleic acids can serve as an information system wherein the composition and order of the bases reflect a set of biological instructions that can be read by other cellular machinery.

33. Discrete sets of encoded information (such as the structure of a given protein) are retained in discrete regions termed “genes,” which are contained within a cell’s DNA. The totality of a cell’s DNA is referred to as a cell’s “genome.” DNA is organized in a helical structure composed of two intertwined strands. At a given location in the genome, each DNA strand is a “complement” of the opposite DNA strand to which it is associated, which allows for both strands of DNA to contain the same genetic information—the first sequence information contained in the “template” strand and the same sequence information mirrored in the complement strand. As I describe in further detail in subsequent sections, the complementary nature of nucleotides such as DNA is an integral phenomenon harnessed by nucleotide sequencing technology.

34. DNA is a molecule that encodes an organism’s genetic blueprint. DNA contains all of the information required to build and maintain an organism. Nearly all of the cells within a single organism include exactly the same DNA. When

required for actionable use within the cell, the genetic information contained in DNA is converted into RNA and then disseminated throughout the cell.

35. Like DNA, RNA is composed of nucleotides containing discrete bases: three bases—adenine (A), cytosine (C), and guanine (G)—shared with DNA and an additional base, uracil (U), corresponding to the thymine (T) base observed in DNA.

36. The genetic information contained in genes is converted to messenger RNA (mRNA) by an enzyme known as RNA polymerase during a process called transcription. mRNA is designed to efficiently traffic information from the DNA to sub-regions of the cell for processing into proteins. The entirety of a cell or organism's mRNA, including the genetic information contained therein, is referred to as its "transcriptome."

37. Complementary DNA (cDNA) is a form of DNA that is synthesized from an mRNA template in a process called reverse transcription. cDNA is DNA that is complementary to the mRNA and thus contains only the exonic sequences of the gene—those sequences that code for protein. This makes cDNA especially useful in genetic studies because it represents the expressed genes in a cell, tissue, or organism, excluding introns and regulatory sequences found in genomic DNA.

38. Some of the earliest efforts to characterize genomic information included genotyping through DNA microarrays and sequencing.

B. Nucleic Acid Genotyping

39. Genetic variation within a population arises when changes in an organism's DNA sequence occur that are then passed down to their descendants. When a specific variant is detected at a considerable frequency in a population—typically above 1%—it is termed a “genetic polymorphism.” In contrast, “mutations” usually refer to the initial rare or novel alterations that arise spontaneously and which can be associated with genetic diseases, but may or may not be passed down to descendants or may arise in a specialized setting (such as a cancerous tumor). A “single nucleotide polymorphism” (SNP)—a single-base change at a specific genomic location—represents one of the most prevalent types of polymorphisms. Though many SNPs are clinically benign, some can markedly affect gene expression and protein function, potentially driving or contributing to disease, as exemplified by the single-base mutation responsible for sickle cell anemia, which has been known since the 1950s to be a disease with a genetic origin and etiology.

40. To systematically identify and characterize these variations, researchers developed the process of “nucleic acid genotyping,” which involves examining a segment of DNA and comparing it to a reference sequence or to the same segment in another individual. In diploid organisms—those that inherit two sets of

chromosomes, one from each parent—each locus is typically present in two copies.² Therefore, an individual’s diploid genotype at a specific SNP site can be homozygous reference [AA], heterozygous [AB], or homozygous non-reference [BB], where “A” denotes the reference (or “wild type”) allele and “B” denotes the non-reference (or “minor”) allele. By systematically determining whether an individual has [AA], [AB], or [BB] at many such loci, scientists can create a detailed map of genetic variation relevant to traits or diseases.

41. This locus-specific approach enabled researchers to organize and interpret genetic data on a large scale, thereby identifying regions of the genome that play pivotal roles in health and disease. Because SNPs and other polymorphisms can provide insight into disease susceptibility, severity, and treatment response, scientists and clinicians benefit from methods that can genotype many loci simultaneously. To meet this need, high-throughput platforms were developed, including Affymetrix’s large-scale genotyping arrays which are discussed in the following section, which rapidly evaluate tens of thousands—or even millions—of SNP positions in a single experiment. By focusing on known sites of variation across

² The exceptions are uniparental inheritance of the mitochondria and Y chromosome, which are only passed on from the maternal or paternal parent and are considered haploid.

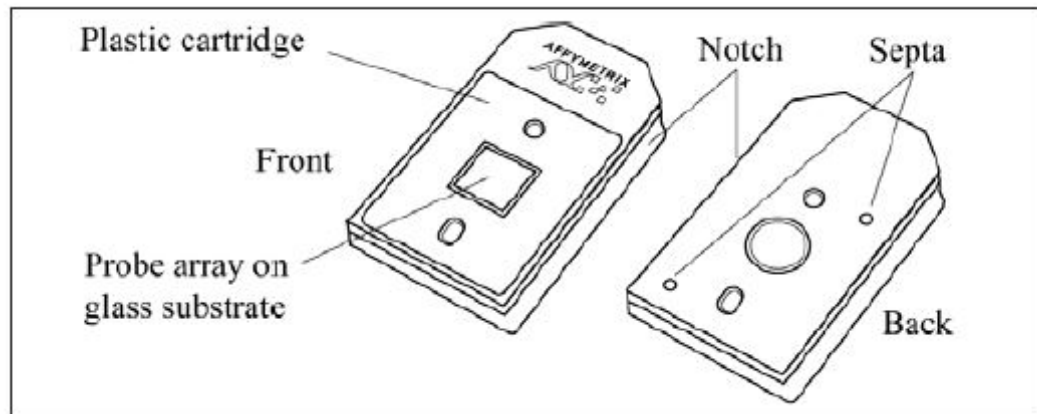
the genome, these arrays generate substantial volumes of data that can be used to identify disease-associated alleles (via genome-wide association studies), pinpoint genetic markers for clinical diagnostics, and facilitate personalized medicine.

C. Hybridization Arrays

42. One key high-throughput genotyping approach involved hybridization arrays, which exploit the principle that complementary nucleic acid strands selectively bind to one another (e.g., adenine pairing with thymine, guanine pairing with cytosine). In the early 2000s, Affymetrix employed a proprietary photolithographic manufacturing process—inspired by semiconductor fabrication—to synthesize short 25-mer oligonucleotide probes directly on a silica or glass substrate. Through iterative cycles of UV light exposure through custom-designed photomasks, nucleotides were selectively deprotected and added in a precise, stepwise manner, creating microscopic “features,” each containing up to a million copies of a single probe sequence. On arrays designed to genotype more than 10,000 SNPs (such as the Mapping 10K array), each SNP was interrogated by over 40 probes, incorporating perfect-match and mismatch designs. Consequently, a single array featured over 400,000 distinct probe sequences, which—multiplied by the millions of replicated copies per feature—resulted in hundreds of billions of physical probe molecules on one chip. During a genotyping assay, only DNA fragments complementary to these probes would hybridize and remain on the array after

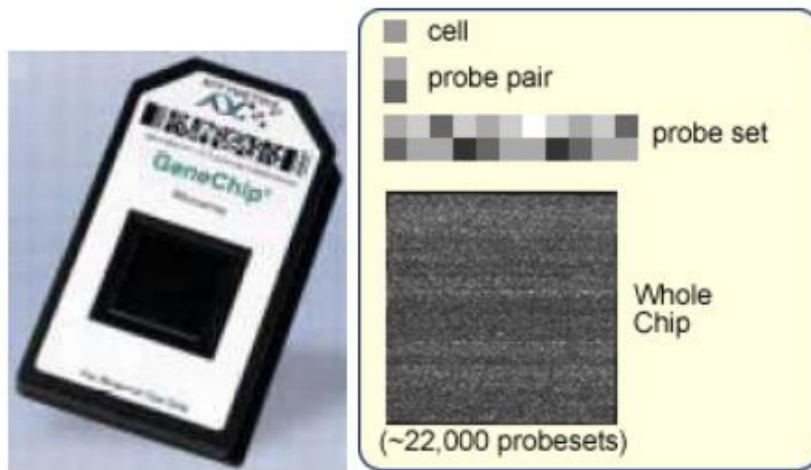
washing, enabling accurate, parallel determination of whether an individual was homozygous reference [AA], heterozygous [AB], or homozygous non-reference [BB] at each interrogated locus. Affymetrix thus enabled high-throughput, highly specific genotyping (~99.8% accuracy) across tens to hundreds of thousands of highly polymorphic SNPs.

43. These arrays were designed for high-throughput screening of known SNPs and could assess hundreds of thousands of SNPs in a single assay. For example, the Affymetrix Genome-Wide Human SNP Array 6.0 (depicted below) consisted of a single array that enabled the genotyping of approximately 900,000 SNPs and contained over 6.8 million unique probes, each replicated hundreds of thousands to millions of times on the array surface.

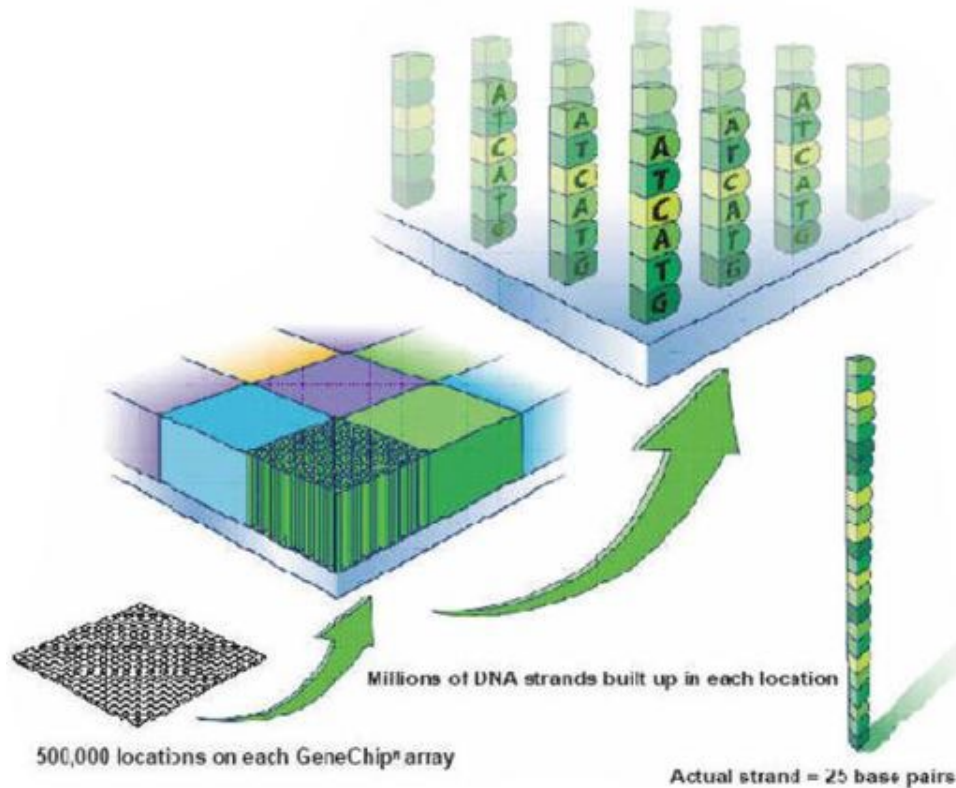


EX2001.0002.

44. Affymetrix produced a series of hybridization arrays known as GeneChips, designed for large-scale genetic analysis. An exemplary GeneChip is shown below, along with a depiction of the single array:



EX2002.0001. Affymetrix continually increased the probe density, incorporating hundreds of thousands to millions of different probes (unique oligonucleotide sequences) onto a single chip, with each 25-mer replicated many times, resulting in hundreds of billions of probes in total. A schematic depiction of the array is shown below:



EX2003.0001. Because each probe was synthesized at a known, fixed location on the array, researchers could interpret hybridization patterns using specialized software to identify genes, relative expression levels (for expression arrays), or genotypes at specific SNPs (for genotyping arrays).

45. To use a GeneChip, a researcher first needed to prepare the sample, often through DNA fragmentation, amplification, and labeling. The prepared sample would then be injected into the array through septa on the back of the device.

EX2004.0004. Once loaded, the sample was allowed to hybridize within the enclosed chamber. The workflow to genotype a sample via the GeneChip Platform is depicted below.

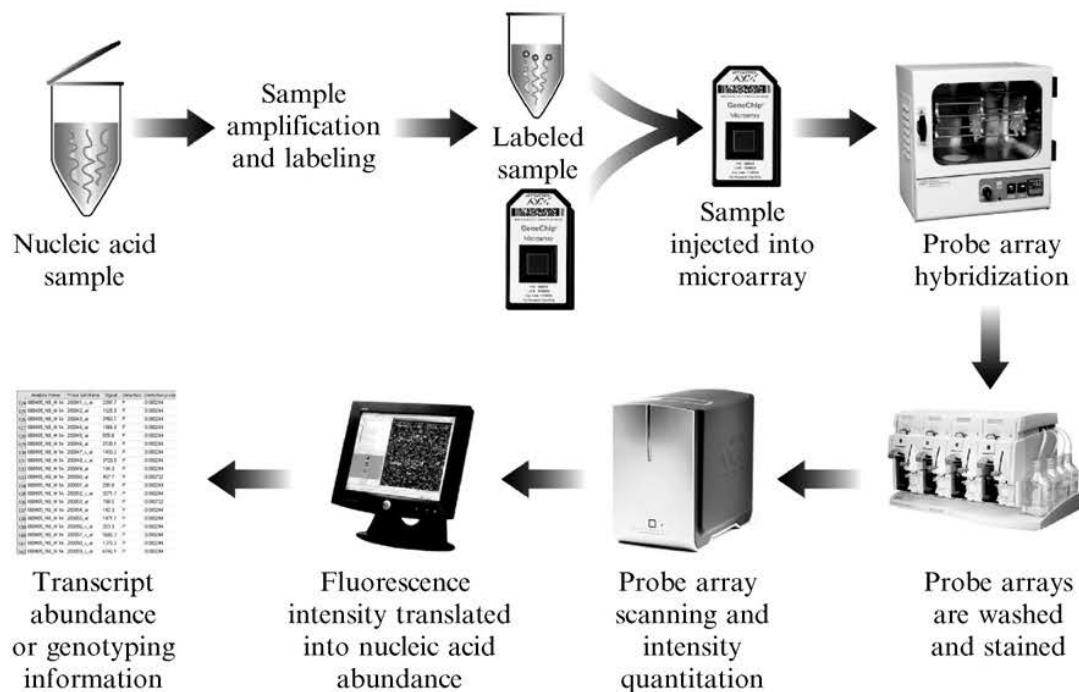


FIG. 1. Flowchart of a GeneChip System microarray experiment. Once the nucleic acid sample has been obtained, target amplification and labeling result in a labeled sample. The labeled sample is then injected into the probe array and allowed to hybridize overnight in the hybridization oven. Probe array washing and staining occur on the fluidics station, which can handle four probe arrays simultaneously. The probe array is then ready to be scanned in the Affymetrix GeneChip scanner, where the fluorescence intensity of each feature is read. Data output includes an intensity measurement for each transcript or the detailed sequence or genotyping (SNP) information.

EX2004.0004.

46. As part of sample preparation, the DNA to be assessed by the array was typically fragmented using restriction enzymes selected for each particular Affymetrix array design (e.g., NspI, StyI, HindIII, or XbaI). For instance, certain early arrays such as the 10K array relied on XbaI or HindIII, while the Genome-Wide Human SNP Array 6.0 employed both NspI and StyI to fragment genomic DNA near the SNPs of interest. After fragmentation, adapters containing common primer-binding sites were ligated to the DNA fragments, enabling PCR-based

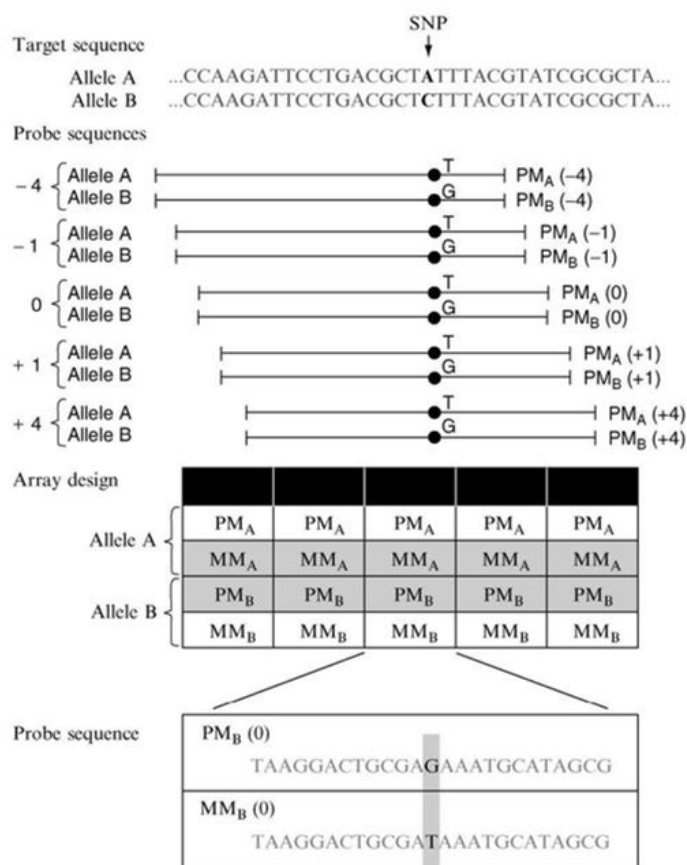
amplification to generate sufficient material for genotyping (EX2004.0013–14). This amplification was size-selective, enriching for fragments within a defined range and thereby standardizing the final library. Such size standardization helped ensure more consistent and accurate genotyping results across the entire genome.

47. After amplification, the DNA was denatured to produce single-stranded fragments. These fragments were then washed over the silica chip, allowing each fragment to bind (hybridize) to complementary oligonucleotide probes. Specifically, probes were designed to discriminate between possible alleles at a SNP locus. For instance, if a SNP of interest was heterozygous [AB], containing both the reference (A) and minor (B) alleles, fragments bearing allele A would hybridize to probes specific for allele A, while fragments bearing allele B would bind to probes targeting allele B. This allele discrimination process underpinned Shapero's use of hybridization arrays.

48. In many cases, probes targeting a specific allele were replicated (duplicates or multiple similar sequences) to increase the aggregate signal. Additionally, slight positional shifts (e.g., -4, -1, 0, +1, +4) were built into the probe design, ensuring robust detection of the SNP by accounting for neighboring sequence context. Often, arrays also employed mismatch probes (MM), which incorporated a deliberate non-complementary base at the SNP locus. These MM

probes served as controls to account for non-specific binding and background signal, thereby refining the accuracy of genotype calls.

49. A representative figure demonstrating array design, including both mismatch probes (denoted as “MM”) and probes designed to vary slightly in target sequence location (denoted as “-4,” “-1,” “+1,” and “+4,” indicating a shift in location from the reference probe denoted as “0”), is provided below:



EX2004.0010. These carefully arranged probes collectively produced a detailed hybridization signature that algorithms could interpret to assign genotypes.

50. Once the prepared DNA had hybridized to the array, each bound probe produced a fluorescent signal corresponding to the presence of complementary DNA. In practice, a biotin label was introduced into the DNA near the end of the amplification process. After hybridization, a streptavidin-phycoerythrin reagent was applied, which bound to the biotin-labeled fragments and generated fluorescence at the probe's location. A scanner or computer-driven imaging system then quantified signal intensities for each probe, enabling the user to analyze the entire microarray and to determine the alleles present at each locus (EX2004.0004). Complex algorithms were developed to optimize signal-to-noise ratios, correct for background fluorescence, and reliably call [AA], [AB], or [BB] genotypes based on the intensity patterns.

51. While genotyping by hybridization arrays provided a powerful, high-throughput platform for genetic assessment, the arrays were inherently targeted in nature. Probes were designed with high specificity to known target sequences, so the arrays could only query the particular SNPs for which they had been manufactured. Additionally, in order to design SNP probes, the location and flanking sequence of the SNP had to be known in advance. This requirement limited the applicability of microarrays in exploratory genomics where the relevant sequences or variants were unknown, driving the development of next-generation sequencing approaches that permit de novo discovery of genomic alterations.

D. Nucleic Acid Sequencing

1. Pre-NGS Technologies for Sequencing

52. Given the role of the genetic code in governing biological function, developing methods of identifying genetic sequences in various biological contexts has been a primary goal of scientific research. Early methods focused on DNA sequencing and technical methods for “reading out” the nucleotide composition of individual DNA strands. Early sequencing methods were time- and resource-consuming and were not suited to scalable applications. These limitations made sequencing large polynucleotides a technical challenge and genomes, basically infeasible. These issues were somewhat ameliorated by the advent of large scale-cloning and/or the parallel sequencing of many regions of DNA that would then be assembled together into a “working draft” of the genome.

53. One of the first sequencing methods, “Sanger Sequencing,” also known as the chain termination method, was developed by Frederick Sanger in 1977. Before the advent of Polymerase Chain Reaction (“PCR”) technology, Sanger Sequencing was performed directly on purified DNA templates, typically from cloned DNA fragments. Sanger Sequencing involved the enzymatic synthesis of DNA strands and their controlled termination using dideoxynucleotides (“ddNTPs”).

54. There were major challenges and limitations to this approach. The need to clone and grow bacterial cultures to obtain sufficient DNA for sequencing made

the process cumbersome and slow. The quality and length of the sequence reads were limited by the efficiency of the cloning process and the resolution of the electrophoresis gel. The method was also less sensitive and less scalable compared to later techniques that utilized PCR for amplification, making it challenging to sequence very small amounts of DNA or conduct large-scale sequencing projects efficiently.

55. The advent of PCR revolutionized Sanger Sequencing. Through PCR, researchers were able to take nucleic acid samples and amplify those samples without the need to clone and grow bacterial cultures. For DNA samples, PCR consists of three main “phases,” dictated in part by the temperature of the reaction mixture: denaturing, annealing, and extending. The denaturation phase separates the double-stranded DNA into single strands. The annealing phase allows for primers to bind to the single-stranded DNA to direct polymerase loading and facilitate the start of the nascent strand. The extension phase allows the polymerase to extend the nascent strand from the primer through the addition of nucleotides complementary to those on the template strand. Completion of all three steps constitutes one PCR “cycle,” after which a copy of the template strand has been produced. By running a series of PCR cycles, the original DNA sample can be exponentially amplified, as the strands produced in each PCR cycle can then serve as template strands in the following cycle. *See* EX2005.0001.

56. Another innovation to Sanger Sequencing was its automation through platforms such as the ABI 3730 DNA Analyzer, which transformed the landscape of genetic analysis by integrating advanced automation and fluorescence-based detection technologies. Sequencing samples were prepared in a mix that included the purified DNA template, a sequencing primer, DNA polymerase, and a mixture of regular dNTPs alongside specially dye-labeled dideoxynucleotides (“ddNTPs”). Each type of ddNTP, which terminates DNA chain elongation upon incorporation, was tagged with a distinct fluorescent dye. This labeling allowed for the simultaneous identification of each nucleotide during the sequencing process, despite the reactions occurring in a single tube. The data collected from the ABI 3730 was processed using software that translated the signals into a readable sequence displayed as a chromatogram, which could be interpreted to identify the DNA sequence. This automated system reduced the manual effort involved in sequencing and increased both throughput and accuracy.

57. Sanger Sequencing was limited to sequencing a single DNA molecule at a time in a sequencing reaction. Even with the advent of automated Sanger Sequencing, this structural aspect of Sanger Sequencing limited its sequencing throughput, making sequencing at scale both costly and logistically challenging. For example, completion of the Human Genome Project took approximately 13 years and \$2.7 billion, while the National Human Genome Research Institute estimated

that sequencing a second human genome using the Sanger Sequencing methods available in 2003 would cost another \$50 million. *See* EX2006.0001, 06. These technical limitations rendered general application of Sanger Sequencing to large or complex genomic sequencing tasks extremely expensive and time consuming, limiting genome-scale activity (in the US at least) to a dozen or so nationally-designated sequencing centers funded through large infrastructure grants from NIH, DOE, and the like.

2. Next Generation Sequencing

58. Coinciding with the completion of the Human Genome Project in the early 2000s, great scientific and public interest in a deeper understanding of the genome led to the commercial development of more affordable and scalable techniques for genomic assessment. These efforts resulted in a series of novel technologies and methods collectively termed “Next-Generation Sequencing (‘NGS’) Technologies.” EX2007.0001. As compared to traditional sequencing methods such as Sanger Sequencing, NGS technologies were characterized as cheaper, more efficient, and capable of assessing both larger genetic samples and longer portions of the genome in high fidelity. As compared to prior methods, NGS sequencing was defined in part by its “massively parallel” nature—i.e. its ability to process tens of thousands to millions of DNA sequences at the same time. Most NGS technologies utilized a “sequencing-by-synthesis (SBS)” strategy.

EX2008.0001-02. SBS leveraged the sequential nature of genomic information to assess each nucleotide in a sequence in order. Polymerases were coupled to a signaling output that allowed for the identification of the incorporated nucleotide.

59. Compared to traditional sequencing methods, early NGS technology afforded researchers several benefits. Due to their design, NGS systems allowed researchers to sequence thousands of reads in tandem in an automated manner, increasing both the platform capacity and the depth and coverage of the generated sequencing data. This made genetic sequencing both cheaper and more scalable as compared to prior methods. The parallel sequencing paradigm allowed researchers to sequence multiple genes and assess millions of variants simultaneously, while reducing the required DNA input and, due to the scaled approach, decreasing sequencing times. These factors led to an overwhelming increase in the amount of sequencing data generated in the course of research and a deeper understanding of the structure and content of many genomes across species. EX2007.0001.

60. Pyrosequencers, such as the 454 sequencers, were among some of the first set of platforms that harnessed this “second generation” sequencing technology. Illumina produced the most commercially successful sequencing instruments in this class, which also included Ion Torrent, Helicos, and ABI/Lifetech SOLiD (among others). Over time, NGS sequencers improved on their ability to process longer read

lengths, which resulted in a “third generation” of sequencers, which included Nanopore and PacBio sequencers.

61. As of January 26, 2012, the industry had largely shifted from first generation NGS to second generation platforms, with third generation NGS on the horizon. At the time, NGS platforms exhibited a higher error rate than Sanger Sequencing per read. *Id.* Additionally, compared to traditional methods, many NGS methods generated significantly shorter individual sequencing reads, while long-read sequencing approaches remained expensive and resource intensive. *Id.* These limitations complicated the application of NGS technology.

62. In addition to these limitations, the sheer volume of genetic material that could now be sequenced exacerbated issues with being able to isolate specific regions of genetic material for analysis. EX2008.0003-04. In an effort to resolve these issues (among other issues), methods were developed to narrow the window of genomic assessment, such as through “targeted enrichment.”

E. Target Enrichment

63. The inherent size and complexity of the genome have presented longstanding issues when attempting genetic sequencing. Often, researchers and clinicians are interested in select regions of the genome, such as those known to be associated with particular diseases or looking to compare a tumor DNA to normal DNA to detect changes in specific genes, that are minute in size compared to the

genome as a whole. Sequencing methods can struggle to sequence smaller regions of interest in an efficient manner while ensuring sufficient signal (region of interest) to noise (signal from other genomic regions) ratios in the sequencing data and minimizing off-target effects (reactions at other regions of the genome outside the area of interest), all of which are necessary to generate accurate sequencing data. Researchers recognized that NGS “possessed a fundamental weakness—the inability to easily target specific regions of a genome.” EX2009.0003.

64. In order to minimize these issues, NGS pipelines were integrated with targeted enrichment approaches designed to enrich a genomic region of interest relative to the rest of the genome prior to sequencing. As understood in the art, the term “enrichment” means to selectively increase the proportion of one part of a sample or reaction mixture over other portions of the sample or reaction mixture. *See, e.g.*, EX2010; EX2011 (describing the use of various prior art target enrichment methods to enrich for target regions). Targeted enrichment methods sought to amplify the nucleotides corresponding to the region of interest while removing or minimizing those reflecting unwanted regions of the genome, thereby enriching the amount corresponding to the signal of the region of interest relative to the rest of the genomic sample.

65. As of the priority date of the '012 and '108 patents, three major categories of target enrichment methods existed: capture-by-hybridization,

polymerase chain reaction (PCR)-based methods, and capture-by-circularization. *See* EX1001.0016 (1:39-47). Each is discussed in further detail below.

1. PCR-based Target Enrichment Methods

66. PCR-based target enrichment methods, as the name suggests, employed PCR to enrich regions of interest from a nucleotide sample prior to sequencing. *See* EX1001.0016 (1:46-50). Primer pairs were designed to target a specific region in a nucleotide sample such that the region was amplified by PCR, while nucleotide sequences outside of the region defined by the primer pair were not amplified. The method could be scaled combining groups of primer pairs that targeted discrete regions to amplify multiple target regions simultaneously, a method termed “multiplex PCR.” *Id.* Multiplex PCR was useful for targeting small-to-medium-sized genomic regions. PCR-based enrichment was often quicker and more cost-effective than hybridization-based capture approaches but was generally suitable for smaller genomic regions due to limitations in multiplexing capacity and primer design. *See* EX1001.0016 (1:51-53).

67. PCR approaches required that sequences within or near the region of interest were known such that primer pairs could be designed to target the region, often precluding true exploratory studies. *See* EX1001.0016 (1:46-50). Additionally, primers were often not entirely specific to the primer target sequence (the exact complementary sequence of the primer) and could bind to genomic or

complimentary DNA with similar, but not exact, sequence homology. *See* EX1001.0016 (1:51-53). When sequencing regions of a genome, this issue led to off-target binding to similar sequences outside the region of interest, both generating confounding sequence products that made sequencing interpretation difficult (or impossible) and sequestering primers that would otherwise bind to the actual target sequence. Further, because both the genome and transcriptome are characterized by frequent repetitive sequences, primers designed to target a sequence in a region of interest could inadvertently bind to the same sequence elsewhere in the genome, leading to further off-target binding. EX2012.0002. As such, primer-based enrichment methods were often characterized by low specificity and high sequencing background noise. These issues were more pronounced with NGS where the platforms could not target or filter samples. *See, e.g.*, EX2013.0006 (“All PCR-based NGS systems share the common disadvantage of bias introduced during amplification. . . . bias [is] introduced during amplicon library preparation.”).

68. Petitioner, which designed multiplex PCR kits at the time, published prior art handbooks discussing these concerns. For example, in the October 2010 QIAGEN Multiplex PCR Handbook, Petitioner explained that “PCR is an exquisitely sensitive technique that can be used to amplify and detect even a single copy of a nucleic acid sequence,” but that “amplification of such a low number of

target sequences is often limited by the generation of nonspecific PCR products and primer-dimers.” EX2014.0037.

69. In addition to the specificity issues discussed above, PCR-based target enrichment methods suffered from design issues that limited their scalability. *See* EX1001.0016 (1:51-53). PCR-based target enrichment methods employed highly parallel PCR amplification, which required that each target sequence corresponded to a pair of unique, sequence-specific primers. *See* EX1001.0016 (1:48-53). At the time, researchers recognized that “primer design is a critical step in all kinds of RT-PCR methods to guarantee specificity and efficiency of a target amplicon.” EX2015.0001.

70. The prior art at the time taught that it was necessary to use primer pairs rather than a single target specific primer. For example, in 1999, Matz reported issues with “amplification produced by a single primer” and proposed PCR suppression methods to minimize such amplification. EX2016.0001. As another example, in 2008, Bru reported that a single primer mismatch could “greatly decrease PCR efficiency” and taught that “the use of multiple sets of primers targeting different subgroups may be preferable when the sequence polymorphism of the targeted gene family is high.” EX2017.0004. Unfavorable sequencing outcomes using single target-specific primers led researchers to outright reject their use, including one research group that wrote:

While the specificity of individual primers may be testing 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.*** In our experience, it is usually necessary to design, synthesize, and validate several primer pairs, until a set is obtained that generates no primer dimers and results in near 100% amplification efficiency.

EX2018.0002 (emphasis added). Other researchers turned to other techniques entirely, such as hybrid capture, to avoid the use of PCR primer pairs. *See, e.g.,* EX2019.0005 (“Unlike PCR-based enrichment methods where both the 3' and 5' ends of targeted DNA must be specified through the use of template-specific primers, hybrid capture allows for the enrichment of sequences containing only partial homology to the viral insertion site.”). Before the claimed inventions, the widely held view in the field was that primer pairs were required to facilitate effective enrichment through amplification, especially PCR amplification. In fact, I am aware of no instances before the priority date in which one target-specific primer was used in connection with PCR amplification to enrich for target sequences.

71. While possible to pool primer pairs together, multiplexing faced several issues. For example, different primer pairs sometimes required different amplification parameters (i.e., temperature and duration settings that facilitate efficient amplification). *See* EX1001.0016 (1:51-53). These diverse amplification parameters were difficult, if not impossible, to uniformly account for in a given PCR as the amplification conditions were often set and held consistent throughout the

PCR cycles. Additionally, pooling multiple primer pairs in the same PCR reaction compounded the issues with primer specificity, as previously discussed. Similarly, pooling multiple samples could lower primer sensitivity on a per-sample basis, as multiple samples competed for primer pairs. Moreover, the introduction of more and varied primers exacerbated the issue of primer dimers, a phenomenon wherein primers bind and amplify each other rather than the true primer target sequence, generating unwanted PCR byproducts and sequestering primers, thereby lowering amplification efficiency. EX2020.0001.

72. In part to address these limitations of multiplex target enrichment by PCR, researchers developed an enrichment method known as “microdroplet-based PCR enrichment” (“microdroplet PCR”) which could be performed using microfluidic devices. *See* EX1001.0016 (1:53-58). Microdroplet PCR required the generation of small solution droplets that contained discrete primer pairs designed for the genomic regions of interest. *Id.* Fragmented DNA samples and PCR reaction mix components could then be introduced into the droplets via a microfluidic chip, which maintained the individual integrity of the primer droplets, generating thousands of discrete PCR reactions while maintaining primer-pair separation. Following targeted enrichment, the droplets could be broken to mix the enriched products into a general solution for sequencing.

73. Microdroplet PCR demonstrated comparable accuracy and coverage to singleplex PCR sequencing while limiting issues with primer specificity and primer-primer interactions, which are characteristic of other multiplex PCR-based target enrichment methods. However, microdroplet PCR required highly sophisticated, specific instrumentation to run. *See* EX1001.0016 (1:58-63). Further, microdroplet PCR required large numbers of primer pairs when enriching for multiple regions of interest. *Id.*

74. Similar methods were proposed where “several dozen primer pairs can be used together effectively in a multiplexing reaction” by running the reactions in parallel or through microfluidics PCR chips that would allow several thousand singleplex PCRs in parallel. EX2021.0007.

75. Other researchers sought ways to optimize pre-existing multiplex PCR methods by optimizing primer pairs. For example, Shen reported a primer design program called MPprimer, which was designed to address issues with primer specificity for primer pairs. EX2022.0001. Researchers for Petitioner even published on a “prerequisite for successful multiplex PCR [being] the design of optimal primer pairs,” offering publications to help consumers design optimal primer pairs. EX2023.0005.

2. Capture-by-Hybridization

76. The second major category of enrichment methods was capture-by-hybridization. *See* EX1001.0016 (1:39-47). Like the PCR-based methods discussed above, capture-by-hybridization sought to generate samples containing primarily the genomic region of interest while limiting the presence of extraneous genetic information. Unlike the PCR-based methods, which seek to amplify the signal of the region of interest by copying the region of interest, capture-by-hybridization methods utilize long oligonucleotide chains, termed “probes,” that are designed to hybridize directly to sequences that define, overlap substantially with, or are in close proximity to the region of interest. *See* EX1001.0016 (1:64-66). The probes could then be selectively isolated, allowing the genomic regions of interest to be physically separated from the unwanted genetic material. *See* EX1001.0016 (1:64-2:4).

77. As capture-by-hybridization relied on target-specific probes to sequester genomic regions of interest, it was generally less susceptible to off-target amplification noise compared to PCR-based enrichment methods. However, capture-by-hybridization typically required larger amounts of input DNA (EX1001.0016 (2:4–10)), as well as more complex probe designs and a lengthy, multi-step workflow for capturing and selecting the target regions. While these probe-based strategies could theoretically cover large panels of genomic sites, practical implementations were often constrained by higher costs associated with

synthesizing individual oligonucleotide probes. *Id.* In addition, capture-by-hybridization could exhibit bias toward repetitive elements in the genome—these repeated sequences can cross-hybridize to the capture probes, leading to over-enrichment of repetitive regions and creating unbalanced coverage in the resulting sequencing data. EX2024.0001.

3. Capture-by-Circularization

78. The third major category of enrichment methods was capture-by-circularization. *See* EX1001.0016 (1:39-47). Capture-by-circularization methods utilized linear nucleotide probes designed such that both ends of the probes hybridized at or near adjacent regions in a genomic region of interest. *See* EX1001.0016 (2:11-16). When properly hybridized, the region between the hybridized regions bound by both ends of the probe could then be copied into the probe while joining the two ends of the probe to create a circle, a process termed “gap fill polymerization.” *Id.* Probe circularization allowed for the selective enrichment of circularized probes by filtering out linear probes and probes that did not circularize properly. Following selection, circularized probes could be re-linearized and the copied region of interest could be further amplified by PCR. *See* EX1001.0016 (2:16-18).

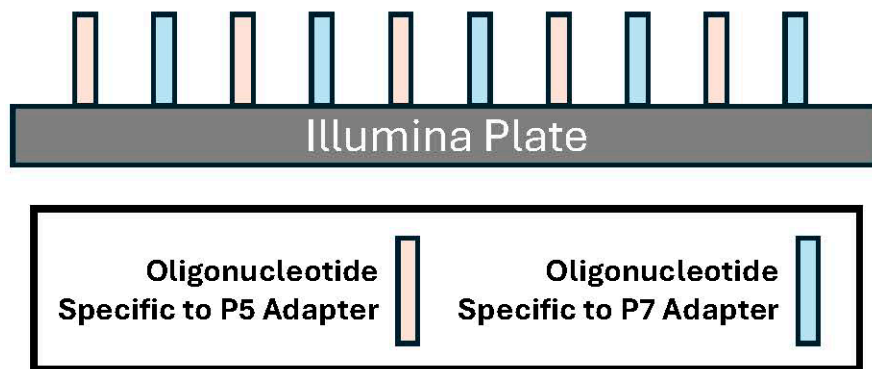
79. Due to the multiple hybridization approach, capture-by-circularization was highly specific for the target region of interest. However, capture-by-

circularization probes exhibited a lack of consistent binding to the desired target region of interest, resulting in a variable amount of sequence coverage. *See* EX1001.0016 (2:18-24). Further, the large size of the probes limited the amount of sequencing real estate for the sequences of interest in a given sequencing read, as regions of the probes themselves often took up a sizable portion of the generated sequencing read.

F. DNA Hybridization Microarrays and NGS Platforms Rely on Different Technology

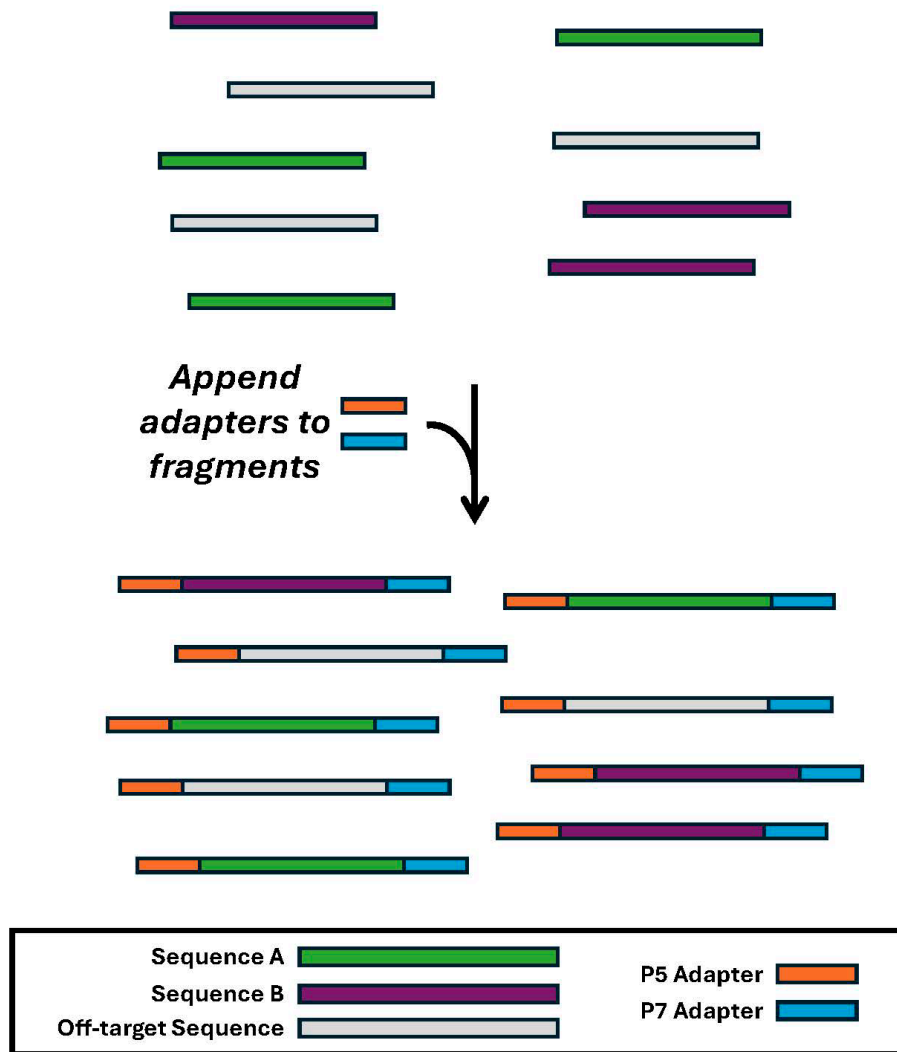
80. As explained above, researchers utilized various methods to understand genetic information, including genotyping through hybridization arrays and NGS platforms. The below examples illustrate the key differences.

81. The surfaces of NGS platforms are designed to bind to universal adapter sequences introduced during sample preparation. EX2007.0004, *see also* EX2030.0002. Taking Illumina as an example, each flow cell contains a dense lawn of two distinct surface-bound oligonucleotides—commonly referred to as P5 and P7 capture oligos—numbering in the millions to billions across the flow cell. These capture oligos are complementary to the adapter sequences (e.g., Illumina’s P5 and P7 primers) ligated to DNA fragments during library preparation, as shown in the image below. By anchoring the prepared DNA fragments to the flow cell surface via these universal adapters, the Illumina platform enables massively parallel sequencing of numerous distinct sequences simultaneously.



82. If a researcher wanted to sequence their samples with Illumina, the researcher would need to prepare their sample library for sequencing by incorporating the adapters containing the Illumina universal primers at the ends of their nucleic fragments, as shown in the below image.³ EX2030.0002.

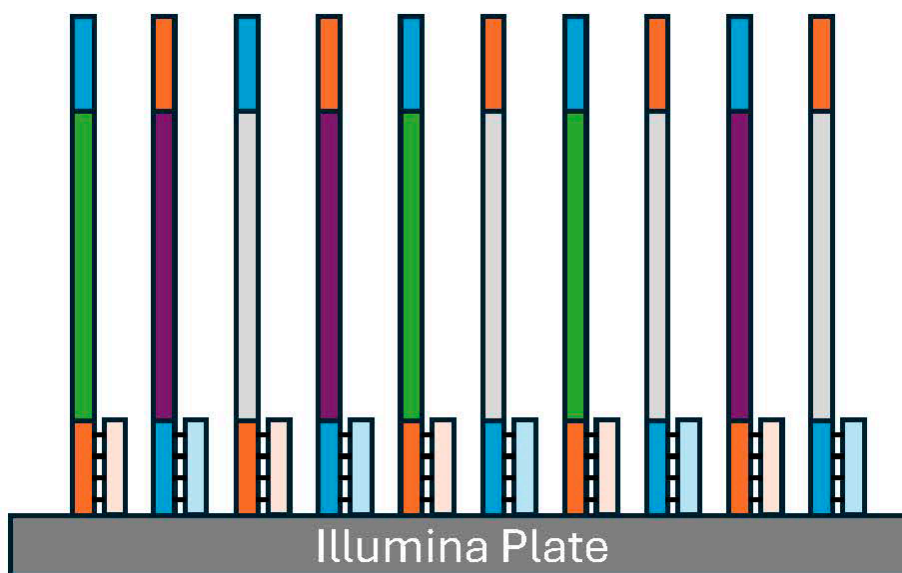
³Note that “Sequence A,” “Sequence B,” and “Off-target Sequence” represent three hypothetical distinct nucleic acid fragments.



83. These samples are then loaded for sequencing, and the adapters containing the universal primers could be used to bind the fragments to the surface of the sequencer, as depicted below.⁴ EX2007.0004. These same primers could then

⁴ This graphical representation is a simplified depiction of how sequences are arranged on an Illumina sequencing surface. It does not reflect the full incorporation of sequences by bridge amplification.

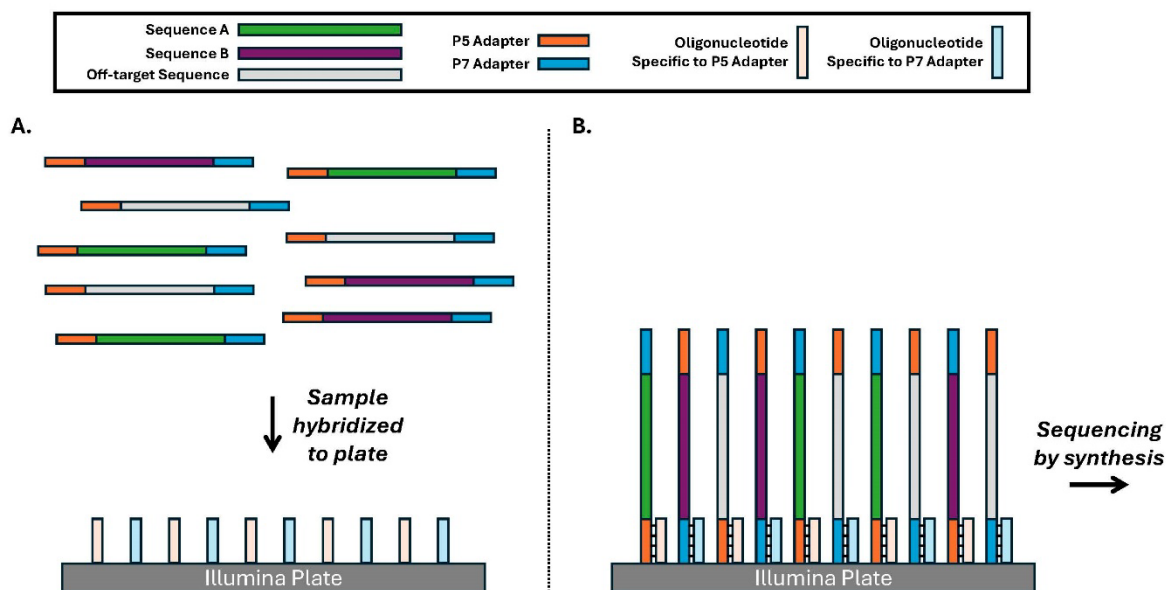
be used for “bridge amplification”—a process by which sequences hybridized to the surface of the sequencer are amplified on the surface to generate clusters of the same sequence prior to sequencing. *Id.* The P5 and/or P7 primers could then be used as starting points for the Illumina platform to read the fragment’s sequence. EX2007.0003-05, *see also* EX2030.0002.



84. Because NGS platforms engaged in massively parallel sequencing, meaning that many different sequences could be sequenced simultaneously, it would have been infeasible to bind samples to the sequencer platform through target-specific probes. In fact, a key feature of the NGS platforms is that the use of common primers enables the binding of many distinct sequences, allowing for massively parallel sequencing. EX2008.0001-02.

85. However, because the surface probes of NGS sequencers are not target-specific, all fragments that contain the universal primer sequences will be sequenced. This generates a significant amount of data about all of the sequences included in the sample. If a researcher was interested in a specific nucleic acid sequence, the researcher would need to prepare sequencing libraries that enrich for the target sequences to avoid the considerable noise from data generated from all the sequences that are not of interest.

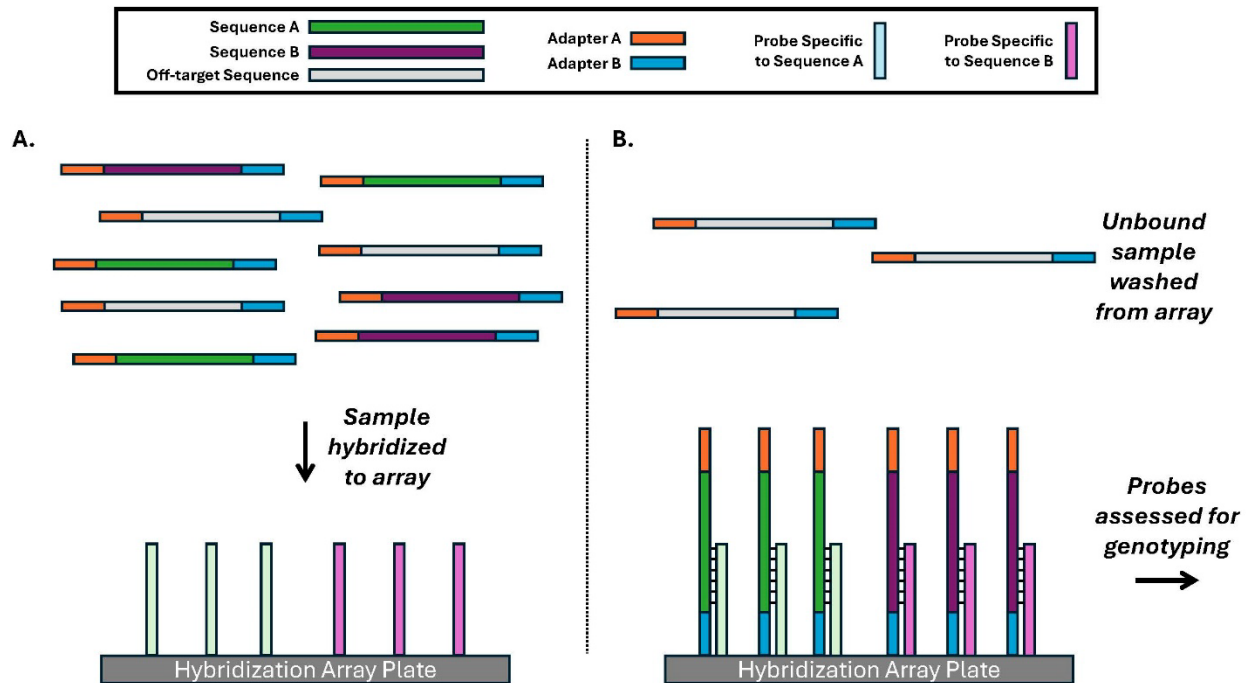
Sequencing by Illumina⁵



⁵ This graphical representation is a simplified depiction of the Illumina sequencing process. It does not reflect the full incorporation of sequences by bridge amplification.

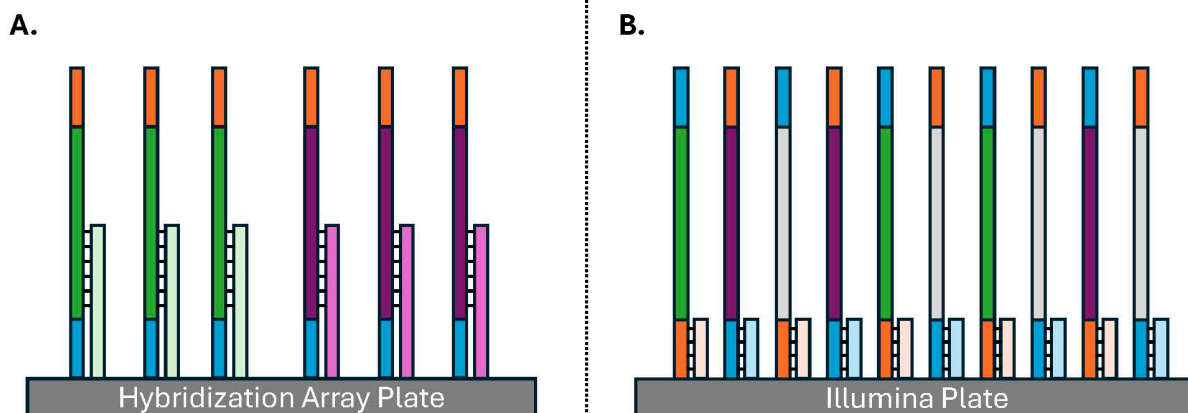
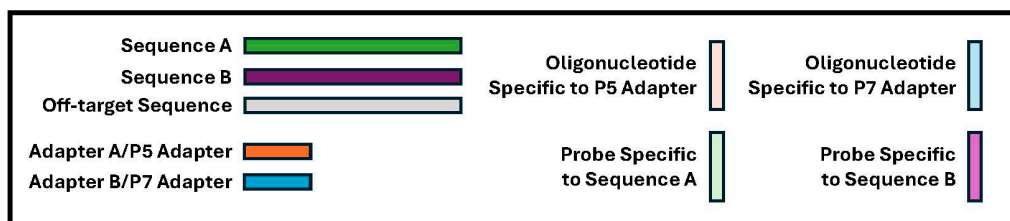
86. In a hybridization array, on the other hand, each probe is highly specific to a target, as discussed above. *See supra*, ¶¶42-44. If a researcher was screening a nucleic acid sample for the presence of certain SNPs, that researcher would utilize a hybridization array with probes complementary to the genomic sequence surrounding that SNP (what would be referred to as the genomic locus). EX2004.0009-11, *see also* EX2031.0002, EX2035.0003-04. After the sample was prepared, the researcher would run that sample over the array. EX2004.0004. If the locus was present, the nucleic fragment would bind to the probe and produce a detectable signal. *Id.* Through the use of software specific to that array, the researcher could then ascertain whether the locus and SNP were present in the sample. EX2004.0016-17.

Genotyping by Hybridization Array⁶



87. As depicted below, hybridization arrays rely on highly specific probes designed to recognize particular nucleic acid sequences, whereas NGS platforms (e.g., Illumina) depend on universal adapters for binding many distinct fragments.

⁶ This graphical representation is a simplified depiction of genotyping by hybridization array. It simplifies the number of distinct hybridization probes present on the array plate. As explained above, a given array plate would usually contain hundreds of billions of probes (including the duplicates of the same probe) as depicted in the graphical representation. Each group of probes would be specific to a particular SNP.



Because hybridization arrays incorporate hundreds of billions of target-specific probes, concerns about off-target hybridization are inherently minimized. In contrast, NGS platforms lack such target-specific surface probes and will sequence any fragment in the library that carries the correct adapter sequences—whether or not the researcher is interested in that fragment. This can result in unwanted or non-relevant reads, increasing both data volume and the complexity of downstream analysis.

V. THE PERSON OF ORDINARY SKILL IN THE ART

88. I understand that QIAGEN proposes the following definition for a person of ordinary skill in the art (“POSA”):

A person of ordinary skill in the art as of the earliest priority date of the ’012 patent (January 26, 2012) would have had (i) a Ph.D. in molecular biology, molecular genetics, bioinformatics, biochemistry, or a related field and at least two years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and sequencing experience, including but not limited to high-throughput sequencing technologies or (ii) a Master’s degree in one of the same fields with at least four years of relevant applied research and/or industry experience in the field of nucleic acid library preparation and high-throughput sequencing technologies.

Petition, 13-14 (same for the ’108 patent). I disagree with QIAGEN’s proposed level of education and specific experiences.

89. Petitioner’s requirement that the POSA possess a Ph.D. with at least two years of relevant applied research or work experience or a Master’s degree with at least four years of relevant applied research or work experience exceeds the ordinary skill in the art. The claims of the ’012 and ’108 patents are directed to methods for sequencing an enriched nucleic acid sequence of interest. The methods describe a series of steps for targeting a sequence of interest in a nucleic acid sample, enriching for that sequence of interest, and sequencing the amplified products using an NGS platform. There is no reason to require that the POSA possess a Ph.D. or M.S. to practice the claimed methods. In my experience, lab technicians and

graduate students regularly perform methods such as these in various laboratory environments. These individuals often possess B.S. degrees.

90. Recognizing that a person holding a Ph.D. in a field related to molecular biology is likely to possess more work experience in the relevant technology than individuals with a B.S. or M.S. degree, it makes sense that a POSA holding a B.S. or M.S. degree would also have approximately three-to-five years of experience working in a molecular biology laboratory. It does not make sense, however, to set the bar as high as to require a Ph.D. and years of additional work experience on top of that.

91. Under either definition of a POSA, I possessed the relevant qualifications as of January 26, 2012. *See supra*, ¶¶11-18.

VI. THE PATENTED INVENTIONS

92. Titled “Compositions and Methods for Targeted Nucleic Acid Sequence Enrichment and High Efficiency Library Generation,” the ’012 and ’108 patents are broadly directed to “methods, compositions and kits for targeted nucleic acid sequence enrichment in a nucleic acid sample and for high efficiency nucleic acid library generation for next generation sequencing (NGS).” EX1001.0001; EX1009.0002. The patents are specifically directed to methods “for the selective enrichment of a plurality of defined target sequences from complex DNA with a set of common primers and adaptors, thus circumventing the need for multiplex PCR

and multiple primer pairs.” EX1001.0018 (6:12-16); EX1009.0018 (6:14-18). The methods improve on the prior art by creating “a simple, low cost, high throughput system for target enrichment and library preparation.” EX1001.0018 (6:25-27); EX1009.0018 (6:27-29).

A. The Claims of the '012 Patent

93. The claimed inventions of the '012 patent are defined in 22 claims. The sole independent claim of the '012 patent, claim 1, is reproduced below:

Claim Element	Claim Language
1[pre]	A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
1[a]	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 a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;

Claim Element	Claim Language
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.

94. The '012 patent contains 21 dependent claims, which are reproduced below:

Claim	Claim Language
2	The method of claim 1, wherein the nucleic acid fragment comprises genomic DNA.
3	The method of claim 1, wherein the nucleic acid fragment comprises cDNA.
4	The method of claim 1, wherein the nucleic acid fragment comprises RNA.
5	The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.
6	The method of claim 1, wherein the one or more oligonucleotides comprise more than one oligonucleotide, and wherein the second adaptor sequence is common to the more than one oligonucleotides.
7	The method of claim 1, wherein the first adaptor sequence, the second adaptor sequence, or both comprise barcode sequence.
8	The method of claim 7, wherein the barcode sequence is at least 8 nucleotides in length.
9	The method of claim 7, wherein the barcode sequence is 12 nucleotides in length.
10	The method of claim 1, wherein the obtaining comprises obtaining a plurality of nucleic acid fragments ligated to a partial duplex adaptor, wherein each partial duplex adaptor of each nucleic acid fragment of the plurality of nucleic acid fragments comprises a barcode, and wherein each barcode is unique.
11	The method of claim 1, wherein the nucleic acid fragment ligated to the partial duplex adaptor is double-stranded prior to step b).
12	The method of claim 11, further comprising denaturing the nucleic acid fragment ligated to the partial duplex adaptor prior to step b), thereby generating a single-stranded nucleic acid fragment

Claim	Claim Language
	comprising the nucleic acid sequence of interest ligated to the first adaptor sequence.
13	The method of claim 1, wherein the polymerase is a DNA polymerase.
14	The method of claim 1, wherein the first strand of the partial duplex adaptor is ligated to a 5' end of the nucleic acid fragment.
15	The method of claim 1, wherein the second strand of the partial duplex adaptor is ligated to a 3' end of the nucleic acid fragment.
16	The method of claim 1, further comprising fragmenting a nucleic acid, thereby generating a nucleic acid fragment; and purifying the nucleic acid fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a).
17	The method of claim 1, further comprising performing bridge amplification of the annealed strand after step e).
18	The method of claim 1, wherein the sequencing comprises use of four labeled reversible terminators.
19	The method of claim 1, wherein the sequencing comprises semiconductor sequencing.
20	The method of claim 1, further comprising fragmenting a nucleic acid, thereby generating a nucleic acid fragment; and performing end repair on the nucleic acid fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a).
21	The method of claim 1, wherein the nucleic acid fragment of the nucleic acid fragment ligated to the partial duplex adaptor in step a) is obtained by performing reverse transcription on an RNA fragment prior to obtaining the nucleic acid fragment ligated to the partial duplex adaptor in step a).
22	The method of claim 1, wherein each end of the nucleic acid fragment is ligated to a partial duplex adaptor.

B. The Claims of the '108 Patent

95. The claimed inventions of the '108 patent are defined in 19 claims. The sole independent claim of the '108 patent, claim 1, is reproduced below:

Claim Element	Claim Language
1[pre]	A method for sequencing an enriched nucleic acid sequence of interest, the method comprising:
1[a]	annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in a nucleic acid fragment, wherein the reaction mixture comprises a plurality of nucleic acid fragments, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest comprises a first adaptor sequence, wherein the one or more oligonucleotides comprise a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;
1[b]	extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment comprising the first adaptor sequence with a polymerase, in the reaction mixture, thereby generating one or more oligonucleotide extension products comprising sequence complementary to the first adaptor sequence at a first end, sequence complementary to the nucleic acid sequence of interest, and the second adaptor sequence at a second end;

Claim Element	Claim Language
1[c]	amplifying the one or more oligonucleotide extension products, in the reaction mixture, using a first primer that anneals to the complement of the first adaptor sequence and a second primer that anneals at its 3' end to a complement of the second adaptor sequence, thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest; and
1[d]	sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.

96. The '108 patent contains 18 dependent claims, which are reproduced below:

Claim	Claim Language
2	The method of claim 1, wherein the nucleic acid fragment comprises genomic DNA.
3	The method of claim 1, wherein the nucleic acid fragment comprises cDNA.
5	The method of claim 1, wherein the first adaptor sequence and the second adaptor sequence are distinct from each other.
6	The method of claim 1, wherein the plurality of nucleic acid fragments comprises the first adaptor sequence, and wherein the first adaptor sequence is common to the plurality of nucleic acid fragments.

Claim	Claim Language
7	The method of claim 1, wherein the one or more oligonucleotides comprises more than one oligonucleotide, wherein the second adaptor sequence is common to the more than one oligonucleotide.
8	The method of claim 7, wherein the first adaptor sequence and/or the second adaptor sequence comprise a barcode sequence.
9	The method of claim 7, further comprising denaturing double-stranded nucleic acid fragments prior to step a).
10	The method of claim 1, wherein the polymerase is a DNA polymerase.
11	The method of claim 1, wherein the sequencing comprises the use of four labeled reversible terminators.
12	The method of claim 11, wherein the sequencing comprises semiconductor sequencing.
13	The method of claim 1, wherein the sequencing comprises nanopore sequencing.
14	The method of claim 1, wherein each of the plurality of nucleic acid fragments comprises the first adaptor sequence at a 5' end.
15	The method of claim 1, further comprising fragmenting nucleic acids prior to step a), thereby generating the plurality of nucleic acid fragments.
16	The method of claim 1, further comprising ligating the first adaptor sequence to a nucleic acid fragment in the plurality of nucleic acid fragments prior to step a), thereby generating the nucleic acid fragment comprising the first adaptor sequence.
17	The method of claim 1, wherein the amplified products comprise a 3' end with sequence complementary to a sequence on a surface.
18	The method of claim 1, further comprising annealing a strand of the products of the amplifying to the sequence on the surface using the 3'

Claim	Claim Language
	end with sequence complementary to the sequence on the surface prior to step d).
19	The method of claim 1, wherein the surface is a surface of a flow cell.

C. Relevant Prosecution History

97. I understand that the patents at issue, the '012 Patent and the '108 Patent, are part of a larger patent family containing additional related patents. I understand that the prior assignee of the patents at issue, NuGEN, filed the first application in the patent family, U.S. Provisional Patent Application No. 61/591,241 on January 26, 2012. EX1001.0001; EX1009.0001. I understand that NuGEN subsequently filed U.S. Patent Application No. 13/750,768 (“the '768 application”), on January 25, 2013. EX1001.0001; EX1009.0001. I understand that U.S. Patent Application No. 13/750,768 issued as U.S. Patent No. 9,650,628 (“the '628 patent”) on May 16, 2017. *See* EX1001.0001; EX1009.0001.

98. I understand that NuGEN filed U.S. Patent Application No. 15/471,785 (“the '785 application”) as a continuation of the '768 application on March 28, 2017. EX1001.0001. I understand that the '785 application issued as the '012 Patent on July 31, 2018. *Id.*

99. I understand that NuGEN filed U.S. Patent Application No. 16/017,340 (“the '340 application”) as a continuation of the '785 application on June 25, 2018.

EX1009.0001. I understand that the '340 application issued as the '108 Patent on December 29, 2020. *Id.*

100. I understand that the '012, '108, and '628 Patents all claim priority to Provisional Application No. 61/591,241, which was filed on January 26, 2012. EX1001.0001; EX1009.0001.⁷ I further understand that, for purposes of this proceeding, Petitioner does not dispute that the priority date as reported on the faces of the '012 and '108 Patents is January 26, 2012. Petition, 7.

101. I understand that during prosecution of the applications that would issue as the '012, '108, and '628 patents, the same examiner rejected the proposed claims arguing that they were obvious over two prior art references: U.S. Patent Publication No. 2005/0142577 (“Jones”) and Tucker et al. “Massively parallel sequencing: the next big thing in genetic medicine” (“Tucker”).

102. I understand that the Applicant traversed the Examiner’s rejections, arguing that a POSA would not have had a motivation to combine Jones and Tucker to practice the claimed inventions with a reasonable expectation of success. I understand that as part of the Applicant’s responses, the Applicant submitted a sworn

⁷ I understand that the '012 and '108 patents share a common specification. Because of this, I sometimes cite to one of the two specifications herein. To the extent relevant, those references apply equally to the other patent.

affidavit by Dr. Andrew I. Brooks, in which Dr. Brooks presented evidence and testimony concerning why a POSA would not have been motivated to adapt a method using a hybridization array for NGS and why a POSA would not have had a reasonable expectation of success. I also understand that Dr. Brooks provided evidence and testimony about the same through his accounts of skepticism and unexpected results.

103. Dr. Brooks was widely known and respected in the industry as being at the forefront of genomic sequencing technology. During his decades of work in the field, Dr. Brooks was the Chief Operating Officer of Rutgers University Cell and DNA Repository (“RUCDR”) Infinite Biologics (in addition to being a long distinguished research professor at Rutgers). At the time, RUCDR was known as the world’s largest university-based biorepositories and one of the largest sequencing laboratories in the country. Dr. Brooks was considered an authority in the field for high throughput sample analysis, having authored numerous publications on the topic. His work included various applied applications to genomic analysis, including diagnostic testing. For example, towards the end of his career at RUCDR, Dr. Brooks develop the first FDA-approved rapid saliva test for COVID-19. The New York Times described this invention as “one of the most reliable means of determining whether someone has the coronavirus.” EX2032.0001. It even

prompted Governor Phil Murphy of New Jersey to call Dr. Brooks “one of the state’s unsung heroes.”

104. Under either Petitioner or Tecan’s proposed definitions of a POSA, Dr. Brooks would have easily met the criteria and would have been considered an authoritative expert on high-throughput sequencing technology.

VII. RELEVANT PRIOR ART

A. Jones (EX1011)

105. U.S. Patent Publication No. 2005/0142577, Methods for Genotyping Selected Polymorphisms (“Jones”) is a patent publication that discloses methods relating “to enrichment and amplification of a collection of target sequences from a nucleic acid sample and methods of analyzing amplified product.” EX1011.0008, [0002]. Jones names three inventors: Keith W. Jones, Michael H. Shapero, and Stephan P.A. Foder. It is a continuation-in-part of U.S. Patent Application No. 10/264,945 (“Jones 2003”).

106. According to Jones, the claimed inventions are directed to “[m]ethods for genotyping polymorphisms using a locus specific primer that is complementary to a region near a selected polymorphism.” EX1011.0001. Jones discloses that the “invention relates to enrichment and amplification of a collection of target sequences from a nucleic acid sample and methods of analyzing amplified product.”

EX1011.0001, [0002]. Jones discloses that “[i]n some embodiments, the invention relates to the preparation of target for array based analysis of genotype.” *Id.*

107. The claims of Jones are directed at methods requiring the use of allele discrimination through hybridization arrays. EX1011.0022. For example, claim 1 requires “hybridizing the amplified extended capture probes to an array of probes comprising allele specific probes for a plurality of the polymorphic positions.” *Id.* As another example, claim 36 requires “hybridizing the amplified fragments to an array of probes comprising probes that are allele specific for allele of each polymorphism in the plurality of polymorphisms.” EX1011.0023.

108. Jones does not disclose any methods of NGS sequencing nor does it make any references to NGS technologies, which were not commercially available at the time.

109. Jones discloses, as a preferred embodiment, the sample preparation method known as “Multiplexed Anchored Runoff Amplification (MARA).” EX1011.0015, [0076]. The MARA method as described in Jones uses locus-specific primers to amplify sequences containing SNPs of interest. EX1011.0015-17. SNPs of interest could be chosen based on several technical criteria, such as whether “the polymorphism is located near a potential priming site (the priming site is where the capture probe hybridizes) for a selected degenerate capture probe, . . . a selected

restriction site is located near the polymorphism, . . . and the polymorphism is between the priming site and the restriction site.” EX1011.0018, [0098].

Jones describes that “[t]he amplified product[s] may be analyzed by hybridization to an array of probes.” EX1011.0015, [0076]. Jones describes hybridization arrays as target sequence specific, wherein the probes “hybridize specifically to one or more SNP containing sequences.” EX1011.0015, [0071]; .0020, [0108].

110. Jones discloses that the preferred embodiment of genotyping samples prepared via the MARA method is with hybridization arrays, most preferably using Affymetrix genotyping arrays. EX1011.0007-08, .0013; [0069], [0076], [0077], [0109]. Affymetrix is the assignee of the patent. EX1011.0001. The named inventors of Jones helped to develop Affymetrix genotyping arrays as employees of the company. *See* EX2034.0001. For example, Keith Jones served as the vice president of assay and application product development at Affymetrix. *Id.*

B. Shapero (EX1006)

111. *MARA: a novel approach for highly multiplexed locus-specific SNP genotyping using high-density DNA oligonucleotide arrays* (“Shapero”) was authored by seven employees of Affymetrix, including the same Michael H. Shapero and Keith W. Jones who were named as co-inventors of the Jones 2003 and Jones

publications. Keith Jones was identified as the senior author. EX1006.0006. The article was published in 2004 in the *Nucleic Acids Research* journal. *Id.*

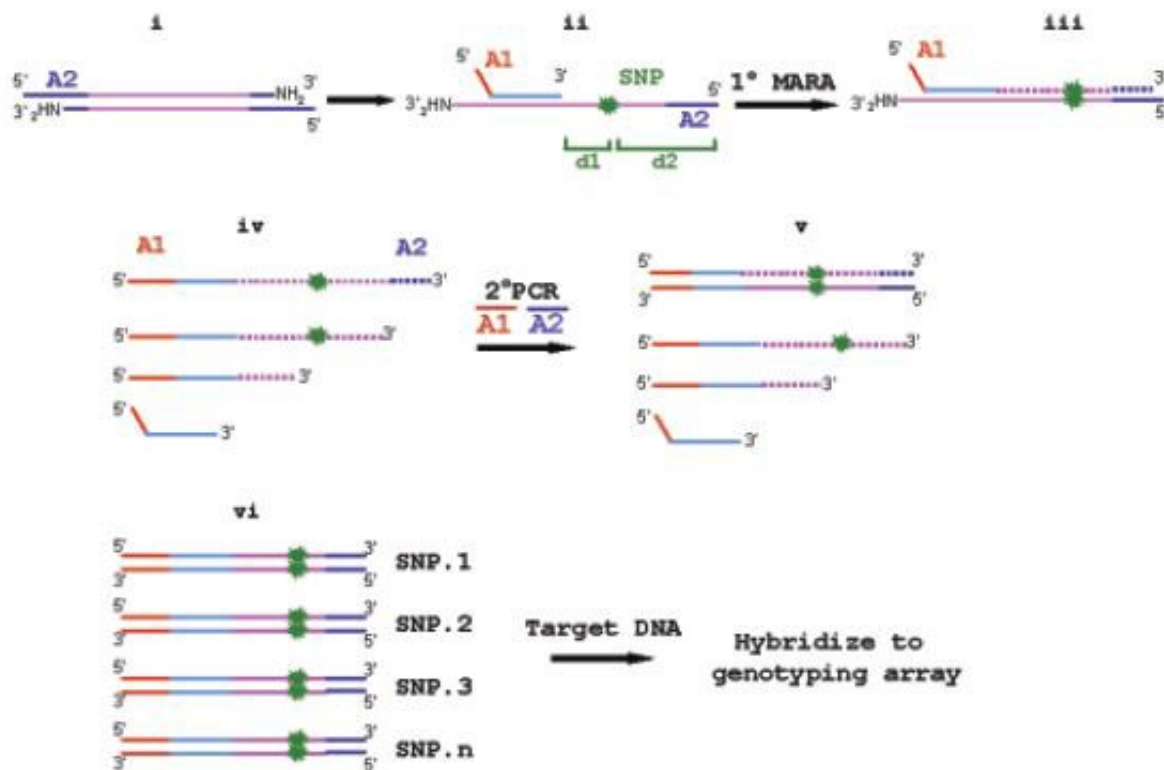
112. As I explain in detail below, Shapero discloses methods for genotyping SNPs using a sample preparation method known as MARA, the same method described as a preferred embodiment of Jones, in conjunction with hybridization arrays. *Id.* Shapero does not disclose any use of NGS methods, platforms, or technologies.

113. As described by Shapero, methods of genotyping in a multiplexed fashion—simultaneous genotyping using multiple primer sets that target different SNPs across the genome—were either technically demanding, limited in their ability to scale beyond 100-plex reactions, or both. EX1006.0006-07. As described above, SNPs are useful markers for studies of genomic function in both health and disease, including complex diseases in which networks of SNPs can be implicated. Shapero was particularly interested in engaging with emerging “haplotype maps,” efforts to link particular groups of SNPs to health outcomes, which Shapero predicted would “identify a standard set of common-allele SNPs that are expected to provide the framework for new genome-wide studies designed to identify the underlying genetic basis of complex diseases, pathogen susceptibility and differential drug responses.” EX1006.0006. Shapero estimated that “the number of SNPs that need to be genotyped for whole genome association studies using large population-based

samples may range from 100,000 to 1,000,000” and therefore “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.” EX1006.0007. To these ends, Shapero sought to develop “a target preparation method for highly multiplexed locus-specific SNP genotyping that far exceeds the capacity of standard traditional multiplex PCR.” *Id.*

1. The MARA Method

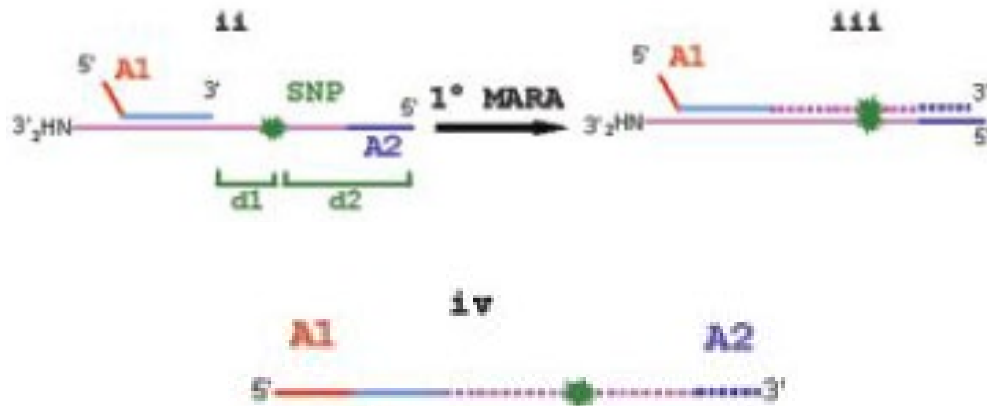
114. Shapero discloses the “Multiplexed Anchored Runoff Amplification (MARA)” method. MARA is disclosed in Figure 1, reproduced below.



EX1006.0009.

115. MARA relies on target-specific primers designed to bind near the loci of interest containing the SNP site. DNA is first fragmented, and “[e]ach biallelic nucleotide is targeted with a single oligonucleotide primer that contains common sequence at the 5' end (designated A1) followed by locus-specific sequence (~25 bases) at the 3' end.” EX1006.0008. Adapters containing the common sequence (designated A2) were added in a non-specific manner, and as such all DNA fragments acquire adapters at both ends of the fragment. EX1006.0007-08.

116. The design of the A1 oligonucleotide primers were “constrained by several parameters” including that “(i) probe sequences tiled on the array (16 bases flanking the SNP on either side) [were] excluded from use in the primers and must not contain the restriction enzyme recognition sequence used to digest genomic DNA in MARA” and “(ii) the total length of the extension product . . . [must be] >100 bases and <750 bases.” EX1006.0008. The single oligonucleotide primers “anneal[ed] to the target and [were] elongated during the first cycle” such that “the adapter sequences ligated to the genomic DNA [were] incorporated into the new extension product provided that elongation [was] complete through the end of the restriction fragment.” *Id.* A representative example of the extension step and extension product are shown below.



EX1006.0009.

117. As all DNA fragments contained adapters, any fragments inadvertently bound by a primer due to off-target primer binding would also result in an extension product. Following the extension step, which includes “[s]ubsequent cycles of amplification [] carried out over a range of annealing temperatures[, a] secondary amplification step [was] then carried out using an aliquot of the primary MARA reaction as template.” EX1006.0008. The secondary amplification step utilized “[u]niversal primers” that “anneal to common sites present in all full-length amplification products” such that “secondary amplification is independent of the sequence of the individual locus-specific amplicons generated in the primary MARA reactions.” *Id.* As such, all extension products, regardless of target specificity, were subsequently amplified during the secondary amplification step.

118. The population of amplified DNA fragments was then assessed by genotyping via a hybridization array. EX1006.0008-09. As previously described, hybridization arrays contain hundreds of billions of oligonucleotide probes designed

to be complementary to the DNA fragments containing the SNPs of interest. As such, only amplified DNA fragments with sequences complementary to the array probes are bound by the array and subsequently genotyped. Amplified DNA fragments not specific to the array probes, including fragments generated by off-target primer binding, are not bound by the array. Instead, those fragments are washed from the array following hybridization and are not reflected in the subsequent genotyping. Following hybridization, the hybridized arrays were stained and scanned to capture the resulting probe signal, and algorithms was employed to make genotyping calls. *Id.*

119. As the MARA workflow was designed for genotyping via a hybridization array, “MARA [did] not require absolute specificity of primer annealing and elongation since target recognition and allele discrimination is achieved through hybridization to high-density arrays.” EX1006.0008-09. Shapero recognized that “[w]ith MARA, allele discrimination is achieved by hybridization to arrays containing SNP-specific complementary sequences rather than a universal array which requires the use of tags or zip codes attached to the primers for genotype de-convolution.” EX1006.0012. Thus, according to Shapero, “the requirement for absolute specificity of primer annealing to target sequences in genomic DNA is alleviated.” *Id.* Shapero further predicted, based on “[t]he theoretical sequence complexity of target DNA generated by MARA” and the genotyping capacity of

high-density sequencing arrays, that “even if the primers contribute to non-specific amplification products, the complexity should not reach a level that would affect array hybridization.” *Id.* Indeed, Shapero made clear that it was the combination of MARA “with a method for highly parallel allele discrimination, such as high-density DNA oligonucleotide array hybridization, [that] afford[ed] a level of locus-specific SNP genotyping that [was] not readily accessible through traditional target preparation methods such as multiplex PCR.” *Id.*

2. Shapero Validates MARA Using Genotyping Array Results

120. In order to assess the viability of MARA, Shapero used the method to genotype different samples using multiple different arrays. The DNA for each MARA assay was first digested using restriction enzymes that generated fragments known to be near SNPs of interest. EX1006.0008-10. In order to assess the quality of the genotyping generated using MARA, Shapero employed a defined scoring system. EX1006.0009-10. Specifically, Shapero reported the genotyping results as (1) a “discrimination score” for a given probe pair, wherein meeting a threshold score “serves as a measure of detection of DNA target sequences,” (2) the “call rate” (the “percentage of successful genotype calls within a DNA sample”), and (3) the “concordance” (a “comparison of MARA genotype calls with WGS [(whole genome sampling assay)] genotype,” which in Shapero served as a metric for

consistency between MARA genotype calls and previously published WGS genotype calls). *Id.*

121. Shapero first validated MARA using a 250-plex MARA assay. EX1006.0009-10. Primers were designed to target known SNPs that exhibited “reproducible high call rates” so that “genotype call rates [could be used] as a surrogate for the presence (successful primer) or absence (unsuccessful primer) of MARA-generated target DNA.” EX1006.0009. DNA samples from nine distinct individuals were genotyped using the MARA protocol. *Id.* Because “[a] small number of primers target amplicons containing more than one SNP tiled on the array,” Shapero predicted that 278 SNPs would be present in the amplified products assessed by hybridization array. *Id.* Shapero used a “predecessor array” that “used the same probe sequences and tiling strategy to generate genotype calls as the commercially available Affymetrix GeneChip 10K Mapping Xba_131 Array.” EX1006.0008.

122. Assessing the SNPs via hybridization array, “99.4% of the SNPs targeted by locus-specific primers across nine individuals had a mean DS > 0.08,” indicating the bulk of the array probes “detect[ed their corresponding] DNA target sequences.” EX1006.0009-10. Shapero further reported a mean call rate of 96.2%

and a mean concordance of 98.6% across the nine DNA samples.⁸ EX1006.0010. Shapero compared these results to control samples where the MARA assay was conducted, but the locus-specific primers were omitted, meaning that no extension or amplification of the DNA sample took place. *Id.* When the MARA assay was conducted in the absence of the locus-specific primers, only 6.6% of the SNPs had a mean discrimination score above the threshold. *Id.* Similarly, in the absence of MARA preparation, Shapero reported a mean call rate of 6.3%, and noted that “only

⁸ Concordance rates are a common way in the industry to report how one instrument performs in genotyping a sample compared to reference genotypes. Affymetrix published that the standard concordance for the GeneChip Mapping 10K Xba 131 Array, which Shapero identified as the analogous array to the predecessor array used in Shapero, is greater than 99.6%. EX2033.0002. A POSA would not read the difference between 98.6% for the 250-plex results in Shapero and 99.6% as a simple difference of 1%. Instead, a POSA would consider these numbers based on the percentage of discordance, which is an indicator of error. Affymetrix reported a 0.4% discordance rate for the general use of the array. Through the method reported in Shapero, Shapero reported a 1.4% discordance, which is almost four times higher than standard discordance. This means that the arrays, as used in Shapero, exhibited higher error rates than standard for the array.

five of these SNPs were called across at least five of the nine DNA samples.” *Id.* This comparison demonstrated that “that the presence of locus-specific primers allows specific target sequences to be amplified, and in the absence of primers, only small quantities of non-specific products are generated.” *Id.* In other words, a small amount of the primers in the MARA reaction generated extension products that were subsequently amplified and detected on the array. *Id.*

123. Shapero then “increased [the multiplexing level] above 250 primer-plex by the addition of 500 primers to the original MARA 250-plex reactions,” raising the total multiplex reaction to 750 primers. *Id.* The array was designed such that only 500 primers generated targets that could hybridize to the array, evaluating 535 SNPs. *Id.* The 750-plex MARA assay resulted in 99.0% of the SNPs achieving a mean discrimination score above the threshold. *Id.* Conversely, the controls indicated that 4.0% of SNPs achieved a mean discrimination score above the threshold when the primers were removed from the MARA assay. *Id.* Similarly, the 750-plex MARA assay achieved a mean call rate of 95.4% and a mean concordance of 98.7% (1.3% discordance) across the nine DNA samples, while the same assay in the absence of the locus-specific primers resulted in a mean call rate of 3.6%. *Id.*

124. Finally, “[i]n order to assess higher levels of multiplexing,” Shapero designed “a new array [] containing 8936 SNPs from human chromosome 21.” EX1006.10-11. Shapero focused on a “total of 4365 oligonucleotides [locus-specific

primers] . . . targeting a total of 4978 SNPs tiled on the array.” *Id.* Using seven DNA samples, Shapero prepared genotyping libraries using these primers via MARA in two ways as, (1) a single bulk reaction containing the 4365 locus-specific primers and, (2) by randomly pooling the locus-specific primers into four groups consisting of 1113, 1140, 1056 and 1056 locus-specific primers prior to the MARA assay (referred to as the “1100-plex(x4)” group). *Id.* Both preparations were then assessed via the designed hybridization array. *Id.* Shapero applied a filter system to the results to group them into “pre-filtered” and “post-filtered” groups, wherein “post-filter subsets of the 4978 SNPs were identified using selection criteria that required at least a 70% (5/7) call rate across the seven DNA samples.” EX1006.0011. In order to assess concordance, Shapero compared the genotype results to public data from Perlegen Sciences. *Id.* Unlike the prior 250- and 750-plex assays, Shapero did not report discrimination scores. I have prepared a table summarizing this filtering below (see EX1006.0010-12 for Shapero’s reporting of the data).

Samples	SNPs	Original SNPs (%)	Call Rate (% Average)	Concordance (%, Average)
Bulk Reaction (Pre-filter)	4976	100	86.4	98.1
Bulk Reaction (Post-filter)	3908	78.5	96.8	99.1
1100-plex(x4) (Pre-filter)	4976	100	84.2	98.5
1100-plex(x4) (Post-filter)	3807	76.5	96.0	99.2

125. As shown in the table above, approximately 25% of the SNPs were not called with enough consistency across samples to meet the 70% call rate threshold. *Id.* When these SNPs were included in the analysis, the overall SNP call rate was 86.4% and 84.2% for the bulk and 1100-plex(x4) samples, respectively. *Id.* When the filter parameter was applied and the lower call rate SNPs were excluded, the average call rates increased to 96.8% and 96.0%, respectively. *Id.* Without filtering, the concordance rates were 98.1% (1.9% discordance) and 98.5% (1.5% discordance), respectively. When compared to the array's standard concordance rate of over 99.6% (0.4% discordance), this data showed error rates four-to-five times higher than the standard. From this experiment, Shapero concluded that "at both multiplex levels, over 3500 independent primers are generating specific target sequences" and that "~75% of the input primers function at multiplex levels >1000 bp." EX1006.0011-12.

126. Shapero evaluated several parameters in an attempt to characterize the approximately 25% of calls that fell below the call rate threshold, noting "[t]here were no observable differences between the groups with regard to G:C% of the primers, G:C% of the probes tiled on the array, and G:C% and length of the Sau3AI genomic DNA restriction fragments," suggesting G:C% was not a factor. EX1006.0011. Shapero disclosed there was "a difference in the length of the extension products, with a higher relative percentage of the SNPs belonging to the

discordant group present on extension products in the range of 600–800 bp,” but did not ascribe this difference as leading to a lower call rate. EX1006.0011-12. Shapero further noted that “the overall primer conversion rates do not differ significantly between 1100 primer-plex (x4) and 4365 primer-plex, suggesting that non-specific primer-primer interactions at the higher multiplex level may not solely be responsible for failed target generation.” EX1006.0012. Ultimately, Shapero did not provide an explanation for the failed target generation. At best, the Shapero data confirmed that the MARA method would work with a hybridization array; however, Shapero did not address how this method may be used for other purposes and did not provide explanations for the higher error rates.

C. Syvänen (EX1012)

127. Syvänen is a 2001 review article concerned with different methodologies for SNP genotyping. Syvänen pre-dates the advent of NGS platforms and does not describe any NGS methods or platforms. Syvänen discusses the role of SNP analysis in studies of disease pathology and as a method of clinical diagnostics. Syvänen “review[s] the current state of the art of SNP-genotyping technology, with an emphasis on how amenable the different methods are to multiplexing to increase throughput and bring down the costs of the assays.” EX1012.0002. Syvänen describes SNP-genotyping methods as underpinned by at least one of six biochemical processes. EX1012.0003. Syvänen further characterizes the features of several SNP-genotyping methods as shown below.

Table 2 | **Features of SNP-genotyping methods**

Method	Most significant advantage	Disadvantage	Special feature
Hybridization methods			
Reverse dot blot ²⁸	Multiplexing possible	Prone to non-specific background	Precursor to microarrays
GeneChip microarrays ³⁹	Very high probe density	High failure rates ^{41,42} , expensive	High-tech manufacturing process ⁴⁰
DASH ⁴⁴	Inexpensive labelling method	Complex design rules	Dedicated instrument
PNA ⁴⁶ and LNA ⁴⁸ probes	Specific as ASO probes	Not widely available	Innovative chemical design
TaqMan ^{49,50}	Simplicity of assay	Expensive probes	Quantitative real-time PCR
Molecular Beacons ^{51,52}	Simplicity of assay	Expensive probes	Versatile stem-loop structure
Allele-specific PCR			
Real-time PCR assay		Requires optimization	
Intercalating dye ⁶⁰	Inexpensive labelling method	Non-specific products detected	Accurate quantification ¹³⁸
FRET primers ^{61,62}	Simplicity of assay	Expensive primers	Universal FRET primers
AlphaScreen ⁶⁴	Detects specific product	Expensive probes	Applicable to ASO hybridization
Primer extension			
Accurate genotyping		Similar reagents as in PCR	
SNPstream, GBA ⁶⁸	Inexpensive and robust	Multiple detection steps	Automated high-throughput process
Multiplex minisequencing, SNaPshot ^{69,71}	Multiplexing capacity	Size separation step	Compatible with capillary DNA sequencers
Pyrosequencing ^{72,74}	Sequencing of up to 50 bases	Expensive, difficult to multiplex	Dedicated instrument
MassEXTEND, MassArray ⁷⁵	Labelling method avoided	Expensive instrument	Multiplexing capacity ⁷⁶
GOOD assay ⁷⁷	Labelling method avoided	Multi-step procedure	Sensitive mass spectrometric detection
Microarray miniseq, APEX ^{37,70}	Potential for high throughput	Requires microarray instruments	Four-colour or single-colour detection
Microarray primer extension ⁸²	Potential for high throughput	Requires microarray instruments	'Array of arrays' format
'Tag' arrays ^{85,86}	Flexible assay design	Requires microarray instruments	Generic 'tag' microarrays
Coded microspheres ⁸⁷	Multiplexing potential	Microspheres not widely available	Flow cytometric detection
TDI, fluorescence polarization ⁹⁴	Simplicity of assay	Difficult to multiplex	Universal detection principle
Oligonucleotide ligation			
Variety of assay formats		Multiple labelled probes required	
Colorimetric OLA ^{95,96}	Robust assay	Multiple detection steps	Resembles ELISA
Sequence-coded OLA ⁹⁷	Multiplexing capacity	Size separation step, expensive probes	Polymer for sequence coding
Microarray ligation ¹⁰⁰	Potential for high throughput	Requires microarray instruments	Universal zip code microarray
Ligase chain reaction ¹⁰²	Alternative to PCR	Lower efficiency than PCR	Thermostable ligase
Padlock probes ¹⁰⁸	Localized detection	Probes difficult to produce	Avoids target amplification
Rolling circle amplification ⁹⁸	Signal amplification	Steric hindrance on solid phases	Based on circularized oligonucleotides
Endonuclease cleavage			
Restriction site analysis	Inexpensive, requires no equipment	Not suitable for high throughput	Traditional method
Invader assay ¹¹²	PCR amplification avoided	Requires large amount of DNA	Interesting FLAP endonuclease

APEX, arrayed primer extension; ASO, allele-specific oligonucleotide; DASH, dynamic allele-specific hybridization; ELISA, enzyme-linked immunosorbent assay; FRET, fluorescence resonance energy transfer; GBA, genetic bit analysis; LNA, locked nucleic acid; OLA, oligonucleotide ligation assay; PNA, peptide nucleic acid; TDI, template-directed incorporation.

EX1012.0005.

128. One of the SNP-genotyping methods disclosed by Syvänen is “mini-sequencing,” the term used by Syvänen to describe “methods based on single nucleotide primer extension”—SNP-genotyping methods that use nucleotide incorporation via a polymerase to identify SNPs of interest. EX1012.0006. Syvänen

discloses that mini-sequencing methods utilize primers specific to target sequences containing the SNPs of interest such that extension from these primers incorporates nucleotides that reflect the presence of different nucleotides at the SNP location. EX1012.0006-09. Syvänen discloses various methods by which the incorporated nucleotide, reflective of the SNP of interest, can be detected, including fluorescent labels and measuring molecular mass. *Id.*

129. Syvänen further describes how the aspects of sequencing machines could be applied to “homogeneous allele-specific PCR,” a class of genotyping methods wherein “PCR primers with the 3'-end complementary to either of the nucleotides of a SNP can be used in combination with a common reverse PCR primer to selectively amplify the SNP alleles.” EX1012.0006. Syvänen discloses that capillary channel systems such as “96-channel capillary sequencing instruments, microplate array diagonal electrophoresis or capillary array electrophoresis microplates” could be used to achieve high-throughput size separation of PCR products. *Id.* Syvänen notes that “without a consecutive target-specific detection reaction or size-separation step, the specificity of the [homogeneous allele-specific PCR] method might be hampered owing to primer dimers and other spurious amplification products that will not be distinguished from the actual PCR products,” and that “[a] limitation of all variants of allele-specific PCR is that the reaction

conditions or primer design for selective allele amplification must be optimized empirically for each SNP.” *Id.*

D. Delseny (EX1007)

130. Delseny is a 2010 textbook review chapter that discusses NGS platforms as of 2010. EX1007.0003-04. Delseny further describes the application of NGS technology to plant biology including efforts to sequence several different plant species, and the broader application of sequencing methods to address biological questions. EX1007.0004. Delseny does not address sequencing library preparation methods in any detail and provides no mention of single-primer enrichment strategies.

131. Delseny “review[s] some of the next-generation sequencing technologies (NGST),” including the 454 sequencer, Illumina platforms, Ion Torrent, and PacBio platform. EX1007.0004-05. For each platform Delseny highlights, Delseny provides a summary of the sequencing technology utilized by that platform. *Id.* Delseny describes “[t]he major advantage of all the NGSTs is that their throughput is much higher than that of classical sequencing.” EX1007.0005. However, Delseny notes that “all these technologies have a number of limitations that, at least initially, restricted their use to some applications” including short read length, sequencing of repeat regions, bias introduced during sequencing library construction, and “sequencing errors and artefacts” EX1007.0005. Delseny further

notes that each sequencing method “ha[s] its own weakness,” noting as an example in the case of the 454 sequencing that “[m]istakes occur with short homopolymers with the 454 technology because multiple incorporation of the same nucleotide instead of single incorporation can occur at each round.” *Id.* As such, Delseny considered Sanger sequencing to have “the highest accuracy . . . and remain[] the ‘gold standard.’” *Id.*

132. Delseny provides a high level overview of NGS technology, and does not concern itself in any detail with the particulars of sequencing library preparation. At most, Delseny describes sequencing library preparation as “remain[ing] tricky and involv[ing] several steps of fragmentation, adapter ligation and PCR amplification,” wherein “[e]ach step can introduce representation bias and artifacts, which must be carefully controlled for.” EX1007.0005.

133. Delseny provides no mention of any single-primer enrichment technology, nor does it provide any disclosure of off-target primer binding. The only concern regarding sequencing library preparation Delseny notes is that “the size of fragments need to be controlled and optimized for efficient sequencing depending on the technology used.” *Id.*

134. Delseny’s discussion of “targeted sequencing” is similarly limited. Delseny provides a brief, high-level discussion of efforts to sequence particular regions of the genome. EX1007.0008-09. Again, Delseny provides no disclosure

of any single-primer enrichment technology or any disclosures related to off-target primer binding. Indeed, the only method of target capture expressly disclosed by Delseny is “immunoprecipitating chromatin with specific antibodies and analy[zing select regions of the genome] by extracting and sequencing the corresponding DNA,” otherwise known as chromatin immunoprecipitation, a protein capture technique wholly distinct from single-primer enrichment. *Id.*

135. Delseny provides a brief discussion on genotyping, noting that SNP genotyping using Affymetrix DNA chips “produce[d] ~350,000 high-confidence SNPs with a false discovery rate of <2%.” EX1007.0008. With respect to NGS, Delseny discloses that “[r]e-sequencing [(sequencing a sample and comparing it to a reference genome)] . . . by use of Illumina technology has been reported,” but that “identifying high-confidence SNPs and small InDels remains a major challenge until base-calling is improved and false discovery rate is reduced.” *Id.*

VIII. Neither Shapero Nor Delseny Disclose All Elements of the Independent Claims

136. For the '012 patent, Shapero fails to disclose or teach multiple claim elements of claim 1. Specifically, Shapero does not disclose or teach at least the following limitations:

- a. “wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface;”

- b. “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
- c. “sequencing the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.”

137. For the ’108 patent, Shapero does not disclose or teach at least the following limitation: “sequencing the amplified products comprising the enriched nucleic acid sequence of interest on a massively parallel sequencing platform.”

138. These claim elements are directed to the incorporation of universal primer sequences that are subsequently utilized for NGS. Shapero does not teach any methods for NGS, including methods incorporating the universal primers that are used for NGS. Instead, Shapero teaches the use of hybridization arrays, which do not require the use of a universal primer sequencing for sample binding, as discussed above. A POSA would not have understood that Shapero’s method using hybridization arrays could be used for NGS, which was not commercially available when Shapero published.

139. For the ’012 patent, Delseny fails to disclose or teach multiple claim elements of claim 1. Specifically, Delseny does not disclose or teach at least the following limitations:

- a. “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
 - i. a 3’ portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and
 - ii. a 5’ tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;”
- b. “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
 - i. sequence complementary to the first adaptor sequence at a first end,
 - ii. sequence complementary to the nucleic acid sequence of interest, and
 - iii. the second adaptor sequence at a second end;” and
- c. “amplifying the one or more oligonucleotide extension products using
 - i. a first primer that anneals to a complement of the first adaptor sequence and

- ii. 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,
- iii. wherein products of the amplifying comprise a 3' end with sequence complementary to a sequence on a surface.”

140. For the '108 patent, Delseny fails to disclose or teach multiple claim elements of claim 1. Specifically, Delseny does not disclose or teach at least the following limitations:

- a. “annealing one or more oligonucleotides in solution in a reaction mixture to the nucleic acid sequence of interest in a nucleic acid fragment, wherein the reaction mixture comprises a plurality of nucleic acid fragments, wherein the nucleic acid fragment comprising the nucleic acid sequence of interest comprises a first adaptor sequence, wherein the one or more oligonucleotides comprise
 - i. a 3' portion with at least 10 bases designed to be complementary to the nucleic acid sequence of interest and
 - ii. a 5' tail portion comprising a second adaptor sequence that is non-complementary to the nucleic acid sequence of interest;”
- b. “extending the one or more oligonucleotides annealed to the nucleic acid sequence of interest in the nucleic acid fragment comprising the first

- adaptor sequence with a polymerase, in the reaction mixture, thereby generating one or more oligonucleotide extension products comprising
- i. sequence complementary to the first adaptor sequence at a first end,
 - ii. sequence complementary to the nucleic acid sequence of interest, and
 - iii. the second adaptor sequence at a second end;” and
- c. “amplifying the one or more oligonucleotide extension products, in the reaction mixture, using
- i. a first primer that anneals to the complement of the first adaptor sequence and
 - ii. a second primer that anneals at its 3’ end to a complement of the second adaptor sequence,
 - iii. thereby enriching the nucleic acid sequence of interest, by generating amplified products comprising the enriched nucleic acid sequence of interest.”

141. Delseny fails to teach these limitations because Delseny fails to teach the claimed methods for enriching sequences of interest through amplification, wherein those amplified products are subsequently sequenced through NGS.

142. The Petitions and Dr. Metzker’s accompanying declarations do not dispute that Shapero fails to teach the use of NGS and that Delseny fails to teach a method of single primer enrichment through amplification.

IX. A POSA Would Not Have Been Motivated to Combine Shapero with Delseny With a Reasonable Expectation of Success

143. Petitioner argues that a POSA would have been motivated to combine Shapero and Delseny, and in doing so, modify the MARA method so that it could be used with NGS. Petitioner also argues that a POSA would have had a reasonable expectation of success in doing so. For the reasons explained herein, I disagree with both arguments.

A. A POSA Would Not Have Been Motivated to Adapt a Method Used with Hybridization Arrays for Use With NGS

144. Shapero discloses the use of the MARA method with a predecessor Affymetrix hybridization array for the genotyping of SNPs. *See supra*, ¶121. A POSA would not have been motivated to combine a publication on hybridization arrays with NGS technology at least because the technologies are fundamentally different, posing different challenges and making it difficult to extrapolate results from one to another.

145. As explained above, a hybridization array utilizes a silica chip containing hundreds of billions of custom probes that are designed to target specific sequences. *See supra*, ¶¶42-44. Generally, these arrays contain numerous probes specific to one target where the various probes are configured slightly differently to optimize their ability to capture the specific target sequence. *See supra*, ¶¶42, 47-49. When samples are ran over the array, these probes bind their target sequences

on the array. *See supra*, ¶¶42, 47, 86. Non-target sequences do not have a corresponding probe containing a complementary sequence, so those sequences are removed from the array during subsequent washing steps. *Id.*

146. By design, the hybridization arrays drive target recognition/specificity. *Id.* It is not necessary for a researcher to prepare a library that is enriched for target genomic material during sample preparation because the targeted design of the array. *See supra*, ¶¶42, 47, 86-87. Instead, the main concern during sample preparation for hybridization arrays is ensuring that enough material is being used to cover the array with an evenly distributed amount of material so as to ensure that target sequences come into contact with their corresponding array probe and are not inadvertently washed away. *See supra*, ¶46. Because of this concern for adequate sample material, researchers generally focus on non-specific amplification during sample preparation as a means of ensuring an adequate amount of sample materials for the hybridization array. *See supra*, ¶¶45-46.

147. Due to the target specificity of the arrays and the washing steps that are used before array analysis, concerns with off-target binding during sample preparation are minimized. *See supra*, ¶87. Hybridization arrays are designed to filter out sequences that are not specific to the array probes. *See supra*, ¶¶42-44, 47, 86. After off-target sequences are eliminated, the arrays are prepared for image

analysis. *See supra*, ¶¶45, 86. From there, researchers can run analyses to obtain outputs that show whether the specific target was present in the sample. *Id.*

148. NGS platforms, on the other hand, are designed differently. Rather than utilizing hundreds of billions of target-specific probes for analysis, NGS platforms seek to leverage a handful of universal primers. *See supra*, ¶¶81-82. These platforms are designed so that any sample fragment containing the universal primer sequence will be affixed to a surface—such as the surface of the sequencer—and then subsequently sequenced. *See supra*, ¶¶81-85. The use of universal primers is a main feature of NGS platforms. These universal primers allow researchers to sequence hundreds of thousands of different sample fragments in one sequencing run without the burden and expense of designing target specific primers. *See supra*, ¶¶58-59, 82-85. The ability to sequence so many different fragments at once allows for the high-throughput sequencing that is characteristic of NGS. *See supra*, ¶¶58-59.

149. Because NGS uses universal primers for high-throughput sequencing, sample preparation techniques must be used to preserve target specificity and eliminate off-target binding. If the sample is amplified without any regard for enriching specific sequences, then all amplified products that contain the universal primer sequences will be sequenced. *See supra*, ¶¶81-85. This would be expensive and would generate a massive amount of data. To reduce this burden and focus the

analysis, the researcher can enrich for (or isolate) specific sequence(s) of interest prior to sequencing. *See supra*, ¶¶63-65.

150. Above, I illustrated the critical differences in target recognition and capture between the analytical platforms. *See supra*, ¶¶87-88. The hybridization array probes will likely detect the presence of the targeted SNP without the need for any additional sample preparation considerations. *See supra*, ¶86. If the researcher attempts to use the same sample preparation methods for NGS—with the one exception being the additional step of incorporating the universal NGS primers, the data will include sample reads that reflect the sequence of the target SNP as well as sequencing reads for all the other sequences in the sample. *See supra*, ¶¶81-85. The considerably higher data output, along with read fidelity issues experienced by NGS, will pose significant challenges for reliably genotyping the SNP because of the sheer volume of additional genomic information as well as the increased risk that any detection of the SNP in the sequencing data is a false positive attributable instead to read errors. *See supra*, ¶¶61-62.

151. Given these technology differences and data outputs, a POSA would have been unlikely to consider hybridization array techniques for use with NGS. A POSA would have known that due to the different issues and limitations with hybridization arrays, sample preparation techniques for hybridization arrays would

not have been designed specifically for the purpose of promoting target specificity and minimizing off-target binding—issues heavily exacerbated with NGS.

152. Additionally, a POSA would not have been motivated to start with a technique specific to a hybridization array (even methods directed to the use of a single target specific primer for preparing libraries for amplification) when designing an NGS method given that the hybridization arrays would make it difficult, if not impossible, to infer how the sample preparation methods affected targeted specificity and off-target binding. The target specificity of the hybridization arrays masks any potential target specificity issues with sample preparation methods so that a POSA could not tell whether the sample preparation contributed to target specificity or diminished such specificity. *See supra*, ¶¶86-87. With the hybridization array, the array specificity coupled with washing steps also masks concerns of off-target binding so that a POSA could not tell whether the sample preparation increased or decreased off-target binding. *See supra*, ¶¶42, 47, 86. As such, a POSA reviewing sample preparation methods for hybridization arrays (even those using a single, locus-specific primer) would be confronted with methods where target specificity and off-target binding were not primary concerns and where potential issues with such were masked by the use of the hybridization arrays. A POSA would be reluctant to use a sample preparation method for hybridization arrays as a starting point for NGS.

B. Shapero Fails to Resolve the Concerns with Target Specificity and Off-Target Binding

153. There is nothing different about the Shapero publication that would make it more likely that a POSA would be motivated to adapt a sample preparation method for hybridization arrays so that it could instead be used for NGS. In fact, Shapero exemplifies that reasons why a POSA would not have been motivated to adapt a method like MARA for NGS, including because (1) Shapero discloses that target specificity is achieved by the hybridization arrays; (2) the experimental data reported in Shapero is only specific to hybridization arrays; and (3) the experimental design used to obtain that data makes it impossible for a POSA to infer what impact, if any, MARA had on target specificity and off-target binding.

154. First, Shapero tells us that target specificity is achieved through hybridization arrays. In discussing the MARA protocol, Shapero notes that “[i]mportantly, MARA does not require absolute specificity of primer annealing and elongation since target recognition and allele discrimination is achieved through hybridization to high-density arrays.” EX1006.0008-09. A POSA reading this statement would have understood that, like with other array hybridization methods, Shapero is relying on the target-specific array probes to recognize SNPs. A POSA would also have understood that target recognition and allele discrimination did not occur as part of sample preparation.

155. Shapero notes that “[w]ith MARA, allele discrimination is achieved by hybridization to arrays containing SNP-specific complementary sequences rather than a universal array which requires the use of tags or zip codes attached to the primers for genotype de-convolution.” EX1006.0012. “Thus, the requirement for absolute specificity of primer annealing to targeted sequences in genomic DNA is alleviated.” *Id.* A POSA reading this statement would again have understood that target specificity is being driven by the hybridization arrays, not the sample preparation.

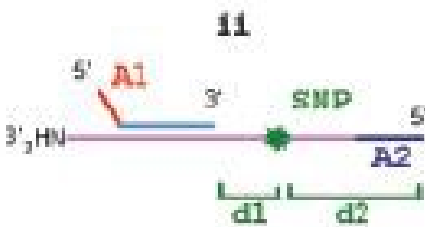
156. Shapero further reinforces the reliance on the hybridization array to promote target specificity in discussing off-target binding. Shapero notes “even if the primers contribute to non-specific amplification products, the complexity should not reach a level that would affect array hybridization.” EX1006.0012. A POSA reading this statement would have understood that Shapero was relying on the hybridization array to ensure that off-target products did not impact the analysis. A POSA considering Shapero’s statements concerning target specificity and off-target binding would have concluded that Shapero relied on the hybridization array and offered no disclosures as to how the MARA method impacted either.

157. Second, Petitioner argues that the data of Shapero would have motivated a POSA to adapt the MARA method for use with NGS. Petition, 34-48. That is incorrect. Petitioner specifically relies on two sets of data, comparing the

call rates where locus-specific primers were used for the MARA method and where the primers were not. As explained above, Shapero relies on the call rates coupled with discrimination scores (“DS”) to evaluate the percentage of SNPs that were detected by the hybridization arrays. *See supra*, ¶¶120-22. The data is wholly obtained through the use of hybridization arrays and not NGS platforms. *See supra*, ¶¶112, 120-22. Given the fact that target specificity was driven by the hybridization arrays, a POSA could not infer from the data what degree of target specificity was driven by the MARA method, let alone how that method might translate to use with NGS where there are not safeguards to ensure target specificity.

158. Third, Petitioner claims specifically the difference in call rates for the MARA 250-plex and MARA 750-plex demonstrate that the MARA method could be used with NGS given its high degree of target specificity. Petition, 41-42. Petitioner, however, misreads the data reported by Shapero. For both sets of multiplex reactions, Shapero examined what the call rates and discrimination scores were for two different sample preparation methodologies. *See supra*, ¶¶120-23.

159. The first methodology relied on the MARA method is illustrated in Figure 1 of Shapero, where one of two amplification primers (A1) is incorporated through the use of a locus-specific primer. *See supra*, ¶¶114-17.



EX1006.0009. As Shapero explains, the MARA method relies on “cycles of secondary PCR with universal A1 and A2 primers [to] amplify all full-length products derived from the first round locus-specific reaction.” *Id.* These amplified products are then prepared for array hybridization. *Id.*

160. The second methodology omits the locus-specific primers in the first reaction. *See supra*, ¶¶122-23. Because of that, there is no incorporation of amplification primer A1. *Id.* As a consequence, the fragments do not undergo amplification as described in the standard MARA method. *Id.* Shapero acknowledges this by stating that the “results show that the presence of locus-specific primers allows specific target sequences to be amplified, and in the absence of primers, only small quantities of non-specific products are generated.” EX1006.0010.

161. This distinction between the two methodologies is critical because it directly impacts what can be inferred from the Shapero data. Shapero is comparing instances where fragments are amplified to instances where fragments are not. As such, a POSA would understand the differences in call rates and discrimination

scores to largely be impacted by the amount of sample material used with the hybridization array. Where the sample material was amplified before analysis, Shapero obtained better coverage and better results. Where the sample material was not amplified, Shapero saw worse coverage and worse results.

162. Shapero does not disclose that the data shows high levels of target specificity by the MARA method or even that the MARA method promoted high levels of enrichment for specific loci. That is because the experimental design described above precludes such conclusions. A POSA cannot infer that the MARA method promoted target specificity given the use of hybridization arrays in both instances (which Shapero tells us drives target specificity) and that Shapero did not amplify the fragments in one instance. Had Shapero amplified the fragments in both instances using amplification primer A1, then it is possible that a POSA could infer that differences in the call rates and discrimination scores are attributable to some level of enrichment. But that is not the case here. Additionally, given the same parameters, a POSA could not conclude with confidence to what degree the MARA method actually enriched any of the target loci. This is, in part, because of the inability to measure the degree of off-target binding. Shapero fails to disclose the relative populations of various SNPs pre- and post-MARA. Shapero also fails to provide a reference amplification population by which a POSA could compare the post-MARA populations of target sequences to assess enrichment. Without these

disclosures, a POSA cannot reliably infer to what degree MARA enriched the sample. Further complicating the data are the concordance rates reported by Shapero, which showed that the uses of the hybridization arrays in Shapero created approximately four-to-five times as many errors (discordances) as the standard uses of the same type of hybridization array. *See supra*, ¶¶120-25. These heightened error rates would only further diminish any interest a POSA would have in using the reported method for new genotyping methods, given that the reported methods were less accurate than other known uses of the hybridization arrays, and it would certainly reinforce why a POSA would not be motivated to adapt this method for NGS, where it was very likely that the genotyping error rates would only increase. *See supra*, ¶¶ 61, 81-85, 131, 135.

163. Putting all of this together, a POSA would not have been motivated by Shapero to modify the MARA method for use with NGS. A POSA would not have started with Shapero given that the MARA method was not designed for NGS, not tested with pre-NGS sequencers, and instead relied on hybridization arrays to ensure target specificity. The data in Shapero was obtained through using the hybridization arrays, and the experimental design would have precluded a POSA from being able to infer the impact of the MARA method on enrichment, target specificity, and off-target binding.

C. A POSA Reviewing Shapero Would Not Have Discerned a Need to Switch from Hybridization Arrays to NGS

164. If a POSA were looking at Shapero for genotyping, a POSA would not have thought that the MARA method could be improved by using it with another analytical platform, whether pre-NGS Sanger sequencing or NGS. Rather, the art at the time promoted the efficacy of using hybridization arrays for the kind of SNP genotyping performed in Shapero. *See supra*, ¶¶42-44, 51. The main issue in the art at the time was how to increase high-throughput genotyping with hybridization arrays. *See supra*, ¶¶42-44, 51, 113. As discussed further herein, a POSA would have perceived this limitation to also impact the hybridization arrays disclosed in Shapero given the unfavorable results observed by Shapero with the higher multiplex reactions. *See supra*, ¶¶124-26. If anything, a POSA would have been motivated to improve on the hybridization array hardware or software. *See* EX2004.0024 (“Since their inception, high-density microarrays have followed the same trend as computer microprocessors. In 1965, Moore predicted that the power of microprocessors would double every 18 months. This trend has been true for the computer industry, where much faster and smaller central processing units are constantly being produced. High-density oligonucleotide arrays have evolved similarly.”). Petitioner’s assumption that a POSA would have automatically viewed

the way to improve on Shapero as integrating other technologies (such as NGS) reflects nothing more than hindsight.

D. A POSA Would Not Have Understood Shapero’s Reference to Syvänen to Teach that the MARA Method Could be Used with Sequencing Technologies

165. Petitioner argues that one reference to Syvänen by Shapero would have been understood by a POSA to mean that Shapero was disclosing that the MARA method could be used with sequencing technologies that existed at the time. Petition, 34-35. I disagree. In the introductory sections of the publication, Shapero refers in passing to the “multitude of genotyping methodologies for SNPs that have been described over the years.” EX1006.0006. Shapero proceeds to note that “[t]hese approaches can vary in terms of how alleles are discriminated, e.g. the use of nucleic acid hybridization with short oligonucleotide probes alone or in combination with enzymes such as DNA polymerases or DNA ligases” and “in the nature of both the assay formats and labeling and detection strategies.” *Id.* Shapero proceeds to state that “many currently used approaches share a common feature in that there is a requirement for an amplification of the region harboring the polymorphism prior to actual genotyping.” *Id.* At no point does Shapero state that these “currently used approaches,” especially as reflected in Syvänen, show that the

MARA method could be used with sequencing technologies. In fact, I have not seen any disclosure to that effect in any part of Shapero.

166. Petitioner argues that Syvänen’s disclosures concerning the use of DNA-sequencing instruments with “minisequencing” support that the MARA method could have been used with sequencing technologies. This argument misunderstands what Syvänen discloses. First, “minisequencing” is a term used by Syvänen to refer to sample preparation methods in which an extension product is created that allows for the subsequent detection of a SNP. *See supra*, ¶128. It does not by itself refer to sequencing technologies such as Sanger and NGS. *See supra*, ¶¶127-28. Second, Syvänen discusses the use of DNA-sequencing instruments in the context of how certain features of the instruments could be used for SNP detection. *See supra*, ¶129. As an example, Syvänen discusses that 96-channel capillary sequencers (i.e. pre-NGS Sanger sequencers) could be used to take advantage of the electrophoretic size-separation features of the sequencers. *Id.* Syvänen proposes using size separation as a means of high-throughput genotyping, not comparing Sanger sequencing read outputs for genotyping. *Id.* A POSA would not have understood that these disclosures supported the use of the MARA method with sequencers.

167. In fact, Syvänen would have discouraged the adaptation of MARA for SNP genotyping with sequencing technologies. As discussed above, Syvänen

discusses the use of allele-specific primers in PCR. *See supra*, ¶129. Syvänen discloses that using such 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 actual PCR products.” EX1012.0006. In fact, Syvänen notes 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,” and as such, “are best suited for the analysis of a limited number of SNPs in large sample collections.” *Id.* A POSA reading these disclosures would understand that Syvänen was advocating for methods like MARA to be used with hybridization arrays (which can serve as a consecutive target-specific detection reaction) and that such sample preparation methods would be ill-suited for high-throughput sequencing, such as NGS. Further, while Syvänen makes a similar observation as Shapero that many genotyping methods relied on PCR amplification, Syvänen discourages the use of PCR amplification in the “next generation technology for SNP analysis.” EX1012.0011. Rather, Syvänen discloses that the technology “should avoid the PCR amplification step, and the technology could be based on the analysis of single DNA molecules, which would allow direct determination of the haplotypes formed by the SNPs.” *Id.* In a table where Syvänen identifies the “most significant advantage,” “disadvantage,” or “special feature” of

various SNP-genotyping methods, Syvänen recognizes that the most significant advantage of one technology is that “PCR amplification [was] avoided” and that a special feature of another is that it “avoids target amplification.” EX1012.0005. Syvänen’s concerns with PCR amplification culminate in Syvänen remarking, “[h]opefully, 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.” EX1012.0011. In view of Syvänen, a POSA would not have been motivated to modify the MARA method, which utilizes PCR amplification, for genotyping with sequencing technologies. Instead, a POSA would have been discouraged from considering the MARA method for SNP genotyping with newer technologies, like NGS, given these disclosures by Syvänen.

E. A POSA Would Not Have Been Motivated by Delseny to Adapt the MARA Method for NGS

168. Petitioner argues that Delseny would have given a POSA the motivation to adapt the MARA method for use with NGS given that “Delseny recognizes that NGS is a replacement for genotyping described in Shapero.” Petition, 35-36. I disagree that Delseny taught that NGS is a replacement for high-throughput allele discrimination for known SNPs, which is the genotyping described in Shapero. Rather, if anything, Delseny would have encouraged the use of pre-NGS Sanger sequencing.

169. Petitioner relies on two specific disclosures from Delseny to argue that a POSA would have been motivated to combine Shapero with Delseny: (1) “NGS ‘allow[s] for many more samples to be analyzed at the same time,’” and (2) “So far, genotyping has involved mostly microsatellites, a technology with limited resolution and requiring much time and human resources. The ultimate resolution is at the base-pair level and NGSTs now open the possibility to genotype a line by sequencing it, provided a reference genome is available.” Petition, 35-36. A POSA would have understood that these disclosures reflected the thinking of the time that high-throughput methods, such as NGS, allowed for researchers to more efficiently than ever before obtain large amounts of genomic information. As Delseny discloses, researchers could sequence more samples at once. Additionally, rather than focusing on specific genotypes, researchers could process reams of sequences to assess

numerous genotypes. As such, Delseny recognizes that the “higher resolution” provided by NGS “can substitute for the genotyping microarray strategy.” EX1007.0008. Delseny does not teach, however, that NGS should be a substitute for the kind of SNP allele discrimination used in Shapero, where Shapero was seeking to optimize a hybridization array that would allow for the screening of known SNPs in genomic material. *See* EX1006.0006.

170. Delseny discloses instead that early NGS technologies suffered from a series of inaccuracies, which would have diminished their ability to be used for SNP genotyping. *See supra*, ¶135; EX1007.0008 (“Nevertheless, identifying high-confidence SNPs and small InDels remains a major challenge until base-calling is improved and false discovery rate is reduced.”). For example, Delseny discloses that NGS platforms suffered from base calling issues,⁹ which could contribute to read artifacts and false positives. *See supra*, ¶¶131, 135. To illustrate these deficiencies, Delseny explains how 454 sequencers struggled to sequence homopolymer sequences because of how stretches of the same repeating nucleotide would throw off the calibration of the machine, leading to read artifacts or incorrect sequencing reads. *See supra*, ¶131. A POSA would have understood that read

⁹ Base-calling refers to the process by which a sequencer reads the specific nucleotides in a nucleic acid sequence.

fidelity issues such as these would pose particular concerns with SNP genotyping where the purpose of the research would be to understand how a single nucleotide varies between samples. Given these read fidelity issues of NGS, Delseny reports that “[s]o far, the Sanger method has the highest accuracy because [of] *E. coli* DNA-polymerase and remains the ‘gold standard.’” EX1007.0005.

171. A POSA considering Delseny in its entirety would not be motivated to modify the MARA method with NGS. The POSA would understand that certain genotyping could be accomplished through NGS and that in some instances, that genotyping could replace the use of hybridization arrays. But the POSA would also understand that the read fidelity issues with NGS made it less reliable at SNP genotyping through allele discrimination than other methods, such as Sanger sequencing and array hybridization.

F. A POSA Would Not Have Had a Reasonable Expectation of Success in Modifying the MARA Method to Practice NGS

172. As explained above, two predominant concerns with sample preparation for NGS were issues with primer target specificity and off-target primer binding. *See supra*, ¶¶66-71. These issues plagued NGS instruments from the beginning given that the instruments were designed to allow for the sequencing of many different samples at once—not to target specific sequences and filter out unwanted sequences. *See supra*, ¶¶81-82. As a means of promoting target specificity and reducing off-target binding, the art focused on the use of primer pairs where PCR amplification was used for enrichment. *See supra*, ¶¶66-75. In fact, it was understood in the art that primer pairs were necessary. *See supra*, ¶¶70-75.

173. A POSA would not have expected the MARA method to be an improvement over the art that already existed given its use of a single locus-specific primer. A POSA would have instead expected that using only one-target specific primer would result in considerably lower levels of target specificity given that the primer was more likely to bind off-target and there was no second primer to help minimize errors resulting from that off-target binding. *See supra*, ¶¶66-75. Due to the higher sensitivities of NGS for off-target sequences, the POSA would have expected that considerably more of the sequencing read outputs would be noise, which would have made it even harder to genotype SNPs. *See supra*, ¶¶66-68, 81-85.

174. Petitioner argues that a POSA would have nevertheless had a reasonable expectation of success in combining Shapero and Delseny because (1) “the experimental data in Shapero shows a high on-target specificity that a POSA would understand would likely work for NGS applications,” and (2) “Delseny expressly teaches that NGS can be a replacement for array-based genotyping, as used in Shapero.” I disagree.

175. First, the experimental data in Shapero does not show “a high on-target specificity” obtained through the MARA method. The data instead shows that when used with a hybridization array, the method at lower throughputs obtains sufficient call rates. *See supra*, ¶¶120-26. As explained above, because Shapero relied on the hybridization array and compared the effects of amplification—not enrichment—on array hybridization, a POSA could not make any inferences about the target specificity of the MARA method. *See supra*, ¶¶153-63. Instead, a POSA would be left with the same expectation as if the data did not exist: the hybridization array promotes specificity and the sole reliance on a single target-specific primer for enrichment through amplification would pose issues with target specificity and off-target binding that would render it ineffective for use with NGS. *See supra*, ¶¶66-71, 153-63.

176. The low expectation of success in using Shapero’s techniques with NGS would have been compounded by Shapero’s reporting of the higher-plex

reactions. When Shapero tested hybridization for reactions using more than 1,000 array probes, Shapero observed that only 75% of primers demonstrated a high SNP call rate. *See supra*, ¶¶124-25. For the other 25%, Shapero could not draw a conclusion about what resulted in low SNP call rates. *See supra*, ¶126. The only conclusion that Shapero could reach was that “non-specific primer-primer interactions at the higher multiplex level may not solely be responsible for failed target generation.” *See supra*, ¶126; EX1006.0012. This uncertainty would have only increased a POSA’s concerns with target specificity and off-target binding for high-throughput methods like NGS. Additionally, the concordance rates reported by Shapero for all four sets of multiplex reactions would have only further lowered a POSA’s expectations given that the concordance rates with the MARA method reflected an error rate that was four-to-five times higher for the hybridization arrays than when the arrays were used with other methods. *See supra*, ¶¶120-25.

177. Second, as previously discussed, Delseny disclosed that NGS “can substitute for the genotyping microarray strategy because of its higher resolution,” but Delseny does not teach that it would specifically work with the MARA method. Delseny does not discuss the MARA method. Nor does Delseny discuss the use of a single target-specific primer to enrich for a target sequence through amplification. Instead, Delseny expresses several concerns with using NGS for SNP genotyping, including base-calling errors, read artifacts, and false discovery rates. *See supra*,

¶¶131, 135. These concerns led Delseny to describe pre-NGS Sanger technology as the “gold standard” given its higher read fidelity. *See supra*, ¶131. A POSA’s concerns with target specificity and off-target binding would not be alleviated by Delseny given these disclosures and Delseny’s failure to teach how to use a single target-specific primer enrichment method for NGS. *See supra*, ¶¶132-34.

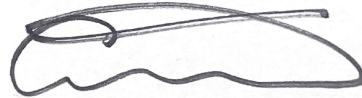
X. CONCLUSION

178. In summation, Shapero and Delseny fail to disclose each element of the independent claims of the '012 and '108 patents. A POSA would not have been motivated to combine the two references to practice the claimed inventions. A POSA also would not have had a reasonable expectation of success in doing so. Because Shapero in view of Delseny fails to render obvious the independent claims of the '012 and '108 patents, Shapero and Delseny necessarily fail to do the same for the dependent claims of the patents.

179. I declare under penalty of perjury that the foregoing is true and correct.

Dated: February 19, 2025

By:

A handwritten signature in dark ink, appearing to read 'Carlos D. Bustamante', written over a horizontal line.

Carlos D. Bustamante, Ph.D.

EXHIBIT A

Curriculum Vitae

Biographical Information

Name: Prof. Carlos D. Bustamante, Ph.D.

Current positions: Founder, President and Chief Executive Officer, Galatea Bio, Inc.

Adjunct Professor of Biomedical Data Science, Genetics, and (by courtesy)
Biology, Stanford University

Venture Partner, F/Prime Capital Partners

Updated: March 1, 2024

Business Contact information

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Assistant: sa.sheng@galatea.bio

Personal Statement

For the past two decades, I have led a multidisciplinary team working on problems in genetics of human health and disease. Much of our research has focused on genomics technology, data science, and its application in medical and basic sciences. My first academic appointment was at Cornell University's College of Agriculture and Life Sciences. There, much of our work focused on population genetics of human health and nutrition motivated by a desire to improve the foods we eat as the basis of health. I moved to Stanford in 2010 to focus on enabling clinical and medical genomics on a global scale. I have been focused on reducing health disparities in genomics broadening representation of understudied groups in large genomic consortia, particularly minority groups from the U.S., the Americas, and Africa. My work has empowered decision-makers to utilize genomics and data science in the service of improving human health and wellbeing. In the next phase of my career, I will focus on opportunities for bringing these technologies to consumer and patients, directly, where this work can have the greatest impact.

I am the Founder, President, and Chief Executive Officer of Galatea Bio, Inc. a company focused on the use of human genomics to power discovery for biopharma. This company was formed while I was a Professor at Stanford and a Venture Partner with Fidelity's early-stage biotechnology and healthcare group, F-Prime Capital Partners. I have a strong interest in building new academic and business units including non-profits and companies. I was the Inaugural Chair of Stanford Medicine's Department of Biomedical Data Science—the first new department that the University had started in 14 years. I serve as an advisor to the US federal government, private companies, startups, and non-profits in the areas of pharmaceutical products, computational genomics, population and medical genetics, intellectual property protection, and business strategy.

Education

Harvard University, Cambridge, MA	B.A.	1997	Biology, <i>magna cum laude</i> with highest honors
Harvard University, Cambridge, MA	M.S.	2001	Statistics
Harvard University, Cambridge, MA	Ph.D.	2001	Biology
University of Oxford, Oxford, UK	Post-doc	2001-2	Mathematical Genetics

Bustamante CV

1

Updated: March 2024

Positions and Employment

04/21-present Galatea Bio, Inc. Founder, President, and CEO
01/24-present Executive-in-Residence, Department of Business Technology University of Miami
Herbert School of Business, Coral Gables, FL
01/19-present F-Prime Capital Partners, Venture Partner
01/16-present Principal and Chairman, CDB Consulting, LTD.
11/22-present Adjunct Professor, Department of Biomedical Data Sciences, Genetics and (by
courtesy) Biology, Stanford University
09/21-06/22 Visiting Lecturer, Department of Business Technology University of Miami Herbert
School of Business, Coral Gables, FL
09/15-11/22 Professor, Department of Biomedical Data Sciences, Stanford University
01/10-11/22 Professor, Department of Genetics and (by courtesy) Biology, Stanford University
03/17-07/22 Investigator, Chan Zuckerberg Initiative (CZI) Biohub
09/15-01/2019 Inaugural Chair, Department of Biomedical Data Science, Stanford University
01/12-09/17 Founding Director, Stanford Center for Computational, Evolutionary, and Human
Genomics
01/12-09/15 Director of Informatics, Stanford Center for Genomics and Personalized Medicine
10/08-01/10 Professor, Department of Biological Statistics and Computational Biology and
Department of Statistical Sciences, Cornell University
08/02-10/08 Assistant Professor, Department of Biological Statistics and Computational Biology
and Department of Statistical Sciences, Cornell University
06/07-01/10 Associate Director, Cornell Center for Comparative and Population Genomics
01/04-06/04 Visiting Scholar, NSF Institute for Pure and Applied Mathematics, Los Angeles

Corporate Leadership

04/21-present Chairman of the Board, Galatea Bio
04/21-present Director, Provaxus, Inc.
01/19-present Board observer, Embark Veterinary, Inc. (Boston, MA)
01/16-present Principal and Chairman, CDB Consulting Group (Miami, FL)
06/18-06/22 Director, Etalon Diagnostics (Palo Alto, CA)
02/15-12/21 Founder, Director, and Chair of Scientific Advisory Board, Arc-Bio, LLC:
formerly Big Data Bio LLC (Boston, MA) and Identify Genomics (Menlo Park, CA)
02/14-06/16 Founder, Director, and Chair of Scientific Advisory Board, Identify Genomics LLC
(Menlo Park, CA)
02/15-12/21 Director, Liberty Biosecurity (Washington, DC)
06/16-12/21 Director, Eden Roc Sciences LLC (Birmingham, MI)
01/19-12/22 Board observer, Genomics PLC (Oxford, UK)

Non-profit and Government Service

06/19-12/22 Chair, ClinGen Complex Disease Working Group
Co-Chair, ClinGen Ancestry and Diversity Working Group
06/15-12/20 Co-Chair, PAGE Analysis Working Group
Chair, ClinGen Informatics Working Group
Member, ClinGen Steering Committee
02/11-12/15 Member, National Human Genome Research Institute (NHGRI) Council
02/11-12/15 National Institutes of Health Council of Councils
01/11-12/14 External Evaluation committee NIDDK T2D GENES project
06/10-12/14 Scientific Advisory Board, SIGMA (Slim Initiative for Genomic Medicine in the
Americas)

11/09-12/20 Scientific Advisory Board, NHGRI Center for Research on Genomics and Global Health

Scientific and Business Advisory Boards (current)

12/23-present Scientific Advisory Board, Colossal Biosciences (Austin, TX)
11/23-present Advisor, Pivotal Biosciences (San Francisco, CA)
06/18-present Scientific and Business Advisory Boards, Awakens, Inc. (Berkeley, CA)
06/18-present Scientific and Business Advisory Boards, Fauna Bio, Inc. (San Francisco, CA)
06/17-present Scientific Advisory Board, LunaDNA, Inc. (San Diego, CA)
06/16-present Scientific Advisory Board, Embark Veterinary (Boston, MA)
06/13-06/22 Scientific Advisory Board, Etalon Diagnostics (Menlo Park, CA)
03/16-12/21 Scientific Advisory Board, Digitalis Ventures (New York, NY)
02/15-12/21 Scientific Advisory Board, Liberty Biosecurity (Washington, DC)
10/17-12/21 Fellow, WebShield, Inc. (San Francisco, CA)
06/18-12/20 Scientific and Business Advisory Boards, Imprimed, Inc. (Palo Alto, CA)
04/18-04/20 Scientific Advisory Board, Columbia Care LLC (New York, NY)
03/18-12/20 Scientific Advisor, Nicklaus Children's Hospital (Miami, FL)
06/11-12/19 Scientific Advisory Board, Ancestry.com (Provo, UT)
06/16-12/18 Mars/IBM Food Safety Board (McClean, VA)
06/13-12/18 Chair of Scientific Advisory Board, Etalon Diagnostics (Menlo Park, CA)
09/11-12/17 Scientific Advisory Board, 23andme "Roots into the Future" (Mountain View, CA)
06/13-12/15 Scientific Advisory Board, National Geographic Genographic Project (Washington, D.C.)
04/12-12/16 Scientific Advisory Board, Personalis, Inc. (Menlo Park, CA)
09/12-12/15 Scientific Advisory Board, InVita (San Francisco, CA)
06/12-12/14 Medical Advisory Board, Med-Tek (Miami, FL)
06/11-06/12 Scientific Advisory Board, Mubadala Healthcare (Abu Dhabi, UAE)
09/09-12/12 Scientific Advisory Board, Nature Source Genetics (Ithaca, NY)

Fellowships and Honors

2017 Chang-Zuckerberg Biohub Investigator
2016 Stanford Prize in Population Genetics and Society
2011-2016 2010 John D. & Catherine T. MacArthur Fellow
2008 Cornell Provost Award for Distinguished Research
2007-2009 Sloan Research Fellowship in Molecular Biology
2001-2002 Marshall-Sherfield Fellowship
1999-2001 Howard Hughes Medical Institute Graduate Research Fellowship
1997-1998 National Science Foundation Graduate Research Fellowship

Editorial Boards

2013-2016 Evolution Section Editor, *PLoS-Genetics*
2013-2016 Editorial Board, *American Journal of Human Genetics*
2010-2020 Editorial Board, *Human Biology*
2008-2017 Editorial Board, *Genome Research*
2008-2012 Editorial Board, *Molecular Biology and Evolution*
2005-2009 Editorial Board, *Bioinformatics*

Other Experience and Professional Memberships

2015-2017	Co-Chair (2015), Chair (2017), Gordon Conference on Human Genetics and Genomics
2012-2014	Co-Chair, Conference on Genomics and Health Disparities
2012-2015	Organizer, Cold Spring Harbor Biology of Genomes Conference
2012-2014	Organizer, Meeting of the Society for Molecular Biology and Evolution
2009-present	Member, The Center for Academic Research and Training in Anthropogeny (UCSD)
2004-2005	Fellow of NSF Institute for Pure and Applied Mathematics

Patents and Patent Applications

1. **US10,981,137 B2. ENRICHMENT OF DNA SEQUENCING LIBRARIES FROM SAMPLES CONTAINING SMALL AMOUNTS OF TARGET DNA.** Priority Date: May 4, 2013. Inventors: **Carlos D. Bustamante**, Meredith Carpenter, Jason Buenrostro, and William J. Greenleaf. **Granted: Apr. 20, 2021.**
2. **US10,954,509 B2. PARTITIONING OF DNA SEQUENCING LIBRARIES INTO HOST AND MICROBIAL COMPONENTS.** Priority Feb 15, 2014. Inventors: **Carlos D. Bustamante** and Meredith Carpenter. **Granted: Mar. 23, 2021.**
3. **US 10,847,248 B2. TECHNIQUES FOR DETERMINING HAPLOTYPE BY POPULATION GENOTYPE AND SEQUENCE DATA.** Priority: Aug. 12, 2013. Inventors: **Carlos D. Bustamante** and Fouad Zakharia. **Granted: Nov. 24, 2020.**
4. **US 10,127,346 B2. SYSTEMS AND METHODS FOR INTERPRETING A HUMAN GENOME USING A SYNTHETIC REFERENCE SEQUENCE.** Priority Date: 2012-04-13. Inventors: Frederick Dewey, Euan A. Ashley, Matthew Wheeler, Michael Snyder, **Carlos Bustamante.** **Granted: Nov. 13, 2018.**
5. **GENOMIC SEQUENCE DATASET GENERATION.** Filing Date: Sep. 14, 2021. Inventors: Daniel Mas Montserrat, Alexander Ioannidis, **Carlos Bustamante.** Pub. No. US20230326542A1.
6. **LOCAL-ANCESTRY INFERENCE WITH MACHINE LEARNING MODEL.** Filing Date: Apr. 15, 2021. Inventors: Daniel Mas Montserrat, Alexander Ioannidis, Arvind Kumar, **Carlos Bustamante**, Richa Rastogi, Helgi Hilmarsson. Pub. No. US20230197204A1.
7. **TECHNIQUES FOR DETERMINING WHETHER AN INDIVIDUAL IS INCLUDED IN ENSEMBLE GENOMIC DATA.** Filing Date: 06.10.2016. Inventors: Suyash Shringarpure **Carlos D. Bustamante.** Pub. No.: WO/2017/062599A1
8. **COMPOSITIONS AND METHODS FOR TARGETED DEPLETION, ENRICHMENT, AND PARTITIONING OF NUCLEIC ACIDS USING CRISPR/CAS SYSTEM PROTEINS.** Filing Date: 19.12.2015. Inventors: Meredith Carpenter, **Carlos D. Bustamante**, Stephane B. Gourguechon. Pub. No.: Wo/2016/100955.
9. **PHASED WHOLE GENOME GENETIC RISK IN A FAMILY QUARTET.** Pub. Date: March 28, 2013. Inventors: Frederick Dewey, Euan A. Ashley, Jake Byrnes, **Carlos D. Bustamante**, Atul J. Butte, Rong Chen. Pub no: 2015/0370959. Grant Number: . **Grant Date: 13.09.2016**
10. **COMPOSITIONS AND METHODS FOR PREDICTING BODY SIZE IN DOGS.** Pub. Date.: 02.11.2007. Inventors: Elaine A. Ostrander, Nathaniel B. Sutter, Pascale Quignon, Robert K. Wayne, Melissa Gray, **Carlos D. Bustamante**, Badri Padhukasahasram, Keyan Zhao, Magnus Nordborg, Ebenezer Satyaraj, Paul G. Jones, Dennis F. Lawler. Pub. No.: WO2008058013A2.

Peer Reviewed Publications (Total 251; 247 peer reviewed)

[star designation (*) denotes I was co-senior author role]

[cross designation (+) denotes I was co-mentor of **lead and/or senior author**]

[Highlighted Note: Describes additional role]

2023

251. Gouveia MH, Bentley AR, Leal TP, Tarazona-Santos E, **Bustamante CD (+)**, Adeyemo AA, Rotimi CN, Shriner D. [Unappreciated subcontinental admixture in Europeans and European Americans and implications for genetic epidemiology studies](#). **Nat Commun**. 2023 Nov 7;14(1):6802. doi: 10.1038/s41467-023-42491-0. PMID: 37935687; PMCID: PMC10630423.
250. Serrano JG, Ordóñez AC, Santana J, Sánchez-Cañadillas E, Arnay M, Rodríguez-Rodríguez A, Morales J, Velasco-Vázquez J, Alberto-Barroso V, Delgado-Darias T, de Mercadal MCC, Hernández JC, Moreno-Benítez MA, Pais J, Ringbauer H, Sikora M, McColl H, Pino-Yanes M, Ferrer MH, **Bustamante CD*+, Fregel R***. [The genomic history of the indigenous people of the Canary Islands](#). **Nat Commun**. 2023 Aug 15;14(1):4641. doi: 10.1038/s41467-023-40198-w. PMID: 37582830; PMCID: PMC10427657.

Co-mentor and senior author / group leader for my lab where trainee was senior author of the paper. I co-led, financed, and jointly oversaw this project from conception to publication with Rosa Fregel, my former trainee.

249. Mantes AD, Montserrat DM, **Bustamante CD+**, Giró-I-Nieto X, Ioannidis AG+. [Neural ADMIXTURE for rapid genomic clustering](#). **Nat Comput Sci**. 2023 Jul;3(7):621-629. doi: 10.1038/s43588-023-00482-7. Epub 2023 Jul 6. PMID: 37600116; PMCID: PMC10438426.

Co-mentor and senior author / group leader for my lab where trainee was senior author of the paper. I co-led, financed, and jointly oversaw this project from conception to publication with Alex Ioannidis, my trainee.

247. Zhou W, Kanai M, Wu KH, Rasheed H, Tsuo K, ..., **Bustamante CD**, ... [Meta-analysis Initiative: Powering genetic discovery across human disease](#). **Cell Genom**. 2022 Oct 12;2(10):100192. doi: 10.1016/j.xgen.2022.100192. PMID: 36777996; PMCID: PMC9903716.

Consortium paper where I was a senior author / group leader for my lab contributing data and methods to the paper. I co-led, financed, and jointly oversaw my groups participation in this project from conception to publication

2022

246. Lopez-Pineda A, Vernekar M, Moreno-Grau S, Rojas-Muñoz A, Moatamed B, Lee MTM, Nava-Aguilar MA, Gonzalez-Arroyo G, Numakura K, Matsuda Y, Ioannidis A, Katsanis N, Takano T, **Bustamante CD**. [Validating and automating learning of cardiometabolic polygenic risk scores from direct-to-consumer genetic and phenotypic data: implications for scaling precision health research](#). **Hum Genomics**. 2022 Sep 8;16(1):37. doi: 10.1186/s40246-022-00406-y. PMID: 36076307

245. Parikh VN, Ioannidis AG, Jimenez-Morales D, Gorzynski JE, De Jong HN, Liu X, Roque J,

Cepeda-Espinoza VP, Osoegawa K, Hughes C, Sutton SC, Youlton N, Joshi R, Amar D, Tanigawa Y, Russo D, Wong J, Lauzon JT, Edelson J, Mas Montserrat D, Kwon Y, Rubinacci S, Delaneau O, Cappello L, Kim J, Shoura MJ, Raja AN, Watson N, Hammond N, Spiteri E, Mallempati KC, Montero-Martín G, Christle J, Kim J, Kirillova A, Seo K, Huang Y, Zhao C, Moreno-Grau S, Hershman SG, Dalton KP, Zhen J, Kamm J, Bhatt KD, Isakova A, Morri M, Ranganath T, Blish CA, Rogers AJ, Nadeau K, Yang S, Blomkalns A, O'Hara R, Neff NF, DeBoever C, Szalma S, Wheeler MT, Gates CM, Farh K, Schroth GP, Febbo P, deSouza F, Cornejo OE, Fernandez-Vina M, Kistler A, Palacios JA, Pinsky BA, **Bustamante CD***, Rivas MA*, Ashley EA*. [Deconvoluting complex correlates of COVID-19 severity with a multi-omic pandemic tracking strategy](#). *Nat Commun*. 2022 Aug 30;13(1):5107. doi: 10.1038/s41467-022-32397-8. PMID: 36042219

244. Gimbernat-Mayol J, Dominguez Mantes A, **Bustamante CD+**, Mas Montserrat D, **Ioannidis AG**. *PLoS Comput Biol*. 2022 Aug 25;18(8):e1010301. doi: 10.1371/journal.pcbi.1010301. [Archetypal Analysis for population genetics](#). eCollection 2022 Aug. PMID: 36007005

Co-mentor and senior author / group leader for my lab where trainee was senior author of the paper. I co-led, financed, and jointly oversaw this project from conception to publication with Alex Ioannidis, my trainee.

243. Liu YC, Hunter-Anderson R, Cheronet O, Eakin J, Camacho F, Pietrusewsky M, Rohland N, **Ioannidis A**, Athens JS, Douglas MT, Ikehara-Quebral RM, Bernardos R, Culleton BJ, Mah M, Adamski N, Broomandkhoshbacht N, Callan K, Lawson AM, Mandl K, Michel M, Oppenheimer J, Stewardson K, Zalzal F, Kidd K, Kidd J, Schurr TG, Auckland K, Hill AVS, Mentzer AJ, Quinto-Cortés CD, Robson K, Kennett DJ, Patterson N, **Bustamante CD**, Moreno-Estrada A, Spriggs M, Vilar M, Lipson M, Pinhasi R, Reich D. [Ancient DNA reveals five streams of migration into Micronesia and matrilocality in early Pacific seafarers](#). *Science*. 2022 Jul;377(6601):72-79. doi: 10.1126/science.abm6536. Epub 2022 Jun 30. PMID: 35771911

Consortium paper where I was a senior author / group leader for my lab contributing data and methods to the paper.

242. **Nieves-Colón MA+**, **Badillo Rivera KM+**, **Sandoval K+**, Villanueva Dávalos V, Enriquez Lencinas LE, Mendoza-Revilla J, Adhikari K, González-Buenfil R, Chen JW, Zhang ET, Sockell A, Ortiz-Tello P, Hurtado GM, Condori Salas R, Cebrecos R, Manzaneda Choque JC, Manzaneda Choque FP, Yábar Pilco GP, Rawls E, Eng C, Huntsman S, Burchard E, Ruiz-Linares A, González-José R, Bedoya G, Rothhammer F, Bortolini MC, Poletti G, Gallo C, **Bustamante CD+**, Baker JC*, **Gignoux CR*+**, **Wojcik GL*+**, **Moreno-Estrada A*+**. [Clotting factor genes are associated with preeclampsia in high-altitude pregnant women in the Peruvian Andes](#). *Am J Hum Genet*. 2022 Jun 2;109(6):1117-1139. doi: 10.1016/j.ajhg.2022.04.014. Epub 2022 May 18. PMID: 35588731

Co-mentor and senior author / group leader for my lab where three trainees were co-senior author of the paper. I co-led, co-financed, and jointly oversaw this project from conception to publication with Julie Baker.

241. Preston CG, Wright MW, Madhav Rao R, Harrison SM, Goldstein JL, Luo X, Wand H, Wulf B, Cheung G, Mandell ME, Tong H, Cheng S, Iacocca MA, Pineda AL, Popejoy AB, Dalton K, Zhen J, Dwight SS, Babb L, DiStefano M, O'Daniel JM, Lee K, Riggs ER, Zastrow DB, Mester JL, Ritter DI, Patel RY, Subramanian SL, Milosavljevic A, Berg JS, Rehm HL, Plon SE, Cherry JM, **Bustamante CD***, Costa HA*; Clinical Genome Resource (ClinGen). [ClinGen Variant Curation Interface: a variant classification platform for the application of evidence criteria from ACMG/AMP guidelines](#). **Genome Med.** 2022 Jan 18;14(1):6. doi: 10.1186/s13073-021-01004-8.PMID: 35039090

2021

240. Venkataraman GR, DeBoever C, Tanigawa Y, Aguirre M, **Ioannidis AG+**, Mostafavi H, Spencer CCA, Poterba T, **Bustamante CD+**, Daly MJ, Pirinen M, Rivas MA. [Bayesian model comparison for rare-variant association studies](#). **Am J Hum Genet.** 2021 Dec 2;108(12):2354-2367. doi: 10.1016/j.ajhg.2021.11.005. Epub 2021 Nov 24.PMID: 34822764

Collaborative paper where I was a senior author / group leader for my lab contributing data and methods to the paper.

239. Fu R, Gillen AE, **Grabek KR+**, Riemony KA, Epperson LE, **Bustamante CD*+**, Hesselberth JR, Martin SL*. [Dynamic RNA Regulation in the Brain Underlies Physiological Plasticity in a Hibernating Mammal](#). **Front Physiol.** 2021 Jan 18;11:624677. doi: 10.3389/fphys.2020.624677. eCollection 2020.PMID: 33536943

Collaborative paper where I was a senior author / group leader for my lab contributing data and methods to the paper. I co-led, financed, and jointly oversaw this project from conception to publication with Sandy Martin, and my trainee, Katherine Grabek.

238. **Ioannidis AG+**, Blanco-Portillo J, **Sandoval K+**, Hagelberg E, Barberena-Jonas C, Hill AVS, Rodríguez-Rodríguez JE, Fox K, Robson K, Haoa-Cardinali S, Quinto-Cortés CD, Miquel-Poblete JF, Auckland K, Parks T, Sofro ASM, **Ávila-Arcos MC+**, **Sockell A+**, **Homburger JR+**, Eng C, Huntsman S, Burchard EG, **Gignoux CR+**, Verdugo RA, Moraga M, **Bustamante CD*+**, Mentzer AJ, **Moreno-Estrada A*+**. [Paths and timings of the peopling of Polynesia inferred from genomic networks](#). **Nature.** 2021 Sep;597(7877):522-526. doi: 10.1038/s41586-021-03902-8. Epub 2021 Sep 22.PMID: 3455225.

Co-mentor and senior author / group leader for my lab where trainees were first author and senior author of the paper. I co-led, financed, and jointly oversaw this project from conception to publication with Alex Ioannidis, my trainee and Andres Moreno-Estrada, my former trainee.

237. **Lopez Pineda A+**, **Pourshafeie A+**, **Ioannidis A+**, Leibold CM, Chan AL, **Bustamante CD+**, Frankovich J, **Wojcik GL+**. [Discovering prescription patterns in pediatric acute-onset neuropsychiatric syndrome patients](#). **J Biomed Inform.** 2021 Jan;113:103664. doi: 10.1016/j.jbi.2020.103664. Epub 2020 Dec 28.PMID: 33359113

Co-mentor and senior author / group leader for my lab where trainees were first author and senior author of the paper. I led, financed, and oversaw this project from conception to publication with G. Wojcik, my trainee at the time the project was initiated.

2020

236. Martin AR, Gignoux CR, Walters RK, Wojcik GL, Neale BM, Gravel S, Daly MJ, **Bustamante CD***, Kenny EE+*. [Human Demographic History Impacts Genetic Risk Prediction across Diverse Populations](#). **Am J Hum Genet**. 2020 Oct 1;107(4):788-789. doi: 10.1016/j.ajhg.2020.08.020. PMID: 33007199

Co-mentor and senior author / group leader for my lab where trainees were first author and senior author of the paper. I led, financed, and oversaw this project from conception to publication with E. Kenny, my trainee at the time the project was initiated.

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Commentaries and non-peer reviewed publications (6)

248. Barnes KC, De La Vega FM, **Bustamante CD**, Gignoux CR, Kenny E, Mathias RA, Pasaniuc B. [Session Introduction: Overcoming health disparities in precision medicine.](#) **Pac Symp Biocomput.** 2023;28:181-185. PMID: 36540975.
216. De La Vega FM, **Bustamante CD**. [Polygenic risk scores: a biased prediction?](#) **Genome Med.** 2018 Dec 27;10(1):100. doi: 10.1186/s13073-018-0610-x. PMID: 30591078
155. **Bustamante CD**, Rasmussen M. 2015. [Beyond the reference genome.](#) **Nat Biotechnol.** 2015 Jun;33(6):605-6. doi: 10.1038/nbt.3249. No abstract available. PMID: 26057977.
79. **Bustamante CD**, Henn BM. *Human origins: Shadows of early migrations.* 2010. **Nature** 468:1044-5.
78. De La Vega FM, **Bustamante CD**, Leal SM. *Genome-Wide Association Mapping And Rare Alleles: From Population Genomics To Personalized Medicine - Session Introduction.* **Pac Symp Biocomput.** 2011:74-5.
24. Abecasis G, Tam PK, **Bustamante CD**, Ostrander EA, Scherer SW, Chanock SJ, Kwok PY, Brookes AJ. *Human Genome Variation 2006: emerging views on structural variation and large-scale SNP analysis.* **Nat Genet.** 2007;39(2):153-5.

Book Chapters

1. Kulathinal R, Sawyer SA, **Bustamante CD**, Nurminsky DI, Ponce R, Ranz JM, Hartl DL. *Selective Sweep in the Evolution of a New Sperm-Specific Gene in *Drosophila*.* In: Nurminsky D, editor. *Selective Sweeps*; Springer; 2005.
2. Przeworski M, **Bustamante CD**. *Genetic signatures of Natural Selection.* *Encyclopedia of Genetics.* London, U.K.: Wiley & Sons; 2005.
3. Ramachandran S, Tang H, Gutenkunst R, **Bustamante C**. *Genetics and Genomics of Human Population Structure.* In: Speicher MR, Motulsky AG, Antonarakis SE, editors. *Vogel and Motulsky's Human Genetics: Problems and Approaches.* Hiedelberg: Springer; 2010. p. 589-615.

Research Support (Active)

None

Research Support (Pending)

Galatea Bio, Inc. has multiple SBIR grants under consideration with NIH

Research Support (Completed)

U41HG009649 (Bustamante [C])

08/01/2017 – 07/31/2021

SPO# 109590

NIH

Clinical Genome Resource (ClinGen)

Major goal is to create a unified, public, and freely available database of genetic alterations relevant to clinical care. Our ultimate goal is to empower clinicians, genetic counselors, and patients to make informed decisions based on DNA testing.

Role: PI

1U01HG009080 (Bustamante [C])

05/20/2016 – 03/31/2020

SPO# 121626

NIH

Center for Multi- and Trans-ethnic Mapping of Mendelian and Complex Disease

Major goal is to accelerate the discovery of DNA variation relevant to health and disease by analyzing data from over 225,000 ethnically and racially diverse patients that will undergo genome sequencing. Of particular importance is ensuring we have powerful statistical methods for analyzing data from underserved groups including U.S. minority populations. Achieving this goal requires expertise across many domains of knowledge including: medical and population genomics, algorithm development for disease mapping, and expertise in large-scale databases.

Role: PI

5R24 HL117756-02 (Wu)

04/15/2014 – 03/31/2019

NIH/NHLBI

SPO# 110465/ Cardiovascular Institute Operations

Biorepository of Human iPSCs for Studying Dilated and Hypertrophic Cardiomyopathy

The project seeks to create a bank of 600 iPSC lines created from cardiovascular patients and distribute to the NHLBI community.

Role: Co-PI

1U54MD01724-01 (Cullen[C], Bustamante)

04/01/2016 – 03/31/2021

SPO# 121927

NIH/NIA

Stanford Precision Health for Ethnic and Racial Equity (SPHERE)

Major goal is to provide services to the different projects in the center as well as any other group in the consortium. We already have a robust infrastructure including equipment, expertise, and personnel for performing state-of-the-art genotyping, genome and exome sequencing, transcriptomics, metabolomics, and microbiome characterization. These activities will be implemented into the individual projects.

Role: Lab Core PI

1U24EB02367401 (Ashley) 12/12/2016 – 11/30/2022
SPO# 124803
NIH

Stanford MoTrPAC Bioinformatics Center

Major goal is to manage the bioinformatics for the MoTrPAC Clinical Site

Role: Co-PI

1R01HG008150-01 (Montgomery) 08/01/2015 – 06/30/2018
SPO# 114738
NIH

SPO# 114738/ Pathology Research

Predicting casual non-coding variants in a founder population

The project seeks to develop methods for interpreting non-coding genetic variation: to provide a Bayesian method for predicting causal variants from full genomes, to identify and validate a large set of functional non-coding variants using CRISPR technology, and to predict disease-relevant traits likely to be affected by each variant.

Role: Co-PI

1U24HG008956-01 (Matis [C], Bustamante) 01/14/2016 – 11/30/2019
SPO# 120615
NIH

Rutgers University

NHGRI Genome Sequencing Program Coordinating Center

Major goal is to identify of relevant control sets for data sets coming through GSPCC, and on the use of diverse trans-ethnic populations in boosting power, identifying novel causal variants, and characterizing the genetic background of the common control resource.

Role: Subcontract PI

IOS-1642184 (Bustamante) 08/01/2016 – 07/31/2018
SPO# 124489
NSF

EAGER: Establishing the genetic basis of hibernation by building and utilizing a next-generation genomics resource for the model hibernator, the thirteen-lined ground squirrel

Major goal is to establish a genetic basis for the hibernating phenotype in the 13-lined ground squirrel by developing a high-quality genome resource for the species. Specifically, we will employ quantitative trait loci analysis to identify genetic variants associated with hibernation to determine whether hibernation-related traits are heritable.

Role: PI

U01FD004979 (Altman) 02/01/2015 – 03/31/2018
SPO# 119541
UCSF

UCSF-Stanford CERSI: Improving the Efficiency and Rigor of Pharmacovigilance (PV) at FDA

Role: Co-PI

4U01HG0074919-04 (Matis [C], Bustamante) 09/01/2013 – 05/31/2018
SPO# 109405
Rutgers University (Prime NIH/NHGRI)

NHGRI PAGE Coordinating Center

The major goals of this study are to provide flexible support in data analysis, management, synthesis, and dissemination, and program logistics, for the PAGE II studies.

Role: Subcontract PI

4U01HG007417 (Loos [C], Bustamante)

09/01/2013 – 05/31/2018

SPO# 109391

MSSM (Prime NIH/NHGRI)

Diverse ancestry biobank to map biomedical traits and elucidate health disparities

The major goal of this project is to characterize the population architecture of differences in disease burden among populations in a multi-ethnic cohort using common and rare coding variants. We will also develop methods for disease mapping based on local ancestry information and will assess aggregate effects of rare variants in the context of the PAGE II network.

Role: Co-PI

66864T (Bustamante, Martin, Pls)

09/01/2011 – 08/31/2017

NIH/NIGMS

Genomic Origins and Admixture in Latinos (GOAL)

The major goal of this project is to generate and analyze dense genotype data from 180 parent-offspring triads of diverse Hispanic/Latino ancestry sampled in Miami, as well as sequence the complete genomes of 30 H/L triads.

ED-9697-STS2 (Bustamante, Dermitzakis[C], Guigo, McCarthy) 08/01/2013 – 06/30/2016

NIH

Methods for High-Resolution Analysis of Genetic Effects on Gene Expression

The major goal of this project is to identify genetic effects on gene expression using GTEx data. Specifically, we will provide statistical expression quantitative trait methodology, network methods for detecting gene regulatory interactions, and bioinformatics methods for improving identification of allele-specific expression.

0255-6424-4609 (Loos, Bustamante)

09/01/2013 - 05/31/2017

NIH/NHGRI

Diverse Ancestry Biobank to Map Biomedical Traits and Elucidate Health Disparities

The major goal of this project is to characterize the population architecture of differences in disease burden among populations in a multi-ethnic cohort using common and rare coding variants. We will also develop methods for disease mapping based on local ancestry information and will assess aggregate effects of rare variants in the context of the PAGE II network.

5943 (Matisse)

09/01/2013 - 05/31/2017

NIH/NHGRI

NHGRI PAGE Coordinating Center

The major goals of this study are to provide flexible support in data analysis, management, synthesis, and dissemination, and program logistics, for the PAGE II studies.

2R01HG003229 (Clark, Bustamante, Nielsen, Pls)

01/01/2010 – 6/30/2013

NIH/NHGRI

Population Genetic Inferences from Dense Genotype Data

The major goals of this project are to develop methods for population genetic inference from next-generation sequence data, including ascertainment bias correction, inference of natural selection, and prediction of functionality for novel SNPs and CNVs in the human genome.

U01HG005715 (Bustamante, PI)

09/09/2010 – 06/30/2014

NIH/NHGRI

Population Structure Admixture and Selection across the 1000 Genomes Data Set

The main goals of the project are to develop novel approaches for characterizing population structure, analyzing patterns of admixture, and localizing signatures of selection across the 2,500 samples sequenced by the 1000 Genomes Project.

58-6631-0-100 (Bustamante, PI)

07/01/2010 – 01/07/2014

USDA

Identification of Genes Regulating Major Agronomic Traits in Cacao Through Association and Linkage Mapping Using Large Sequence Data Sets

The major goal of this project is provide analytical and bioinformatic support to the MARS-USDA *Theobroma cacao* L. sequencing project, including SNP diversity and association mapping analysis of cacao populations as well as gene expression analysis of diverse *Theobroma* species.

1R01GM083606 (Bustamante, PI)

08/01/2007–07/31/2012

NIH/NIGMS

Association Mapping in Structured Populations

The major goal of this project is to develop novel statistical methods for association mapping in structured populations and to use these methods to map several complex traits in ethnically diverse African populations.

1R01MH084695 (Clark, Bustamante, Nielsen, PIs)

09/28/2008–07/31/2012

NIH/NIMH

Inferring multiple-SNP disease association with DNA resequence data

The major goal of this project is to develop novel statistical methods for association mapping of genetic variants underlying risk for complex disease, using resequenced DNA samples from cases and controls.

DBI 0701382 (Purugganan, PI, Bustamante, Co-PI)

09/01/2007–08/31/2012

NSF/DBI

GEPR: The Evolutionary Genomics of Rice Domestication

The major goals of this project are to fine-map domestication genes and examine the role of evolutionary selection in the origin of cultivated rice.

DEB 0516310 (Bustamante)

09/01/2005 – 08/31/2010

NSF

Computational Methods for Detecting Natural Selection using Comparative Population Genomic Data

The major goal of this project is to develop novel population genetic methods for identifying genes and genomic regions that are involved in adaptive molecular evolution through the comparison both within and between species genomic variation data.

5U01HL084706 -03 (Clark, PI, Bustamante, Co-PI)

06/15/2006 – 05/31/2010

NIH/NHLBI

Dimension Reduction Approaches for Genome-Wide Association Testing

The major goal of this project is to develop novel Bayesian shrinkage methods for genome-wide association mapping and to apply these methods to genome-wide expression level and genotype data from the 270 HapMap cell lines in order to map expression quantitative trait loci (eQTLs).

BIO 0948510 (Bustamante, PI)
NSF/DBI/EAGER

08/15/2009–7/31/2011 (NCE)

Genome-wide diversity in village dogs: uncovering the history of dog domestication, the genetics of natural dog populations, and consequences of artificial selection in breed dogs.

The major goals of this project are to develop population genetic methods for inferring the evolutionary history of dog domestication from genotyping and sequencing data, and to determine the impact of dog domestication on the genetic basis of complex traits in dogs.

DBI 0606461 (McCouch, PI, Bustamante, Co-PI) 08/01/2006 – 07/31/2011 (NCE) NSF/DBI
GEPR: Exploring the Genetic Basis of Transgressive Variation in Rice

The major goal of this project is to perform association mapping in rice (*Oryza sativa*) using 500 individuals genotyped at 10,000 SNPs in order to identify quantitative trait loci underlying 26 agronomic traits of interests.

1R01AI073368 (Stanhope, PI, Bustamante, Co-PI) 5/1/2010–6/15/2011 NIH/NIAID
Evolutionary Genomics and Population Genetics of Pathogenic Streptococci

The major goal of this project is to reach a thorough understanding of the molecular specifics correlated with adaptive differences within and between the pathogenic taxa of the genus *Streptococcus*.

673446Z (Nickerson, PI, Bustamante, Co-PI) 09/30/2009 - 06/30/2012 NIH
Northwest Genomic Center

The main goals of my subcontract on this project is to develop population genetic methods for quantifying population structure from whole-genome exome data and estimate selection coefficients on different categories of functional sites in the human genome.

Educational and Outreach Activities

Post-doctoral fellows trained

1. Dr. Adam Auton, D. Phil. (10/2007—6/2009), Statistical Geneticist, 23andme
2. Dr. Maria Avila-Arcos, Ph.D. (05/2014—12/2017), Assistant Professor, National Autonomous University of Mexico
3. Dr. Linda Boettger (Goodman), Ph.D. (1/2018 – 8//2018), Co-founder and CTO at Fauna Bio
4. Dr. Adam Boyko, Ph. D. (9/2005—8/2011), Associate Professor, Cornell University
5. Dr. Jake Byrnes, Ph. D. (9/2010—10/2011), Population Genomics Manager, Ancestry.com
6. Dr. Meredith Carpenter, Ph. D. (7/2011—1/2014), Chief Scientific Officer, ArcBio LLC
7. Dr. Jessica Chen, Ph.D. (3/2017 – 9/2019), Research Scientist, Genentech
8. Dr. Omar Cornejo, Ph. D. (8/2009—8/2013), Assistant Professor, Washington State University
9. Dr. Christopher DeBoever, Ph.D. (10/2016—4/2018), Vice President of Platform at Data4Cure, Inc.
10. Dr. Matthew J. Dimmic, Ph. D. (3/2003—2005), Genomics and Data Science Lead, Monsanto
11. Dr. Anna Katharina Elmer, Ph.D. (4/2014—9/2014), Senior Scientist, ArcBio LLC
12. Dr. Rosa Lorenzo Fregel, Ph.D. (6/2014—8/2017), Assistant Professor Tenerife
13. Dr. Christopher Gignoux, Ph.D. (8/2013—2/2017), Associate Professor, University of Colorado
14. Dr. Ryan Gutenkunst, Ph. D. (1/2008—12/2008), Assistant Professor, University of Arizona
15. Dr. Katherine Grabek, Ph.D. (7/2014—8/2018), Co-founder and CSO at Fauna Bio
16. Dr. Simon Gravel, Ph.D. (10/2009—12/2012), Assistant Professor, McGill University
17. Dr. Ragan Hart, Ph.D. (9/2018—6/2019), Entrepreneur-In-Residence, F-Prime Capital
18. Dr. Brenna Henn, Ph. D. (12/2009—12/2012), Assistant Professor, SUNY Stony Brook
19. Dr. Patrick House, Ph. D. (9/2014—9/2015), Neuroscientist and writer

20. Dr. Aashish Jha, Ph.D. (9/2015—6/2019), Director of Bioinformatics, NomNomNow, Berkeley, CA
21. Dr. Alex Ioannidis, Ph.D. (9/2018—6/2022), Postdoctoral scholar, Stanford
22. Dr. Joanna Kelley, Ph. D. (8/2010—8/2013), Assistant Professor, Washington State University
23. Dr. Eimear Kenny, Ph. D. (10/2010—10/2012), Professor, Mount Sinai School of Medicine
24. Dr. Jeffrey Kidd, Ph. D. (2/2010—12/2011), Associate Professor, University of Michigan School of Medicine
25. Dr. Carolin Kosiol, Ph. D. (9/2006—1/2009), Bioinformatics Group Leader, University of Veterinary Medicine (vetmeduni) Vienna, Austria
26. Dr. Tuuli Lappalainen (1/2013—12/2013), Professor, Department of Systems Biology, Columbia University and Junior Investigator and Core Member, New York Genome Center
27. Dr. Arturo Lopez Pineda (1/2016—4/2019), CEO, Amphora Health, SA
28. Dr. Fernando Mendez, Ph.D., (7/2013 – 7/2017), Senior Scientist - Population Geneticist at Helix
29. Dr. Babak Moatamed Ph.D. (7/2020 – 3/2022), Director of Clinical Informatics, Galatea Bio, Inc.
30. Dr. Nilah Monnier Ioannidis, Ph.D. (9/2013—10/2019), Assistant Professor, U. California Berkeley
31. Dr. Andres Moreno Estrada, M.D./Ph. D. (3/2009—12/2014), Professor and Group Leader, Langebio (Mexico)
32. Dr. Sonia Moreno Grau, Ph.D. (10/2020-1/2022), Director of Collaborations, Galatea Bio, Inc.
33. Dr. Marina Muzzio, Ph. D. (8/2011—8/2013), Researcher, Instituto Multidisciplinario de Biología Celular (IMBICE), National Scientific and Technical Research Council (CONICET), Buenos Aires, Argentina
34. Dr. Sean Myles, Ph.D. (1/2008—7/2010), Associate Professor, Dalhousie University
35. Dr. Badri Padhukasahasram, Ph. D. (9/2006—1/2008), Bioinformatics Scientist, Illumina, Inc.
36. Dr. Alice Popejoy, Ph.D. (11/2017 – 10/2021), Assistant Professor, U. of California Davis
37. Dr. Morten Rasmussen, Ph.D., (8/2013—7/2016), Director of Technology, ArcBio, LLC
38. Dr. Arindam RoyChoudhury, Ph. D. (7/2008—8/2009), Assistant Professor, Columbia University
39. Dr. Anna Rychkova, Ph.D. (9/2013—04/2016), Scientist, Amgen Comparative Biology and Safety Sciences Department
40. Dr. Suyash Shringarpure, Ph.D. (9/2012—06/2016), Statistical Geneticist at 23andme
41. Dr. Karla Sandoval Mendoza, Ph.D. (4/2010—12/2014), Postdoctoral Scholar, Langebio (Mexico)
42. Dr. Martin Sikora, Ph. D. (7/2010—6/2014), Associate Professor and Group Leader, Center for GeoGenetics, Copenhagen, Denmark
43. Dr. Elena Sorokin, Ph. D. (9/2015—2/28), Statistical geneticist at Ancestry DNA
44. Dr. Scott Williamson, Ph. D. (6/2003—6/2006), deceased (was Assistant Professor at Cornell University)
45. Dr. Genevieve Wojcik, Ph. D. (1/2014—9/2019), Assistant Professor, John Hopkins School of Public Health
46. Dr. Keyan (Kevin) Zhao, Ph.D. (9/2007—12/2010), Staff Scientist, IonTorrent
47. Dr. Ashley Zehnder, DVM, Ph.D. (10/2016—8/2018), Co-founder and CEO at Fauna Bio

Graduate Students Trained

1. Abra Brisbin (Ph. D. Applied Math) (2006 – 2010, joint with J. Mezey), Assistant Professor of Mathematics, University of Wisconsin-Eau Claire
2. Kasia Bryc (Ph. D. Biometry) (2006 — 2010), Population Geneticist, 23andMe
3. Thomas Cooke (Ph. D. Genetics) (2011—2017), Postdoc at Whitehead Institute
4. Helio Costa (Ph. D. Genetics) (2011—2015), Fellow in Molecular Clinical Genetics at Stanford
5. Roxana Daneshjou (M.D./Ph.D. Genetics) (2012—2014, joint w/ Russ Altman), MSTP student at Stanford, completing medical training
6. Joe Davis (Ph. D. Genetics) (2012—2017, joint with S. Montgomery), Data Scientist at Cardinal Analytix Solutions

7. Jeremiah Degenhardt (Ph. D. Biometry) (2005 — 2010), Senior Scientist in Bioinformatics, Onyx Pharmaceuticals
8. Kirsten Eilertson (Ph. D. Statistics) (2007—2011), Assistant Professor, Penn State
9. Hong Gao (Ph. D. Genetics) (2004—2008), Senior Bioinformatics Scientist, Illumina, Inc.
10. Alex Han (Ph.D. Genetics) (2014—2020)
11. Ryan Hernandez (Ph. D. Biometry) (2003—2008), Associate Professor, UCSF
12. Julian Homburger (Ph. D. Genetics) (2014—2017, joint with E. A. Ashley), Data Scientist at Color Genomics
13. Alex Ioannidis (Ph.D. Computational and Mathematical Engineering) (2013—2018), Postdoctoral scholar, Stanford
14. Sandra Indarraga (M.S./Ph. D. Genetics) (2009—2011), self-employed
15. Emilia Huerta-Sanchez (Ph. D. Applied Math, joint with R. Durrett) (2005—2009), Assistant Professor, UC Merced
16. Jeffrey Jensen (Ph. D. Genetics & Development, joint with C.F. Aquadro) (2002—2006), Head of Laboratory and Professor, Ecole Polytechnique Federale de Laussane
17. Lin Lin (Ph. D. Computational Biology) (2006—2010), Postdoctoral Scholar, Harvard University
18. Kirk Lohmueller (Ph. D. Genetics & Development) (2005 – 2009, joint with A. G. Clark), Assistant Professor, UCLA
19. Xin (Maria) Ma (Ph. D. Statistics) (2008—2011), Postdoctoral Scholar, Stanford University
20. Brian Maples (Ph.D. Biomedical Informatics) (2011–2014), Computational Data Scientist, Nuna, Inc.
21. Alicia Martin (Ph.D. Genetics) (2011—2015), Assistant Professor, Mass General Hospital, Harvard University
22. Kimberly McManus (M.S. Genetics) (2012—2015), Data Scientist, LinkedIn
23. Shaila Musharoff (Ph.D. Genetics) (2009—2015), Assistant Professor, Cornell University
24. Patricia Ortiz-Tello (M.D./Ph.D. Genetics) (2010—2016), independent
25. Armin Pourshafeie (Ph.D. Physics) (2015—2019), Citadel
26. David Poznik (Ph.D. Biomedical Informatics) (2011—2015), Computational Biologist and Population Geneticist, 23andme
27. Jessica Torres (Ph.D. Biomedical Informatics) (2014—2021)
28. Mark Wright (Ph.D. Genetics & Development) (2007—2010), 23andMe
29. Fouad Zakharia (Ph.D. Genetics) (2010—2012), Vice President, Morgan Stanley
30. Lan Zhu (M.S. /Ph.D. Biometry) (2002—2006), Associate Professor (tenured), Oklahoma State University

Courses Taught

BIODS210: Configuration of the Health Care System and the Application of Big Data/Analytics (F2016)

BTRY 407: Principles of Probability and Theoretical Statistics (F2007)

BTRY 694: Statistical inference in Population Genomics (S2004,S2006, F2006, F2007, S2008, F2010)

BTRY 484/684: Statistical Genomics (F2005, F2006)

BTRY 694: Statistical Inference in Evolutionary Genomics (S2005)

BTRY 384: Intro. Bioinformatics and Statistical Genomics (F2004, F2005)

BTRY 652: Computationally Intensive Statistical Inference (S2003)

CSRE 110: Comparative Studies of Race and Ethnicity (W2011, guest lecture)

GENE 210: Personalized Genomics (S2010, S2011, guest lecture)

GENE 203: Graduate Genetics (S2013, F2010, lectures on human genetics and genomics)

GENE 203: Graduate Genetics (F2011, primary lecturer)

GENE 202: Genetics for Medical Students (F2010, lectures on human population genetics)
GENE 209: Population Genetics (S2011, S2012, S2013, S2014)

Invited Conferences, Keynote Lectures, and Departmental Seminars (>175 total)

2024

1. CHDI's 19th Annual Huntington's Disease Therapeutic Conference, Feb. 29, 2024; Palm Spring, CA)
2. JP Morgan Biotechnology Conference, Feb. 22, 2024; Taipei, Taiwan

2023

1. ABRCMS (Annual Biomedical Research Conference for Minoritized Scientists) 2023 Keynote Speaker, Nov. 11, 2023; Phoenix, AZ
2. F/Prime, Foresite Capital, Pivotal Biosciences AI in Healthcare Conference 2023, Nov. 6, 2023; San Francisco, CA
3. AI and Quantum Computing, Nov. 21, 2023; Miami, FL
4. WCPG (World Congress in Psychiatric Genetics), Oct. 11, 2023; 2023 Keynote Speaker, Montreal, CA
5. Regeneron Research Center Keynote Speaker, Sept. 18, 2023; Terrytown, NY
6. Fidelity Biosciences Research Institute Post-Acute Infection Syndrome (PAIS) 2023 Conference, Aug. 4, 2023; Newport, RI
7. Colombia Congress on Human Genetics Keynote Speaker, June 15, 2023; Medellin, Colombia
8. Gruter Institute Conference 2023, April 18, 2023; Lake Tahoe, NV
9. Stanford University Biostatistics Workshop, Sept. 28, 2023; Stanford, CA

2022

1. F/Prime Conference on AI and Healthcare, Nov. 14, 2022; London, UK
2. Cornell University, Nov. 4, 2022; Ithaca, NY
3. Harvard Medical School, Sept. 20, 2022; Boston, MA
4. Genetic Health Information Network Summit, Sept 14, 2022; Nashville, TN
5. Yale University, New Haven, CT
6. Fidelity Biosciences Research Institute Post-Acute Infection Syndrome (PAIS) 2022 Conference, Aug. 11, 2022; Newport, RI
7. Pharmacogenetics Research Network (PGRN 2022) University of Colorado, Aurora, CO
8. University of California, San Francisco, San Francisco, CA
9. Gruter Foundation, Mar 22, 2022; London, UK
10. Executive War College, April 29, 2022; New Orleans, LA
11. Post-Covid Summit 2022, April 19, 2022; Brussels, Belgium
12. Tec de Monterrey, Feb 2-4, 2022; Monterrey, Mexico

2021

1. University of Miami, Board of Trustees
2. Harvard University, Cambridge, MA
3. Stanford University Medical Grand Rounds, Stanford, CA
4. Johnson and Johnson, Inc.
5. Cambridge University, Cambridge, UK

2020

1. E.E. Just Lecture University of Chicago, Chicago, IL

2. Stanford University School of Law, Stanford, CA

2019

1. Etalon Diagnostic Leadership Retreat, Santa Rosa, CA
2. Helix Leadership Retreat, Menlo Park, CA
3. DRIFT Symposium, American Society of Human Genetics 2019, Houston, TX
4. NHGRI Workshop: Perspectives in Comparative Genomics & Evolution, Washington, D.C.
5. Human Genetics and Genomics Gordon Research Conference 2019, Closing Keynote, Waterville, NH
6. Stanford Executive Summer Program, Stanford University Graduate School of Business
7. STAT+ Inaugural Event on Venture Capital in Pharma and Biotechnology, San Francisco, CA
8. RECOMB 2019 Keynote Speaker, Washington, D.C.
9. California Institute of Regenerative Medicine (CIRM) Conference on Brainstorming Neurodegeneration” Keynote, San Francisco, CA
10. Nation Health Care Council (NHCC) Fellow’s Program 2019, Nashville, TN
11. Personalized Medicine World Conference 2019, Santa Clara, CA

2018

1. Advances in Genome Biology and Technology Personalized Medicine Keynote, San Diego, CA
2. Genomic Medicine XI, San Diego, CA
3. Genetic Health Information Network Summit, Nashville, TN
4. Siriraj Hospital Genomics and Medicine Keynote, Bangkok, Thailand
5. NHGRI Town Hall, Stanford, CA
6. 2018 Marshall Scholars’ Forum, Stanford, CA
7. Distributed18 (Blockchain in Healthcare) Conference, San Francisco, CA
8. Big Data in Biomedicine 18 (Blockchain organizer), Stanford, CA
9. Stanford Executive Summer Program, Stanford University Graduate School of Business
10. Broad Institute of Harvard/MIT Medical and Population Genomics, Cambridge, MA
11. Frontiers in Genomic Medicine Keynote, Sioux Falls, SD
12. American College of Medical Genetics Annual Meeting Keynote, Charlotte, NC
13. Vanderbilt University Medical Center Personalized Medicine Keynote, Nashville, TN
14. Colorado State University on Veterinary Electronic Health Records, Ft. Collins, CO
15. Pacific Symposium on Biocomputing (PSB 2018) Keynote, Hilo, HI

2017

1. Health 2.0 Keynote Speaker, San Francisco, CA
2. 2017 Distinguished Presidential Scholar, University of Miami, FL
3. CSHL’s Second Annual Double Helix Day, NY, NY
4. Stanford Symposium for Genomics & Personalized Medicine, Menlo Park, CA
5. Stanford Executive Summer Program, Stanford University Graduate School of Business
6. Big Data in Biomedicine Conference 2017, Stanford, CA
7. Stanford-China Cardiovascular Research and Medicine Symposium, Stanford, CA
8. FH 2017 Global Summit, Miami, FL
9. Genetic Health Information Network Summit, Nashville, TN
10. IMSS XXVI National Health Research Forum, San Luis Potosí, Mexico

2016

1. 2016 Darwin Day Keynote Speaker, University of Iowa, Iowa City, IA
2. University of Iowa Medical School Distinguished Speaker, Iowa City, IA

3. University of Iowa Department of Biology Seminar, Iowa City, IA
4. 2nd Annual NIH-wide Pi Day Speaker, National Institutes of Health, Bethesda, MD
5. Personalized Medicine World Conference (PMWC 2016), Silicon Valley, CA
6. Rockefeller University Friday Seminar Speaker, New York, NY
7. UCSF Parnassus Institute for Human Genetics Seminar, San Francisco, CA
8. UCB Supernetwork Conference, London, UK
9. New York City Medical Examiner's Office, NY, NY
10. SAP Sapphire 2016, Orlando, FL
11. Stanford Institute for Computational and Mathematical Engineering (ICME) Expo, Stanford, CA
12. Miami Children's Hospital Speaker Series, Miami, FL
13. Stanford Pediatric Grand Rounds and Retreat Keynote Speaker, Stanford, CA
14. Big Data in Biomedicine Conference 2016, Stanford, CA
15. 2016 CARDIA Conference Keynote Speaker, Napa, CA
16. Perspectives in Genomics Speaker, Cancun, Mexico
17. UCLA Institute for Pure and Applied Mathematics Seminar, Los Angeles, CA
18. Immunogenomics 2016, HudsonAlpha Institute, Huntsville, AL
19. Baylor College of Medicine Molecular & Human Genetics Seminar, Houston, TX

2015

1. Cornell University Department of Biological Statistics and Computational Biology Seminar, Ithaca, NY
2. Festival of Genomics, San Francisco, CA
3. Human Genome Variation and Complex Genome Analysis (HGV 2015) Conference, San Francisco, CA
4. Member, Iconiq Capital Patients Like You Panel, San Francisco, CA
5. Invited lecture at San Francisco Mexican Museum, San Francisco, CA
6. Gordon Conference on Human Genetics and Genomics Speaker and Vice Chair, Newport, RI
7. Inaugural lecture on "Genomics and Health Disparities" at the National Institutes of Health, Bethesda, MD
8. Graduate Student invited Speaker, Department of Human Genetics, University of Chicago, Chicago, IL
9. Keynote speaker, UCLA/IPAM "Latinos in Mathematics" conference, Los Angeles, CA
10. Panelist at "Big Data, Genomics, and Precision Medicine," Tech Museum, San Jose, CA
11. University of Chicago Department of Genetics Seminar, Chicago, IL
12. Keynote speaker, "Human Genome Meeting 2015", Kuala Lumpur, Malaysia
13. Advances in Genome Biology and Technology (AGBT), Marco Island, FL
14. "Genomics and Sequencing Data Integration, Analysis and Visualization" Symposium, San Francisco, CA
15. CIENCIAS—a forum for presenting science in Spanish, Stanford University, Stanford, CA
16. Plant and Animal Genome Conference, San Diego, CA

2014

1. TEDMED 2014 inaugural cohost and invited speaker, San Francisco, CA
2. New York Genome Center Seminar, New York, NY
3. MacArthur Foundation Fellows Forum, Chicago, IL
4. Why We Can't Wait: Conference to Eliminate Health Disparities, Chair and Speaker, Washington D.C.
5. Human Genome Meeting on "Genome Variation and Human Health" (HUGO 2014), Geneva, Switzerland

6. Universidad Nacional del Altiplano, Puno, Peru
7. Illumina Users Meeting, South San Francisco, CA
8. "1000 Genomes and Beyond" Community Meeting, Cambridge, UK
9. Thermo Fisher Next Generation Sequencing seminar, South San Francisco, CA
10. University of Minnesota / Illumina "Understanding Your Genome", Minneapolis, MN
11. SAP Sapphire, Orlando, CA
12. Harvard Medical School Department of Genetics, Student-Invited Speaker, Boston, MA
13. Broad Institute of Harvard and MIT Medical and Population Genomics Seminar, Cambridge, MA
14. Advances in Genome Biology and Technology (AGBT) 2014, Marco Island, FL
15. University of California Riverside Department of Biology, Riverside, CA

2013

1. University of Miami Department of Human Genetics, Miami, FL
2. Willamette University Department of Biology, Portland, CA
3. Gordon Research Conference on Human Genetics and Genomics, RI
4. Arizona State University, MTBI program, Phoenix, AZ
5. Society for Mathematical Biology (SMB) Keynote Speaker 2013, Phoenix, AZ
6. 9th Molecular Biology of Hearing and Deafness Conference, Stanford, CA
7. 2013 Genome 10K Meeting Invited Speaker, Ft. Lauderdale, FL
8. Stanford/Oxford Big Data Conference, Stanford, CA

2012

1. Memorial Sloan Kettering Presidential Invited lecture
2. Oxford-Stanford Conference on Big Data, Oxford, UK
3. Illumina Users Meeting, American Society of Human Genetics 2012
4. Royal Society 2012 Galton and Fisher Lecture invited speaker, London, UK
5. 50th Anniversary of NIGMS DeWitt Stetten Jr. Lecture
6. UCSF Parnassus Seminar, San Francisco, CA
7. University of Helsinki Conference on Next-Generation Sequence Analysis
8. 2012 Green Mountain Conference on Forensic DNA Keynote Speaker
9. 2012 US/Indonesia Kavli Symposium (Solo, Indonesia)
10. University of Oxford Wellcome Trust Center for Human Genomics, Oxford, UK
11. Why We Can't Wait: 2012 Conference on Genomics and Health Disparities, Miami, FL
12. Boston College Landmarks in Biology Seminar, Boston, MA
13. North Carolina State Department of Genetics, Raleigh, NC
14. University of North Carolina Conference on Genetics of the Peoples of Africa and the Transatlantic African Diaspora, Chapel Hill, NC
15. University of California Davis, Davis, CA
16. University of California Berkeley, Berkeley, CA
17. Stanford University School of Law, Stanford, CA

2011

1. Institute for Pure and Applied Math Keynote Speaker, Los Angeles, CA
2. Society for Advancement of Chicanos and Native Americans in Science (SACNAS) 2011 conference, San Jose, CA
3. International Congress of Human Genetics 2011 Satellite Conference on Populations of the New World
4. University of California, Santa Cruz
5. University of Washington, Genome Sciences

6. 3rd EMBO Conference on Host Genetics and Infectious Disease, Pasteur Institute
7. Human Genome Variation (HGV) Meeting 2011
8. American Genetic Association Meeting 2011
9. European Society of Human Genetics 2011
10. University of Oregon (student invited speaker)
11. MacArthur Fellows Meeting
12. Stanford University Medical Grand Rounds
13. Slim Initiative in Genomic Medicine in the Americas
14. Commonwealth Club of California
15. Broad Institute of Harvard/MIT (Population and Medical Genetics)
16. Yale University School of Medicine (Genetics)
17. Harvard University (Organismic and Evolutionary Biology)
18. Florida International University (Biology and Human Genetics)
19. 2011 Genome 10K Conference
20. 2011 Gordon Conference on Quantitative Genomics
21. U. California Berkeley (Computational Biology)
22. Advances in Genome Biology and Technology (AGBT)

2010

1. U. California San Francisco (Human Genetics)
2. National Science Foundation Invited Speaker
3. LifeTech Users Meeting 2011
4. Cold Spring Harbor Banbury Conference on "DNA and Human History"
5. CARTA Symposium on Evolution of Human Biodiversity (UCSD)
6. Princeton University Lewis Sigler Institute
7. UCLA Human Genetics Retreat Invited Speaker
8. Johns Hopkins University School of Medicine (Genetics)
9. Genetic Society of America (GSA) 2010 Model Organism Conference invited speaker
10. European Molecular Biology Lab (EMBL) Workshop
11. Institute Pasteur, Paris, France (Immunology)
12. Duke University Computational Biology Graduate Student Invited Speaker
13. Advances in Genome Biology and Technology (AGBT) 2010)
14. University of Alabama ALLELE Invited Speaker
15. Graduate University for Advanced Studies (Hayama, Japan)

2009

1. Plant and Animal Genome XVI Meeting Aquaculture Keynote speaker
2. Office of AIDS Research Workshop on "Genomic Analyses of HIV Infection"
3. Conservation Genetics (ConGen) Workshop Smithsonian Tropical Research Institute
4. University of Pennsylvania (Genetics)
5. University of Pennsylvania (Veterinary School)
6. University of Miami Miller School of Medicine (Human Genetics)
7. Mexican National Institute of Genomic Medicine (INMEGEN)
8. Inter American Development Bank (IADB) 50th Annual Meeting (Medellin, Colombia)
9. Broad Institute of Harvard and MIT Medical and Population Genetics Seminar Series
10. University of Massachusetts at Amherst (Biology)
11. University of Miami Miller School of Medicine, HIV Grand Rounds
12. University of Washington St. Louis School of Medicine and UW Genome Center
13. RECOMB 2009 Symposium Speaker

14. Stanford University School of Medicine (Genetics)
15. 74th Cold Spring Harbor Symposia on Quantitative Biology
16. Pritzker School of Medicine University of Chicago (Human Genetics)
17. Society for Molecular Biology and Evolution 2009 Meeting (Iowa State University)
18. Gordon Research Conference on Human Genomics invited speaker
19. NGS2009 Conference on Next Generation Sequencing: Challenges and Opportunities (Barcelona, Spain)
20. American Society of Human Genetics (ASHG) 2009 Special Symposium Speaker
21. Columbia University Computational Biology Seminar Series
22. University of Indiana and University of Oregon NSF IGERT Invited Speaker
23. PABEW: Second Biological Evolution Workshop in (Porto Alegre, Brazil)
24. National Academy of Sciences Sackler Symposium "In the light of Evolution IV"

2008

1. Plant and Animal Genome XVI Meeting
2. University of California Los Angeles (History and Language Seminar Series)
3. University of Washington (Genome Sciences)
4. Gordon Conference on Molecular Evolution
5. Cornell University (Baker Institute for Animal Health)
6. University of Michigan (Biostatistics)
7. Harvard University (Anthropology)
8. Cornell University Plant Breeding and Genetics)
9. Stanford University (Biology)
10. Third International Conference on Primate Genomics
11. Cold Spring Harbor Biology of Genomes Meeting
12. 70th Anniversary Celebration for Centro Nacional de Investigacion en Cafe (CENICAFE) Bogota (Colombia)
13. Miami Institute of Human Genomics
14. HGM 2008: HUGO's 13th Human Genome Meeting in Hyderabad, India
15. Banbury Conference on Kinship, Race, and Ancestry
16. Cold Spring Harbor Symposium on Personalized Genomics
17. NHGRI Workshop on "Ethics and the Study of Natural Selection"
18. American Society of Human Genetics (ASHG) 2008 Invited Speaker
19. Stanford University (Biology)
20. 23andMe
21. Cornell-Weill School of Medicine (Pediatric Grand Rounds)

2007

1. Recomb Satellite Workshop
2. University of Arizona Ecology and Evolutionary Biology
3. American Institute of Biological Sciences Annual Meeting
4. NIH Workshop on Macaque Genetics
5. Society for Molecular Biology and Evolution 2007 Annual Conference
6. Banbury Conference on Domestication Genomics
7. National Association of Biology Teachers (NABT)
8. Konrad Lorenz Institute Workshop on Selective Sweeps

2006

1. Institute for Pure and Applied Math Short Program
2. University of Chicago
3. Universitat Pompeu Fabra
4. Arizona State University
5. Society for Molecular Biology and Evolution 2006 Annual Conference)
6. SNP Meetings 2006
7. American Society of Human Genetics ASHG 2006
8. Cornell Center for Vertebrate Genomics

2005

1. Eastern Great Lakes Molecular Evolution Meeting invited speaker
2. Mathematical Biosciences Institute Conference on Evolutionary Genomics
3. Hunter College, invited speaker

2004

1. Max Planck Institute for Evolutionary Anthropology
2. Cornell University (Field of Genetics)
3. North Carolina State (Bioinformatics)
4. Cornell University (Plant Biology)
5. University of Southern California (Computational Biology)
6. University of California Los Angeles (Human Genetics)
7. NSF Institute for Pure and Applied Mathematics
8. ETH Zurich (Student Invited Speaker)
9. University of Bergen
10. Blackwell-Tapia Conference
11. University of Maryland (Ecology & Evolutionary Biology)

2001-2003

1. University California Los Angeles (Biology)
2. University California Los Angeles (Human Genetics)
3. University of Arizona (Biology)
4. California Institute of Technology (Biology)
5. University North Carolina Chapel Hill (Genetics)
6. Brown University (Biology)
7. Cornell University (Biometry)
8. University of California Berkeley