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**IN THE UNITED STATES DISTRICT COURT**
**DISTRICT OF UTAH, CENTRAL DIVISION**

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| UNIVERSITY OF UTAH RESEARCH FOUNDATION et al.<br>Plaintiffs,<br>vs.<br>AMBRY GENETICS CORPORATION,<br>Defendant. | **DEFENDANTS AMBRY GENETICS CORPORATION'S AND GENE BY GENE LTD'S OPPOSITION TO PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTION**<br><br>CASE NO. 2:13-CV-00640-RJS<br>CASE NO. 2:13-CV-00643-RJS<br><br>Honorable Robert J. Shelby |
| UNIVERSITY OF UTAH RESEARCH FOUNDATION et al.<br>Plaintiffs,<br>vs.<br>GENE BY GENE LTD.,<br>Defendant. | |

# TABLE OF CONTENTS

**TABLE OF CONTENTS**
**(continued)**

**Page**

**TABLE OF CONTENTS**
**(continued)**

**Page**

**TABLE OF CONTENTS**
**(continued)**

**Page**

## I. INTRODUCTION

The Supreme Court's June 13, 2013, *Myriad* decision unanimously held that a laboratory-generated synthesized DNA which is a copy of a portion of the native DNA sequence is unpatentable subject matter. This widely-heralded opinion laid down a principle that the public well understood: Lab-generated DNA segments with the identical sequence as a native DNA segment are not patentable because they are products of nature. By contrast, the Court held that a cDNA, which Plaintiffs characterized to the *Myriad* Court as "a wholly synthetic molecule with a *sequence nowhere found in native DNA*," did constitute patentable subject matter. The sequence of the DNA, and not how it is made, governs whether the DNA is an unpatentable product of nature under 35 U.S.C. § 101.

Plaintiffs ignore their previous representations and misconstrue *Myriad* as affirming the patentability of any DNA that is made in a lab. Plaintiffs effectively argue that any synthesis of DNA in a laboratory, instead of by nature, regardless of the DNA sequence made, turns the lab-isolated DNA product of nature into a patentable "synthetic" DNA. Plaintiffs' advance this argument to try to preserve the patentability of their four asserted DNA primer claims so as to stifle Defendants' legitimate competition that the Supreme Court's decision validated.

But Plaintiffs already lost this argument before the Supreme Court. Plaintiffs contended throughout the prior *Myriad* litigation that lab-generated DNA primers with a natural DNA sequence had "markedly different characteristics" than natural DNA. These DNA primers, Plaintiffs argued, constituted synthetic, patentable products under the Supreme Court's 1980 *Diamond v. Chakarbarty* decision. Both the District Court and the unanimous *Myriad* Supreme Court rejected that argument. One cannot copy by synthesis a segment of the human race's

DNA sequences in a lab and prevent the rest of the human race from using those sequences. Plaintiffs' four primer claims are clearly invalid under Section 101.

Plaintiffs springboard off their unsupported reading of *Myriad* to argue that their six asserted method claims are likewise patentable. Here again, they run into a 9-0 Supreme Court decision. In *Mayo v. Prometheus*, the Court held that method claims purporting to apply a patent-ineligible law of nature or an abstract mental concept were still patent-ineligible if the claims simply appended additional steps involving "well-understood, routine, conventional activity previously engaged in by researchers in the field." This Court need look no further than the asserted patents for such invalid method claims. They append admittedly generic and well-known additional steps of "screening" or "amplifying" to claims that the Federal Circuit *Myriad* Court already declared as patent-ineligible mental processes or laws of nature. Compelling evidence supports their invalidity.

While built on unpatentable subject matter under Section 101, Plaintiffs' asserted claims are also clearly and convincingly invalid because they are either obvious or anticipated under Sections 102 and 103. Defendants place before this Court clear anticipating references for the four primer claims. Defendants place before this Court clear evidence that the six method claims are anticipated and obvious. Testimony from leading researchers and the admissions in Plaintiffs' patents confirm the claims clear invalidity.

Plaintiffs err in painting to this Court that infringement is a foregone conclusion. That is not so. Defendants' primers do not infringe, nor do Defendants infringe the method claims. Plaintiffs further fail to carry their burden of proof to show that each limitation in the asserted claims is practiced.

Finally, there are the three other preliminary injunction factors of irreparable injury, balance of hardships and the public interest. Plaintiffs stretch in these factors to try to maintain their monopoly. For example, they (1) cast aspersions against Defendants' BRCA tests (while they copy Defendants' tests), (2) ignore the long need in this country for competition to provide legitimate options to women for BRCA testing, (3) overstate their alleged irreparable injury, when damages will suffice, and (4) disregard the hardships to Ambry and Gene by Gene if this injunction is granted.

Defendants have not only raised substantial questions; they have shown compelling evidence that none of the four preliminary injunction factors is present here. Plaintiffs' motion should be denied so that the competition the Supreme Court's decisions fostered may continue.

## II. STATEMENT OF FACTS

### A. RESPONSE TO PLAINTIFFS' STATEMENT OF FACTS

#### 1. Ambry's Responses

Ambry denies all alleged facts except those specifically admitted below.

**Statement of Fact ("SF") No. 1:** Myriad Genetics, Inc., was formed in 1991 as one of the first genomic companies by a group of scientists who were studying the role that genes play in human disease, and were interested in bringing to market molecular diagnostic products to assess an individual's risk for developing such diseases and to provide important clinical information to assist patients and their healthcare providers in making treatment decisions. *See* http://www.myriad.com/history-2.

**Response to SF No. 1:** Ambry lacks knowledge or information sufficient to form a belief as to the truth or falsity of SF No. 1 and therefore disputes SF No. 1.

**SF No. 2:** After successfully discovering genetic sequences of the BRCA1 and BRCA2 genes and mutations that increase a woman's risk of developing breast and ovarian cancer, Plaintiffs sought and obtained patent protection on various applications of this discovery. *See* Complaint, ¶¶ 5-9; 14.

**Response to SF No. 2:** Ambry admits that Plaintiffs have sought and have been issued patents and disputes the rest, especially that any patent protection is available to Plaintiffs for the reasons stated in this Response and all of the evidence and authorities supporting it showing that the patent claims asserted are invalid and/or not infringed. *See also, e.g.*, Ledbetter Decl., ¶¶ 11-47.

**SF No. 3:** In 1996, Myriad Genetics introduced its BRACAnalysis® test, a molecular diagnostic test for hereditary breast and ovarian cancer. BRACAnalysis® testing is used to detect the presence and characterization of a mutation in the BRCA1 or BRCA2 gene. These mutations are responsible for the majority of hereditary breast and ovarian cancers. Declaration of Alexander Ford ("Ford Decl."), ¶¶ 1, 3.

**Response to SF No. 3:** Ambry admits the first two sentences. Ambry objects to the term "these mutations" as vague and there lacks knowledge and information sufficient to form a belief as to the truth or falsity of the third sentence and therefore disputes it.

**SF No. 4:** The results of BRACAnalysis® testing enable a patient and her medical provider to develop specific, targeted medical management plans to significantly reduce the risk of developing those types of hereditary cancer. To date, BRACAnalysis® testing has benefited over one million patients. *Id*., ¶ 1.

**Response to SF No. 4:** Ambry disputes SF No. 4. *See, e.g.*, Swisher Decl., ¶¶ 12-18.

**SF No. 5:** BRACAnalysis® testing is very important to Myriad Genetics' business model. As the first genetic test for a common, major disease (breast cancer), Myriad Genetics has created and nurtured to maturity a new market for clinical diagnostic testing for hereditary cancer predisposition. *Id*., ¶ 2.

**Response to SF No. 5:** Ambry disputes the second sentence of SF No. 5. Ambry lacks knowledge or information sufficient to form a belief as to the truth or falsity of the rest of SF No. 5 and therefore disputes it.

**SF No. 6:** In reliance upon its patents, and for the seventeen years that it has been on the market, Myriad Genetics dedicated significant effort and substantial investment toward bettering the quality, accuracy and reliability of its BRACAnalysis® test. *Id*., ¶¶ 3, 4.

**Response to SF No. 6:** Ambry disputes SF No. 6. *See, e.g.,* Swisher Decl., ¶¶ 12-128; Ledbetter Decl., ¶¶ 11-47.

**SF No. 7:** These efforts have also led to an extensive database of genetic variant information, which was developed in part utilizing research and a $100 million investment by Myriad Genetics. This database has allowed Myriad Genetics to further improve its test quality by ensuring that over 97% of the patients tested with BRAC*Analysis*®*,* who receive a report identifying a genetic variation, will be informed as to the clinical significance of the variant. *Id*., ¶¶ 6, 7.

**Response to SF No. 7:** Ambry disputes SF No. 7. *See, e.g.,* Swisher Decl., ¶¶ 12-128; Ledbetter Decl., ¶¶ 11-47.

**SF No. 8:** Myriad Genetics has also invested heavily in creating from scratch the market for breast/ovarian cancer genetic testing, including conducting extensive clinical studies in

support of medical industry guidelines regarding hereditary cancer predisposition testing, developing a market of insurance reimbursement, both public and private, for such testing, and promoting physician and patient education surrounding the importance of hereditary cancer awareness and testing. Myriad Genetics has expended over $500 million in developing its BRACAnalysis® test and the market for molecular diagnostic testing. *Id*., ¶ 4.

**Response to SF No. 8:** Ambry disputes SF No. 8. *See, e.g.,* Swisher Decl., ¶¶ 12-128; Ledbetter Decl., ¶¶ 11-47.

**SF No. 9:** In 2009, the Association for Molecular Pathology, along with a number of professional groups of clinical pathologists and individual physicians filed suit against Myriad Genetics and the University of Utah, seeking a declaratory judgment that certain of Plaintiffs' patent claims were unpatentable subject matter under 35 U.S.C. § 101. On June 13, 2013, after a lengthy procedural history, the Supreme Court held that certain claims pertaining to naturally occurring DNA were not patent eligible. However, the Court emphasized the limited scope of its ruling and endorsed the validity of claims pertaining to synthetic DNA and methods of testing and using isolated genes in medical diagnosis and treatment. *See Association for Molecular Pathology v. Myriad Genetics, Inc., et. al*., 133 S.Ct. 2107 (2013).

**Response to SF No. 9:** Ambry admits the first sentence and disputes the rest for the reasons set forth in Section IV.A, *infra*.

**SF No. 10:** Just hours after the Supreme Court decision issued, Ambry announced that it is now offering a number of its own tests that include BRCA1 and BRCA2 testing. *See* http://ambrygen.com/tests/brcaplus-%E2%80%93-high-risk-breast-cancer-panel. Ford Decl., ¶ 9.

**Response to SF No. 10:** Ambry admits SF No. 10.

**SF No. 11:** Ambry also released a Cancer Test Requisition Form that offers various different tests, four of which (BreastNext, BRCAPlus, CancerNext and OvaNext) offer BRCA1 and/or BRCA2 testing. *Id*., ¶ 10; (Exh. 1).

**Response to SF No. 11:** Ambry admits SF No. 11.

**SF No. 12:** Ambry further indicated that it will offer its BRCAPlus test for $2,280, significantly below the price of Myriad Genetics' integrated BRACAnalysis® test, which is priced at $4,040. *Id*., ¶ 11. While Ambry's tests do not offer the accuracy, quality and reliability of Myriad Genetics' integrated BRAC*Analysis*® test, they present a significant competitive threat as third-party payors, rather than patients and their health-care providers, frequently decide where testing will be performed and such payors are often not well-informed about the competitive quality of such tests. *See id*., ¶¶ 17-20.

**Response to SF No. 12:** Ambry disputes SF No. 12. *See, e.g.*, Chao Decl., ¶¶ 11-75; Swisher Decl., ¶¶ 12-128.

**SF No. 13:** Ambry is able to offer testing at this discounted price by unfairly and improperly "free-riding" off of the hundreds of millions of dollars invested by Myriad Genetics in developing the science and market for clinical diagnostic testing for hereditary cancers. *See supra* at ¶¶ 6-8.

**Response to SF No. 13:** Ambry disputes SF No. 12. *See, e.g.*, Chao Decl., ¶¶ 11-75; Swisher Decl., ¶¶ 12-128.

**2. Gene by Gene's Responses**

As to Statements of Fact numbers 1-9, Gene by Gene's responses are the same as Ambry's above.

**SF No. 10:** Just days after the Supreme Court decision issued, Gene by Gene announced on its website that it is now offering BRCA1 and BRCA2 testing. Ford Decl., ¶ 9 (Exh. 1).

**Response to SF No. 10:** Gene by Gene admits SF No. 10.

**SF No. 11:** Gene by Gene also issued a press release of the same date as the decision stating that it is now offering BRCA breast and ovarian cancer testing. *Id*., ¶ 10 (Exh. 2).

**Response to SF No. 11:** Gene by Gene admits SF No. 11.

**SF No. 12:** Gene by Gene further indicated that it will offer combined BRCA 1 and BRCA2 testing for $995.00, significantly below the price of Myriad Genetics' integrated BRACAnalysis® test, which is priced at $4,040. *Id*., ¶ 11. Gene by Gene's tests do not offer the quality and reliability of Myriad Genetics' integrated BRAC*Analysis*® test, which has been honed and improved over 17 years of experience and has the benefit of a proprietary database aiding in the interpretation of test results. *Id*., ¶¶ 5-6; 18-19. However, Gene by Gene's newly offered tests present a significant competitive threat as third-party payors, rather than patients and their health-care providers, frequently decide where testing will be performed and such payors are often not well-informed about the competitive quality of such tests. *See id*., ¶¶ 12-13.

**Response to SF No. 12:** Gene by Gene admits that it indicated that it will offer BRCA1 and BRCA2 testing for $995, and disputes the rest. *See, e.g.*, Mittelman Decl., ¶¶ 9-32; Swisher Decl., ¶¶ 12-128.

**SF No. 13:** Gene by Gene is able to offer testing at this discounted price by unfairly and improperly "free-riding" off of the hundreds of millions of dollars invested by Myriad Genetics in developing the science and market for clinical diagnostic testing for hereditary cancers. *See supra* at ¶¶ 6-8.

**Response to SF No. 13:** Gene by Gene disputes SF No. 12. *See, e.g.*, Chao Decl., ¶¶ 11-75; Swisher Decl., ¶¶ 12-128.

**B. DEFENDANTS' STATEMENT OF FACTS**

**1. Unpatentable Subject Matter Under § 101**

1. The information contained in a segment of DNA is contained in the sequence of nucleotides of that segment. *E.g.*, Pribnow Decl., ¶¶ 22-27; Tait Decl., ¶ 32.

2. Segments of "natural" DNA in the human body are indistinguishable from identical DNA segments chemically synthesized, both structurally and in the information the two types of segments contain. *E.g.*, Pribnow Decl., ¶¶ 19, 52-54.

3. Single-stranded DNA exists in nature during the steps of DNA replication and DNA transcription, processes that occur literally trillions of times in the human body. *E.g.*, Pribnow Decl., ¶¶ 35-38, 43, 81.

4. Where a chemically synthesized DNA segment and the natural DNA segment have the same nucleotide sequence, the types of DNA segments are indistinguishable. *E.g.*, Pribnow Decl., ¶¶ 52-54.

5. The natural law of Watson-Crick base pairing requires that the following nucleotides in opposite DNA segments pair as follows: adenine (A) and thymine (T); guanine (G) and cytosine (C). *E.g.*, Pribnow Decl., ¶¶ 28-32; Tait Decl., ¶ 22.

6. DNA segments that are complementary will associate (hybridize) through Watson-Crick base pairing regardless of whether both DNA segments are "natural" DNA found in the body, DNA segments chemically synthesized in the laboratory, or a combination of the two. *E.g.*, Pribnow Decl., ¶¶ 28-38, 66-68, 91.

7. A PCR synthesized copy ("amplicon") of genomic DNA is indistinguishable from the genomic DNA segment that is used as a template. *E.g.*, Pribnow Decl., ¶¶ 16, 58, 64, 68, 70; Tait Decl. ¶¶ 29-32.

8. "Complementary DNA," or "cDNA," is a term of art that means a DNA molecule chemically synthesized from a messenger RNA ("mRNA") transcript from which the introns have been removed. *E.g.*, Pribnow Decl., ¶¶ 78, 82.

9. "Complementary DNA" and "primers" do not refer to the same type of molecule, because primers are not synthesized from a mRNA from which the introns have been removed. *E.g.*, Pribnow Decl., ¶ 78.

10. PCR was well known in the art by August 12, 1994. *E.g.*, '999 patent at col. 17 ll. 14-34, col. 25 ll. 52-57; Pribnow Decl., ¶¶ 74, 75; Tait Decl., ¶ 29.

11. DNA sequencing was well known in the art by August 12, 1994. *E.g.*, '999 patent at col. 14 ll. 1-7, col. 17 ll. 14-34; Tait Decl., ¶ 35.

12. Using probes to hybridize to DNA sequences was well known in the art by August 12, 1994. *E.g.*, '999 patent at col. 15 ll. 9-20, col. 17 ll. 14-34, col. 21 l. 37 - col. 22 l. 27.

**2. Equitable Factors**

13. Abel (1993) and Anderson (1993) each discloses a pair of PCR primers that are derived from human chromosome 17q. The primer pairs were used to amplify intragenic marker D17S855. Gregory Decl., ¶¶ 60-62, 68-70, Exs. A, B; Bowcock Decl., ¶¶ 65-66, 72, Exs. B, C.

14. Intragenic markers D17S855 and D17S932 became publicly available no later than July 12, 1993. Both markers are part of the *BRCA1* gene. Gregory Decl., ¶¶ 76-79, 86-88, Exs. A, B, C; Bowcock Decl., ¶¶ 66, 80-82, Exs. B, C, K.

15. Bowcock (1993) describes the steps and techniques researchers in the field would use to identify the sequence of *BRCA1*. Each step adopts conventional approaches that were known in the field. Gregory Decl., ¶¶ 122-124, Ex. G; Bowcock Decl., ¶¶ 30-31, 34, 37-39, 42-45, 48, 52-53, Ex. G

16. Genetic screening, such as screening the ΔF508 mutation for cystic fibrosis, was widely used by 1994. Gregory Decl., ¶ 104; Bowcock Decl., ¶ 61.

17. Miki (1994) discloses the identification of neutral sequence variations in BRCA1 that are not associated with breast or ovarian cancer (Table 3), as well as sequence variations that do cause a pre-disposition to breast or ovarian cancer (Table 2). Gregory Decl., ¶¶ 138, 167, Ex. AA; Bowcock Decl., ¶¶ 114-115, Ex. H.

18. Friedman (1994) discloses the identification of neutral sequence variations in BRCA1 that are not associated with breast or ovarian cancer (Table 3), as well as sequence variations that do cause a pre-disposition to breast or ovarian cancer (Tables 2a and 2b). Gregory Decl., ¶¶ 147, 175, Ex. BB; Bowcock Decl., ¶¶ 118-119, Ex. L.

19. U.S. Patent No. 5,747,282 discloses the identification of neutral sequence variations in BRCA1 that are not associated with breast or ovarian cancer, as well as sequence variations that do cause a pre-disposition to breast or ovarian cancer (Tables 11). Gregory Decl., ¶¶ 155, 183-184; Bowcock Decl., ¶ 120.

20. Schutte (Oct. 1995) discloses two pairs of PCR primers derived from human chromosome 13. The primer pairs were used to amplify intragenic markers 886s186 (91 base pairs) and 886s239 (76 base pairs), located within the *BRCA2* gene. Gregory Decl., ¶¶ 238-239, Ex. M.

21. "H47777" and "H48122" each is an EST sequence submitted to GenBank by RZPD Deutsches Ressourcenzentrum fuer Genomforschung GmbH, Inge Arlart on February 20, 1995. Both ESTs are located entirely within the *BRCA2* gene. Gregory Decl., ¶¶ 246-247, 256-257, Exs. EE, FF.

22. Schutte (June 1995) compared normal (wild-type) DNA and tumor DNA, and discovered that the tumor DNA has a deletion in the *BRCA2* chromosomal region. Later it was confirmed that the deletion is within the *BRCA2* gene. Gregory Decl., ¶ 270, Ex. L.

23. Three U.S.-based authors listed in Wooster (1995) reviewed and approved the manuscript before it was submitted to Nature on December 5, 1995. Gregory Decl., ¶¶ 274-275, Ex. Q.

24. Wooster (1994) mapped the *BRCA2* gene to a 6 centiMorgan region. It also discloses that the most likely region for *BRCA2* is between D13S260 and D13S267 (1 centiMorgan apart). Gregory Decl., ¶¶ 278-280, Ex. P.

25. A specific PAC contig that comprises the *BRCA2* gene, as well as the partial sequence of this contig, were released to the public domain no later than November 23, 1995. Gregory Decl., ¶ 288, Ex. K.

26. PAC clones that contain the *BRCA2* gene, or fragments of the *BRCA2* gene, were available no later than February 1994. Gregory Decl., ¶ 291.

**3. Noninfringement**

27. All of the accused Ambry tests screen the same way for point mutations in *BRCA1* and *BRCA2*. Elliott Decl., ¶ 6.

28. Ambry technicians use PCR to amplify all of the sequences of the exons of *BRCA1* and *BRCA2* as well as at least 20 nucleotides of the intronic sequences adjacent to each exon. *Id.* ¶ 8.

29. The primers used by Ambry to perform PCR contain sequences that are not derived or isolated from the sequences of human chromosomes 17q and/or 13. *Id.* ¶¶ 15-19.

30. The primers used by Ambry to sequence amplicons do not have any sequences derived or isolated from the sequences of human chromosomes 17q and/or 13. *Id.* ¶ 26.

31. Ambry aligns patient DNA sequences to the sequence for the whole human genome. *Id.* ¶¶ 32-34.

32. Ambry does not use allele specific probes to identify the presence of particular known variants. *Id.* ¶ 49.

33. Gene by Gene technicians intend to use PCR to amplify all of the sequences of the exons of *BRCA1* and *BRCA2* as well as 50 nucleotides of the intronic sequence flanking each exon. Mittelman Decl., ¶ 16.

34. The primers Gene by Gene intends to use to perform PCR contain sequences that are not derived or isolated from the sequence of human chromosomes 17q and/or 13. *Id.*

35. Gene by Gene intends to align patient DNA sequences to the sequence of the whole human genome. *Id.* ¶ 20.

36. Gene by Gene does not intend to use allele-specific primers. *Id.* ¶ 21.

**4. Equitable Factors**

37. Monetary damages for price erosion and market loss can be calculated using accepted and customary financial accounting methods. Hampton Decl., ¶¶ 31, 40, 49.

38. On August 13, 2013, Myriad forecast 14% to 18% revenue growth for its core test products, including BRCA1/2 tests, in Fiscal Year 2014. The forecast takes into consideration the recent emergence of competition for BRCA1/2 tests and also is in line with Myriad's May 2013 forecast, prior to Defendants' entry into the BRCA1/2 market. *Id.* ¶¶ 52-53, Ex. R.

39. Myriad currently holds over $400 million of cash and cash equivalents. *Id.* ¶ 66, Ex. U.

40. Myriad sets prices for its BRCA1/2 tests through contracts with insurers. Ford 2nd Decl., ¶ 4. Customarily, prices set by such insurance contracts do not change frequently or quickly. Hampton Decl., ¶ 28.

41. Myriad has licensed one or more of the patents-in-suit. Ford 2nd Decl., ¶ 6.

42. Following the Supreme Court's June 13, 2013 *Myriad* decision, the University of Washington Department of Laboratory Medicine, GeneDX Inc., Quest Diagnostics Inc., Pathway Genomics Inc., and Ethigen, LLC began offering or announced they will offer BRCA1/2 testing. Plaintiffs have not sued any of these entities for patent infringement. Hampton Decl., ¶ 30.

43. If enjoined, Ambry and Gene by Gene will lose their headstart advantage of being first entrants in the market to offer an alternative BRCA1/2 test to Myriad. *Id.* ¶ 58.

44. Ambry invested an estimated $46.7 million in capital resources to be positioned to offer the first comprehensive multi-gene hereditary test for breast and ovarian cancer. Ambry expanded its laboratory and hired 110 additional employees. If enjoined, Ambry expects it will go out of business and layoff most or all of its 180 employees. *Id.* ¶ 57.

45. Breast and ovarian cancers are deadly diseases affecting a large number of women. Early risk detection of these cancers through BRCA1/2 testing saves lives by assisting with diagnosis, preventative measures, and treatment. Swisher Decl., ¶¶ 19-20.

46. Many patients who want BRCA1/2 testing cannot afford Myriad's BRCA1/2 test price of $4,040. Swisher Decl., ¶¶ 122-24; Chao Decl., ¶¶ 26-28; Gaede Decl., Ex. H (Raker Decl., ¶¶ 6-10), Ex. I (Thomason Decl., ¶¶ 6-9). Ambry offers a multi-gene panel test including BRCA1/2 for $2,200. Gene by Gene offers its BRCA1/2 test for $995. Chao Decl., ¶ 26; Mittelman Decl., ¶ 14. Patients who could not afford or whose insurance did not cover Myriad's BRCA1/2 test have now been tested by Ambry. Matloff Decl., ¶ 10.

47. Myriad cannot offer second opinion testing of its own BRCA1/2 tests. Swisher Decl., ¶ 121.

48. Ambry currently provides hereditary cancer tests that include testing of BRCA1 and BRCA2 and offer features not available for Myriad's BRCA1/2 test offerings, including test results reports containing the bases for variant classifications, both full sequencing and large rearrangement testing billed for one price under one insurance code, testing under health plans that currently do not cover Myriad testing, and multi-gene breast and ovarian cancer panel tests. Chao Decl., ¶ 16-21, 29, 50-51.

49. Myriad's BRCA1/2 tests do not automatically include large rearrangements, which are known to account for about 10% of all deleterious mutations. Swisher Decl., ¶¶ 63, 70-98. Ambry's BRCA1/2 tests automatically include large rearrangements. Chao Decl., ¶ 17. Without large rearrangements, patients will receive false negatives. Swisher Decl., ¶¶ 72-82, 95-96; Morris Decl., ¶ 7; Matloff Decl. ¶ 7; Ledbetter Decl., ¶¶ 15-17, 20.

50. Comprehensive public databases of BRCA1/2 data allow genetic testing laboratories and researchers to better understand and classify more variants with more reliability, thereby advancing patient care. Nussbaum Decl., ¶¶ 27-40; Ledbetter Decl., ¶¶ 35-44; Swisher Decl., ¶¶ 26-32. Myriad does not share BRCA1/2 data with public databases. Ledbetter Decl., ¶¶ 36-40. Ambry and Gene by Gene have committed to sharing BRCA1/2 data with public databases, and Ambry has already begun doing so. Chao Decl., ¶ 64; Mittelman Decl., ¶¶ 25-26.

51. In 1996, Myriad established a public database to collect and organize data and personal and family cancer histories for persons tested for mutations in *BRCA1* and *BRCA 2*. Nussbaum Decl., ¶ 17.

52. In 2004, Myriad made its last major deposit to the public database, and in 2005 Myriad stated its intention of keeping as a trade secret patient sequence data. Nussbaum Decl., ¶ 21.

53. The lack of comprehensive, publicly available databases of patient sequence variants is one of the most critical problems facing clinical geneticists and their patients today. Nussbaum Decl., ¶ 27

54. Ambry's VUS rate (*i.e.*, how often a variant is classified as a variant of unknown significance) is presently 4.5%. Chao Decl., ¶¶ 52-53. Gene by Gene estimates an initial VUS rate less than 12-13%. Mittelman Decl., ¶ 28. Myriad reports a 3% VUS rate but, unlike Ambry, does not disclose the internal data upon which it relies to make its classifications, so Myriad's VUS rate is unverifiable. Swisher Decl., ¶¶ 43-49; Chao Decl., ¶¶ 59-60.

55. Ambry's analytic sensitivity is greater than 99%, with a false negative rate much less than 0.1%. Ambry's false positive rate is virtually 0% because Ambry confirms any variant

it finds by next-gen sequencing with a second Sanger sequencing test. Myriad does not report the analytical sensitivity of BRACAnalysis or BART. Chao Decl., ¶¶ 37, 41, 42; Swisher Decl., ¶¶ 63, 65.

56. Myriad announced this year that it intends to offer a new multi-gene panel test where it will switch to next-generation sequencing, a sequencing method Ambry has long used in its tests but Myriad has not used. If implemented, Myriad's new myRisk panel test will be nearly identical to Ambry's CancerNext test, including using the same third party, RainDance Technologies, Inc., to aid in the design of primers. Chao Decl., ¶¶ 45-47.

57. Myriad has asserted its patents to block scientific research, collaborative data collection and sharing, patient screenings at cancer diagnostic facilities, and development and offering of additional, alternative, and more affordable technologies. Stiglitz Decl., ¶¶ 23-40; Leonard Decl., ¶¶ 26-44; Ledbetter Decl., ¶¶ 11-21, 35-47; Matloff Decl., ¶¶ 6-7; Gaede Decl. Ex. B (Ganguly Decl., ¶¶ 3-14), Ex. E (Kazazian Decl., ¶¶ 3-11), Ex. F (Ostrer Decl., ¶¶ 5-12).

58. A 2001 survey of laboratory directors throughout the United States conducted through a grant from the National Human Genome Research Institute of the National Institutes of Health showed that "patents on genes used for clinical diagnostics inhibit the conduct of research to further the development of improvements to genetic tests [and] . . . inhibit clinical diagnostic laboratories from providing clinical tests and services. The survey further showed such "patents are not necessary to incent either the research on initial discoveries or the development of clinical applications and commercializable products." Cho Decl., ¶¶ 24-25.

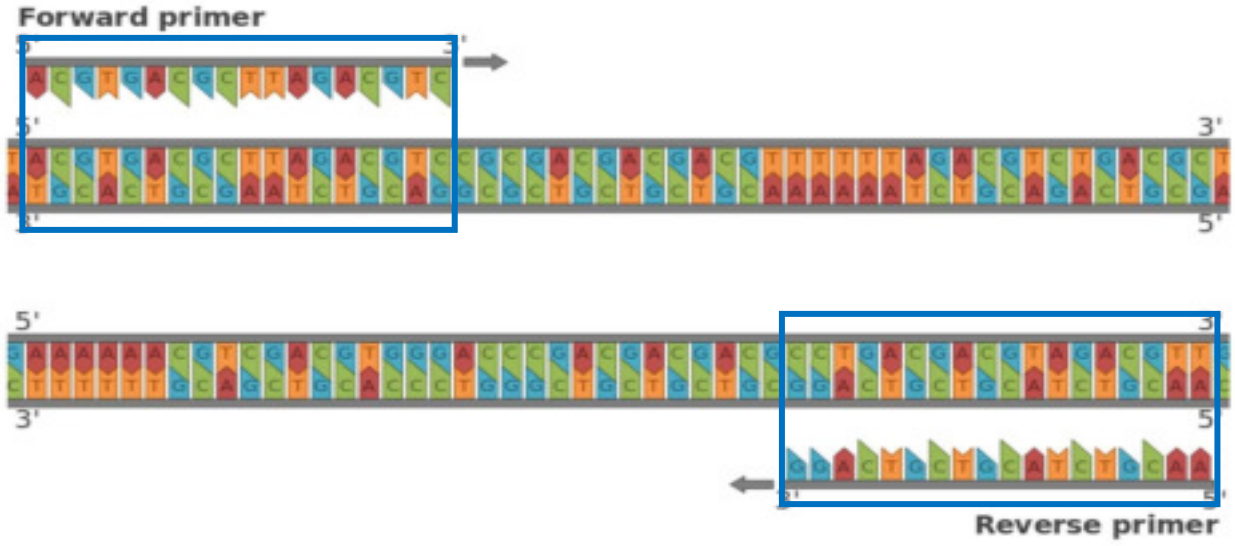
### C. BACKGROUND OF TECHNOLOGY AT ISSUE

The technical subject matter of Plaintiffs' Motions is the comparison of isolated patient *BRCA* sequences with "wild-type," or "normal," *BRCA* sequences to identify variants in the patient sequences that may predispose the patient to a higher likelihood of developing hereditary breast, ovarian or other cancers. Specifically, the technical subject matter involves isolation of patient DNA sequences by polymerase chain reaction (PCR) amplification and sequencing or "probing" patient sequences to identify the presence of variants in the patients' *BRCA* genes.

PCR makes an exact copy of a target gene sequence through the use of chemically synthesized DNA molecules called "primers" that, just like DNA made by the cell, behave according to the natural law of Watson-Crick base pairing. DNA is a polymer of subunits called "nucleotides." The nucleotide sequence the DNA in a person's chromosomes (all 23 pairs of them) contains the information for all the processes carried out in the body. Pribnow Decl., ¶¶ 33-34, 37. There are four nucleotides in DNA: adenine (A), cytosine (C), guanine (G), and thymine (T). *Id.* ¶ 24.

Generally – but not always - DNA in nature exists as a "double-stranded" molecule where the two strands of DNA are associated through noncovalent, Watson-Crick base pair interactions. *Id.* ¶¶ 28-38. The law of Watson-Crick base pairing is exemplified in Plaintiffs' depiction of double-stranded DNA, a portion of which is reproduced below, and dictates that in DNA A's always and can only associate with T's, and C's always and can only associate with G's. Myriad Ambry P.I. Br. at 17; Pribnow Decl., ¶¶ 28-32. Importantly, this law applies to DNA segments irrespective of whether the segments are created by Mother Nature or chemically synthesized in the lab to follow Mother Nature's order, making the DNA indistinguishable

between "natural" and chemically synthesized DNA. Pribnow Decl., ¶¶ 52-54, as Plaitiffs' moving papers depicted:

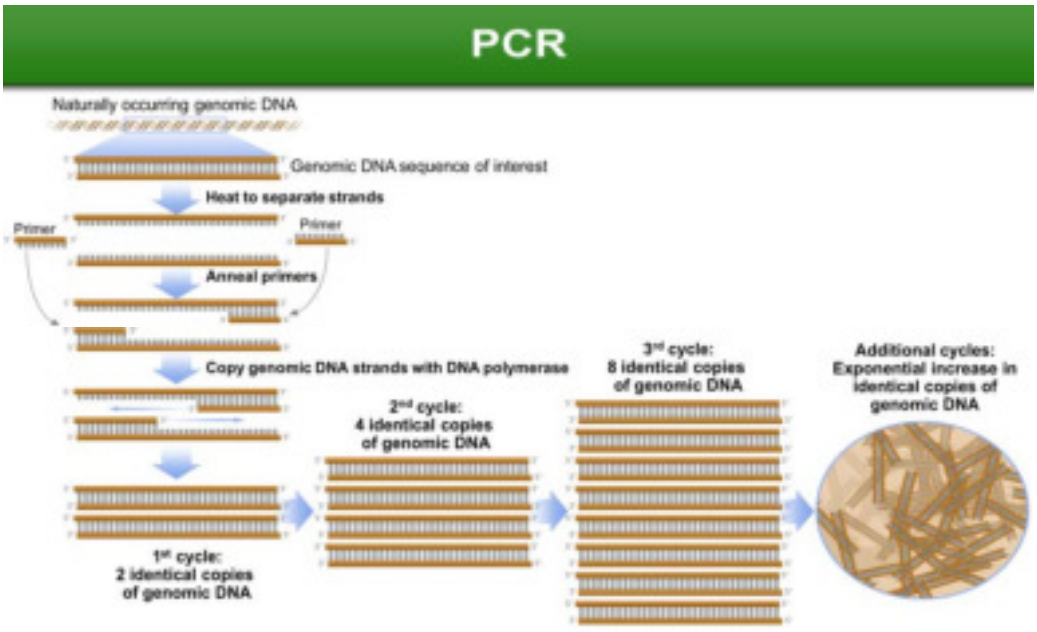



When a researcher uses PCR to isolate a DNA sequence of interest, the first step is to identify primer sequences that will hybridize to a segment adjacent to the sequence he or she wants to isolate. [1] *Id.* ¶¶ 57-59, 91; Tait Decl., ¶ 22. This hybridization occurs according to the law of Watson-Crick base pairing. This principle also is exemplified in Plaintiffs' diagram (forward and reverse primers flanking the region to be isolated). Note that the sequences of the primers are indistinguishable from the corresponding segments of the DNA strand when both are read in the 5′ → 3′ direction, as identified by the blue boxes.

During PCR, as depicted below, the strand of the DNA are separated, the primers anneal to the primer binding sites on based on Watson-Crick base pairing, and the primers are "extended," meaning that synthetic DNA strands are created that are complementary to the

[1] Note that Plaintiffs' exemplary DNA molecules are not contiguous (*i.e.*, there is intervening sequence between the two double-stranded DNA molecules that is not pictured). For the purposes of this background discussion, Defendants are presuming that both molecules are part of the same DNA segment being amplified.

natural DNA. Pribnow Decl., ¶¶ 57-59, 91. These steps complete one PCR "cycle." After the first cycle of PCR, the target sequence between the primers will have been isolated in a hybrid molecule consisting of a "natural" DNA strand and its chemically-synthesized complement. *Id.* ¶¶ 57-59. During subsequent cycles, the "natural" DNA strands are diluted in the sense that the vast majority of the copies made consist of identical, chemically synthesize strands. With every additional cycle, the amount the isolated target sequence doubles: X, 2X, 4X, 8X, etc. *Id.*




Ultimately, billions of copies of target sequence are isolated during a typical PCR reaction.

Patient sequences isolated by PCR can be used to determine whether a patient has a mutation in his or her *BRCA* genes. The amplicons can be "sequenced," which means that the exact nucleotide sequence of the PCR copies of the patient's DNA is determined. Tait Decl., ¶ 35; '282 Patent col. 14, ll. 1-7. Once the sequence of the patient's DNA is determined, it is compared to the wild-type *BRCA* gene sequence to identify any variations, whether previously known or not.

Another method of determining whether a patient carries a mutation is to use "probes" specific for known variations. Probes are molecules similar to primers inasmuch as they typically are short, chemically synthesized segments of DNA that follow the natural DNA's sequence and are designed to hybridize to a particular DNA segment via Watson-Crick base pairing. Pribnow Decl., ¶¶ 85-87; Tait Decl., ¶¶ 23-26.

Probes are used differently than primers, however. Rather than being extended during an amplification reaction, probes are incubated with patient DNA to determine whether a particular sequence is present. Pribnow Decl., ¶¶ 85-89; Tait Decl., ¶¶ 23-26; '441 Patent col. 15, ll. 29-43, col. 19, ll. 24-30, col. 21, ll. 35-41. A probe is designed to hybridize only to a certain target; thus, if the sequence complementary to the probe is not present, then the probe will not hybridize. Pribnow Decl., ¶¶ 85-89; Tait Decl., ¶¶ 23, 26; '441 Patent col. 15, ll. 29-43, col. 19, ll. 24-30, col. 21, ll. 35-41. Generally, probes can only be used to identify known mutations, because the probe sequence is designed to hybridize to a known sequence. Pribnow Decl., ¶¶ 85-89; Tait Decl., ¶¶ 23-26; '441 Patent col. 15, ll. 29-43, col. 19, ll. 24-30, col. 21, ll. 35-41. A patient sample can be incubated with several probes at once, and the presence of a known mutation is identified by determining which – if any – probe hybridizes to the patient sequence. Pribnow Decl., ¶¶ 85-89; Tait Decl., ¶¶ 23-26.

PCR, DNA sequencing and probing for specific sequences well known in the art as of 1994. The asserted patents make this clear: "The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology." '282 Patent at col. 25, ll. 50-60 (citing to references published between 1982 and 1992). Specifically, PCR admittedly was

known in the art. *E.g.*, *id.* at col. 17 ll. 15-34 (citing patents issued in 1990); *see also* Pribnow Decl., ¶ 74 (describing invention of PCR in 1980s); Tait Decl., ¶ 29 (same). As were using probes to identify specific DNA sequences, (*e.g.*, '282 Patent at col. 21, l. 33 - col. 22, l. 25 (citing references from 1989 and 1992)), and DNA sequencing. *Id.* at col. 14, ll. 1-7 (describing that DNA sequencing was "well known in the art"); Tait Decl., ¶ 35 (describing that DNA sequencing was developed in the late 1970s).

## III. LEGAL STANDARDS FOR CONSIDERING AN APPLICATION FOR A PRELIMINARY INJUNCTION

"As a preliminary injunction is an extraordinary remedy, the right to relief must be clear and unequivocal." *Schrier v. Univ. of Col.*, 427 F.3d 1253, 1258 (10th Cir. 2005). Accordingly, to grant Plaintiffs' application, the Court must find that each of four factors weigh in Plaintiffs' favor[2]: "A plaintiff seeking a preliminary injunction must establish that he is likely to succeed on the merits, that he is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in his favor, and that an injunction is in the public interest." *Winter v. Natural Res. Def. Council, Inc.*, 555 U.S. 7, 20 (2008); *Roda Drilling Co. v. Siegal*, 552 F.3d 1203, 1208 (10th Cir. 2009) (*citing Winter*); *Aria Diagnostics, Inc. v. Sequenom, Inc.*, --- F.3d. ---, No. 2012-1531, 2013 WL 4034379, at *6 (Fed. Cir. Aug. 9, 2013) ("On remand, if the district court finds no substantial questions of validity or infringement, it must address the traditional equitable factors for a preliminary injunction.").

[2] Plaintiffs imply that the Court may issue a preliminary injunction even where some factors favor Defendants. (*E.g.*, Plaintiffs' Ambry PI Br. at 8.) Plaintiffs are wrong. The Supreme Court and Tenth Circuit law post-*Winter* clearly require that all factors weigh in favor of the movant before a preliminary injunction can issue.

All questions considered in the four-factor analysis are decided in light of the same standards and burdens of proof that will apply at trial. *Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1364 (Fed. Cir. 2008). Issues involving patent law are decided according to Federal Circuit precedent, and other questions are decided according to Tenth Circuit law.[3] *Id.* at 1367; *Hybritech, Inc. v. Abbott Labs.*, 840 F.2d 1446, 1451 n. 12 (Fed. Cir. 1998); *Revision Military, Inc. v. Balboa Mfg. Co.*, 700 F.3d 524, 525 (Fed. Cir 2012).

### A. PLAINTIFFS HAVE NOT DEMONSTRATED A LIKELIHOOD OF SUCCESS ON THE MERITS

To establish likelihood of success on the merits, Plaintiffs must show that "in light of the presumptions and burdens that will inhere at the at trial on the merits: (1) [they] will likely prove that [Ambry] infringes the asserted patent[s]; and (2) [their] infringement claim will likely withstand [Ambry's] challenges to the validity and enforceability of the patent[s]." *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012).

In other words, Defendants need only demonstrate meritorious arguments that they infringe no valid claims. An invalidity or noninfringement defense is meritorious so long as it does not "lack substantial merit." *See Astrazeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1050-51 (Fed. Cir. 2010) (citations omitted) ("A preliminary injunction should not issue if an alleged infringer raises a substantial question regarding either infringement or validity, *i.e.*, the alleged

[3] Plaintiffs incorrectly represent that the Federal Circuit standards apply to the entire analysis, *citing Abbott Labs.* and *Revision Military.* (*E.g.*, Pl.'s Ambry Br. at 8). In *Abbott Labs*. the court plainly states, "This court has observed that the standard for granting or denying a motion for a preliminary injunction is not unique to patent law, and has ruled that the standard of the regional circuit should apply, here the Seventh Circuit." 544 F.3d at 1367. The issue in *Revision Military* was whether the Second Circuit's test for likelihood of success on the merits - which involves predominantly patent law - was the correct test. 700 F.3d at 525. The court in *Hybritech.* - in the same footnote cited by Plaintiffs - also recognized that procedural issues are governed by the law of the circuit in which the district court sits. 840 F.2d at 1451 n.12 (cited in Pl.'s Ambry Br. at 8 n. 3).

infringer asserts an infringement or invalidity defense that the patentee has not shown lacks substantial merit."). Indeed, raising substantial questions either of validity or infringement is sufficient to defeat a preliminary injunction, regardless of the outcome of the equitable factors. *Sequenom*, --- F.3d ---, 2013 WL 4034379 at *6 (instructing district court to consider equitable factors only if no substantial validity or infringement questions raised); *LL& L Innovs., LLC v. Jerry Leigh of Calif., Inc.*, No. 10-CV-829, 2010 WL 3956815, at *8 (D. Utah Oct. 8, 2010) (denying application for preliminary injunction where question of likelihood of succeeding on infringement was "close," and, "[g]iven the ambiguities in the record, the court finds that Plaintiffs have not established a likelihood of success on the merits and so are not entitled to injunctive relief at this time.").

### B. PLAINTIFFS ARE LIMITED TO THE CLAIMS AND THEORIES ARGUED IN THEIR OPENING BRIEF

Plaintiffs have asserted fifteen patents against Ambry and nine against Gene by Gene. But in their Application they attempt to show only 10 claims from six patents are valid and infringed. Plaintiffs also have alleged only direct, literal infringement by Defendants. If Plaintiffs had other theories of infringement, such as indirect or by the doctrine of equivalents, or wished to raise other patents, they had the opportunity to raise them in their opening brief, and failed to do so.

All arguments other than those specifically advanced in Plaintiffs' Application are waived, as arguments cannot be first raised in a reply brief. *See, e.g.*, *Utah Environ. Congress v. MacWhorter*, No. 08-CV-118, 2011 WL 4901317, at * 16 (D. Utah Oct. 14, 2011) (declining to consider issue raised for first time in reply that was "not clearly raised, could not be identified by [movant], and certainly was not adequately briefed" in the opening papers) (*citing Merrifield v.*

*Board of Cnty. Comm'rs,* 654 F.3d 1073 (10th Cir.2011) (declining to address argument that was not raised in opening brief but was raised later at oral argument); *U.S. v. Waseta,* 647 F.3d 980, 989 n.6 (10th Cir.2011) (refusing to address argument developed for first time in reply brief).

## IV. THE ASSERTED CLAIMS ARE INVALID UNDER SECTION 101 AS UNPATENTABLE SUBJECT MATTER

Patentable subject matter under 35 U.S.C. § 101 includes any "new and useful process, machine, manufacture or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. "Laws of nature, natural phenomena, and abstract ideas are not patentable." *Mayo Collaborative Servs. v. Prometheus Labs, Inc*., __U.S.__, 132 S. Ct. 1289, 1293, 182 L. Ed. 2d 321 (2012) (internal quotation marks omitted). These exceptions make ineligible, for example, mental processes, *see Gottschalk v. Benson*, 409 U.S. 63, 67, 93 S. Ct. 253, 34 L. Ed. 2d 473 (1972), and products of nature, *cf. Diamond v. Chakarbarty*, 477 U.S. 303, 313, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980). "Limiting an abstract idea to one field of use or adding token postsolution components [does] not make [a] concept patentable." *Bilski v. Kappos*, __U.S.__, 130 S. Ct. 3218, 3231, 177 L. Ed. 2d 792 (2010) (finding unpatentable subject matter in process claim limited to particular area of hedging risk in one market). For the reasons discussed below, each of the ten asserted patent claims is invalid under Section 101.

### A. THE SUPREME COURT'S UNANIMOUS DECISION IN *MYRIAD* PROHIBITS THE PATENTING OF SYNTHESIZED DNA COMPOSITIONS THAT MIRROR THE NATURAL GENOMIC DNA SEQUENCE RENDERING INVALID PLAINTIFFS' FOUR PRIMER CLAIMS DIRECTED TO BRCA1 AND BRCA2 GENE SEQUENCES IN THE '282 AND THE '492 PATENTS

Plaintiffs' claim that their four primer claims directed to "synthetic" DNA constitutes patentable subject matter. This reflects an untenable recasting of a position Plaintiffs' already argued for and lost in the courts. If the DNA primer nucleotide sequence created in the lab

corresponds to a natural DNA nucleotide sequence, then it is an unpatentable product of nature under *Myriad*. To understand why requires a close analysis of the prior *Myriad* litigation and why the decisions rendered clearly and convincingly invalidate the four primer claims that Plaintiffs wrongfully seek to resuscitate in this litigation.

### 1. Judge Sweet Rejects Plaintiffs' Position That DNA Primers Constitute Patentable Subject Matter

The four DNA primer composition claims come from the '282 and the '492 Patents that were at issue in the *Myriad* litigation. There, the patent eligibility of BRCA "isolated DNA" composition claims was challenged. The District Court, the Federal Circuit, and the Supreme Court divided the challenged "isolated DNA" composition claims into two categories.

The first group of DNA composition claims covered "isolated DNA" that comprised all or part of the BRCA *natural* gene sequence set out in each patent's "**Seq ID 2**." Independent claim 1 and dependent claim 5 of the '282 patent are illustrative of the first group of claims, capturing isolated DNA segments as short as 15 nucleotides:

> 1. An **isolated DNA** coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in **SEQ ID No:2**.
>
> 5. An **isolated DNA** having **at least 15 nucleotides** of the DNA of Claim 1.

The second group of DNA composition claims was directed to isolated DNA that captured just the nucleotide sequence of the natural DNA "coding region" sequence (exons only). This group was referred to in the litigation as the "cDNA claims" because the cDNA generated in the lab reflected the sequence of just the coding region in SEQ ID. No. 1 and was not present in nature. Claim 2 of the '282 Patent illustrative: "The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in **SEQ ID. No:1**." Plaintiffs framed the scope of their cDNA claims before the Supreme Court as: "cDNA is a wholly synthetic

molecule with a ***sequence nowhere found in native DNA***." Myriad S.Ct. Br. at 36 (emphasis added) (Gaede Decl., Ex. J).

Turning to the district court litigation, Judge Sweet adopted the patents' definition of "isolated DNA" and construed "isolated DNA" to "refer to a segment of DNA nucleotides existing separate from other cellular components normally associated with native DNA, including proteins and other DNA sequences comprising the remainder of the genome, *and includes both DNA originating from the cell* ***as well as DNA synthesized through chemical or heterologous biological means***." *A'ssn for Molecular Pathology v. USPTO*, 702 F. Supp. 2d 181, 217 (S.D.N.Y. 2010) (adopting the definition in the patents' specification) (emphasis added); *see also* '282 Patent, col. 19:8-18; '492 Patent, col. 17:62-18:5. Plaintiffs advocated for this construction before Judge Sweet and never appealed or disputed their own patents' definition that isolated DNA could be DNA synthesized in a laboratory. *AMP*, 702 F.Supp.2d at 216-17.

Armed with this construction, Plaintiffs then embraced it and argued that the challenged "isolated DNA" claims' subject matter comprised the DNA tools used in molecular diagnostics, such as DNA primers synthesized in the lab:

- Plaintiffs presented expert testimony that laboratory synthesized "isolated" DNA tools, such as single stranded primers and probes, preserved patentability because they were not products of nature. Kay Decl., ¶¶ 134-38 (Gaede Decl., Ex. D).
- Plaintiffs argued these isolated DNA tools had "markedly different characteristics" under the Supreme Court's *Chakarbarty* decision despite having the same nucleotide sequence as natural DNA and thus were not products of nature. *Id*. 702 F.Supp. at 230.

- Judge Sweet characterized Plaintiffs' positions as follows: ". . . Plaintiffs rely on the fact that isolated DNA may be used in applications for which native DNA is unsuitable, namely, in 'molecular diagnostic tests (*e.g.*, as probes, primers, templates for sequencing reactions) . . . ." *Id*. at 230.

Judge Sweet rejected Plaintiffs' argument, finding that the isolated DNA's utility as primers and probes did not preserve their patentability because they had the *identical* natural sequence. He wrote: "[T]he basis for [a probe or primer's] utility is the fact that the isolated DNA possesses the *identical nucleotide sequence* as the target [genomic] DNA sequence, thus allowing target specific hybridization between the DNA primer and the portion of the target DNA molecule possessing the corresponding sequence." *Id*. at 231 (emphasis added).[4] The DNAs contained the identical nucleotide sequence as the natural nucleotide sequence. The "isolated DNA" primers and probes that comprised subject matter for the first group of claims lacked the hallmark "markedly different characteristics" from native DNA. Judge Sweet thus held the claims invalid because they contained patent ineligible product of nature subject matter. *Id*. at 231.

**2. The Federal Circuit Finds That Synthesized Diagnostic DNA Tools Such as Primers Are Markedly Different Under *Chakarbarty* From Natural DNA and Thus Not Patent Ineligible Products of Nature**

The Federal Circuit reversed, finding that isolated DNAs used in molecular diagnostics were markedly different DNA compositions and thus not products of nature. Writing for the Court, Judge Lourie found that "isolated DNA results from human intervention to cleave or ***synthesize*** a discrete portion of a native chromosomal DNA, imparting on that isolated DNA a

[4] "To be precise, the isolated single-stranded DNA molecule has the identical sequence as the complementary strand to the DNA strand containing the target DNA sequence." *Id*. at 231, n 54.

distinctive chemical identity as compared to native DNA." *A'ssn for Molecular Pathology v. USPTO*, 689 F.3d 1303, 1328 (Fed. Cir. 2012) (emphasis added).[5] Chemical synthesis of the isolated DNA primer subject matter was clearly at issue – consistent with Judge Sweet's binding construction of isolated DNA.

Judge Moore concurred, finding that the use of the short isolated DNA primer or probe tools rendered the claims' isolated DNA subject matter markedly different from the natural DNA, despite having the same short nucleotide sequence. *Id*. at 1341-42. (Judge Moore further noted by contrast that cDNA did not have a naturally-occurring sequence.) *Id*. Judge Bryson found that "isolated DNA" was a product of nature and dissented, rejecting the argument that new uses in the laboratory imbued the DNA with patentability. *Id*. at 1354. Plaintiffs appealed.

**3. The Supreme Court Unanimously Reverses The Federal Circuit and Holds That Isolated DNA Segments That Comprise Primers Are Unpatentable Products of Nature**

Before the Supreme Court, Plaintiffs maintained their position that a DNA "primer" was an "isolated DNA molecule" with different characteristics that reflected human ingenuity and thus was not a product of nature. In doing so, Plaintiffs again acknowledged that the isolated DNA primers had the same order of sequence of natural DNA (unlike cDNA). Consider these quotes from Plaintiffs' Supreme Court Brief:

- "Two critical uses of the claimed molecules [(isolated DNA]) are to "probe" for target DNA in a patient sample or to "prime" the production of copies of the target DNA in the laboratory." Myriad S. Ct. Br. at 7 (Gaede Decl., Ex. J).

[5] Judge Lourie further wrote "Isolated DNA . . . is a free standing portion of a larger, natural DNA molecule. Isolated DNA has been . . . ***synthesized*** to consist of just a fraction of a naturally occurring DNA molecule." *Id.* (emphasis added).

- "[A]n ***isolated DNA*** molecule can be used as a cancer-mutation-detecting probe or ***primer*** because of ***natural qualities*** (***their ordering of nucleotides***, which in some case other than cDNA molecules ***follows the ordering of native nucleotides***) in combination with the inventors' scientific work and ingenuity in characterizing and defining the molecule's starting and end points. . . ." Myriad S. Ct Br at 41 (emphasis added) (Gaede Decl., Ex. J).
- "As a 'primer,' the isolated DNA molecule is used in a reiterative process called a polymerase chain reaction ("PCR"). Myriad S. Ct. Br. at 8 (Gaede Decl., Ex. J).
- "Long strands of isolated DNA molecules are useful as probes and pcr templates." Myriad S. Ct. Br. at 42 (Gaede Decl., Ex. J).

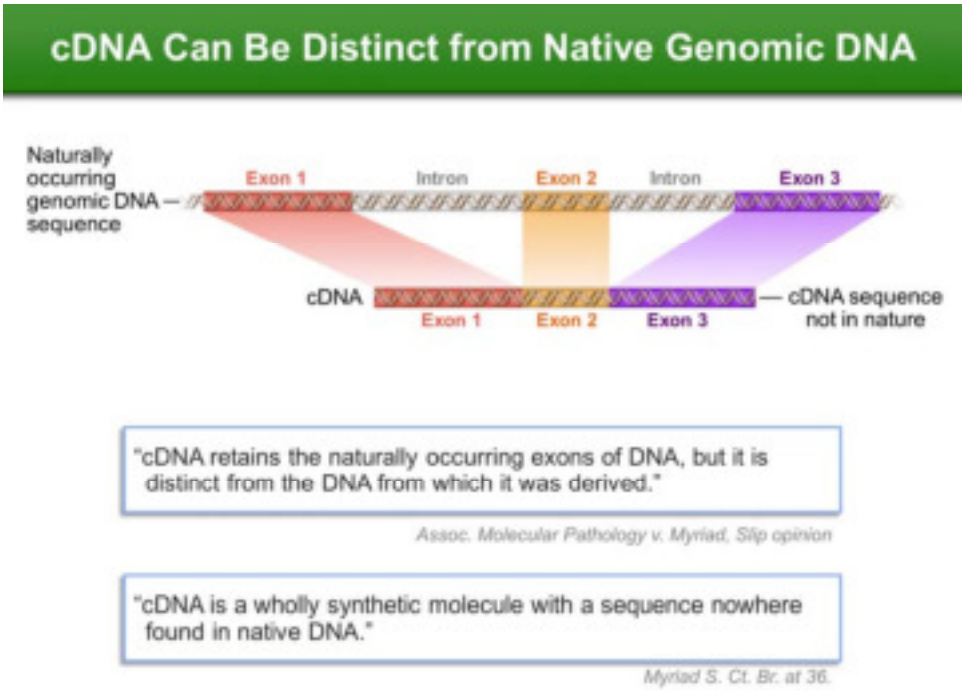
The Supreme Court 9-0 rejected Myriad's arguments. The Court held that the isolated DNA claims (*e.g.*, primers) were not patentable.[6] *Myriad*, 133 S. Ct. at 2111. The Supreme Court held that a "segment" of DNA that corresponded to the naturally occurring sequence was not patent eligible by virtue of its "isolation" from the genomic DNA. *Id*. In doing so, the Court understood the isolated DNA could be chemically synthesized and was "technically" a new molecule, quoting Judge Lourie. *Id*. at 2115 ("Isolated DNA . . is *synthesized* to consist of just a fraction of a naturally occurring DNA molecule."). But such synthesized DNAs, *inter alia*, were not "markedly different" under *Chakarbarty* from the natural DNA (which precedent the Court said Plaintiffs "recognize[d]" was "central to this inquiry.") *Id*. at 2116-17. Nor did Plaintiffs'

[6] This unanimous holding was consistent with the position advocated by the United States, which argued: "All of these applications [(*e.g.*, primers]) depend on the fact that isolated DNA's nucleotide sequence is identical to that of the same gene segment as it exists within a cell so that the isolated DNA binds with the same complementary nucleotide sequences as it would in non-isolated form." United States S. Ct. Amicus Br. at 21 (Gaede Decl., Ex. A).

isolated DNA claims rely "in any way on the chemical changes that result from the isolation of a particular section of DNA." *Id.* at 2018.

Instead, the isolated DNA claims were "*primarily concerned with the information contained in the genetic sequence*, not with the specific chemical composition of a particular molecule." *Id*. (emphasis added). The Court concluded: "We merely hold that genes ***and the information they encode*** are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material." *Id*. at 2120 (emphasis added).

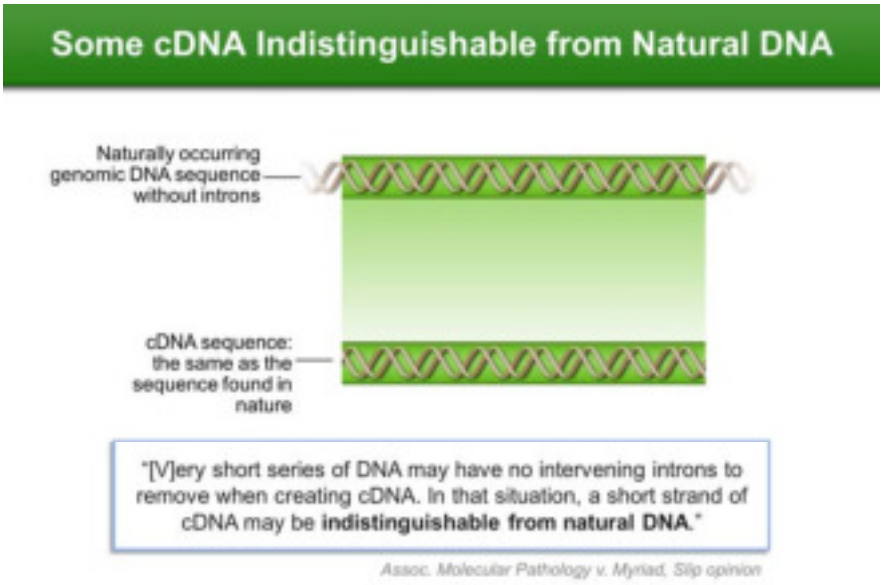
As to the cDNA claims, as stated above, Plaintiffs argued to the Court that the cDNA claims did not encompass unpatenable products of nature because cDNA is a DNA with a ***sequence nowhere found in native DNA***. Myriad S. Ct. Br. at 36 (Gaede Decl., Ex. J). The Court agreed in part, initially stating that cDNA did not pose the same obstacles to patentability "as naturally occurring, isolated DNA segments." *Myriad*, 133 S. Ct. at 2119. The Court found that the lab technician who makes a cDNA containing only the coding region of the exons makes a new DNA molecule not found in an isolated DNA segment. *Id*. cDNA created a DNA sequence not found naturally because it consisted of just the gene's exon sequences without the intervening intron sequences. *Id.*




In this way it created a new contiguous DNA sequence not found in nature, and thus could not be a product of nature. However, if the cDNA reflected just a contiguous portion of a single exon genomic sequence, it would be "indistinguishable" from natural DNA and would not be patent eligible, viz.:

> As a result, cDNA is not a "product of nature" and is patent eligible under §101, ***except*** ***in so far as very short series of DNA may have no introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA***."

*Id*. (emphasis added).




One month later, despite having argued and unanimously lost on the issue that primer "isolated DNA" was patentable subject matter, whether chemically synthesized or not, Plaintiffs turned around and sued Ambry and Gene by Gene on claims containing the exact same subject matter.

**4. Claims 29 and 30 of the '492 Patent and Claims 16 and 17 of the '282 Patent Are Invalid Under *Myriad* Because These Isolated DNA Primer Molecules Are Products of Nature.**

Plaintiffs' primer claims are patent ineligible because they claim as subject matter the "isolated DNA" primers that the Supreme Court held to be unpatentable products of nature. The primer claims contain subject matter that comprise DNA segments with a nucleotide sequence that is identical to natural DNA and thus patent ineligible under *Myriad*.

Plaintiffs argue that the primer claims "are claims for synthetic chemical compositions, namely artificial DNA primers useful in the laboratory PCR process of creating synthetic DNA molecules complementary to all or part of either the BRCA 1 or the BRCA2 gene." *See, e.g.,*

Plaintiffs' Ambry P.I. Br. at 13. In making this argument, Plaintiffs provide no proper claim construction of the term "primer" in the claims and do not delineate the proper scope of the primer claims. But more importantly, it is further squarely at odds with (1) the Supreme Court's holding that claim 5 of the '282 Patent, which is directed to short 15-nucleotide segments of isolated DNA, is unpatentable because such DNAs are products of nature, and (2) the Supreme Court's rejection of Plaintiffs' position that short segments of isolated DNA, which include segments made in a lab with a natural sequence, is patentable subject matter. *See* Section IV.A.3, *supra*.

We turn first to the two primer claims in the '492 Patent: claims 29 and 30. Claim 29 of the '492 Patent clearly states that the single-stranded DNA primers sequence is "isolated" from the natural chromosome sequence:

> A pair of single-stranded DNA primers of at least 15 nucleotides in length for determination of the nucleotide sequence of a BRCA2 gene by a polymerase chain reaction, *the* ***sequence*** *of said primers being* ***isolated*** *from human chromosome 13*, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA comprising all or at least *15 contiguous nucleotides* of the BRCA2 gene. (Emphasis added.)

Plaintiffs argued before the *Myriad* Supreme Court that a primer is a single stranded segment of *isolated DNA* that can be used to prime a DNA reaction, *e.g.*, amplification, sequencing, *etc*. The claim's plain language requires that the DNA primer's sequence be "isolated" from chromosome 13, *i.e.*, be identical to a DNA sequence in the chromosome, thereby expressly sweeping in the Supreme Court's *Myriad* decision on "isolated DNA."[7] It further requires that it be a single-stranded DNA, which is a natural form of the DNA. The

[7] Even if the claim could be read to cover also non-naturally occurring sequences, there is no question its subject matter encompasses naturally-occurring DNA sequences, as Plaintiffs acknowledge.

*Myriad's* Supreme Court expressly recognized this in describing natural DNA: "When the bonds between the DNA nucleotides separate," "the DNA helix unwinds into *two single strands*." *Myriad*, 133 S. Ct. at 2111 (emphasis added).

Plaintiffs also presented expert testimony that short chemically-synthesized primers (and probes) comprised "isolated DNA" within the meaning of its patents. Kay Decl., ¶¶ 134-38 (Gaede Decl., Ex. D). Plaintiffs repeatedly represented throughout the litigation that "isolated DNA" comprised primers and probes, which by definition are single-stranded. (*See, e.g.,* "***As a 'primer,' the isolated DNA molecule*** is used in a reiterative process called a polymerase chain reaction ("PCR")." Myriad S. Ct. Br. at 8 (Gaede Decl., Ex. J).) Plainly, Plaintiffs cannot avoid *Myriad's* ruling on "isolated DNA" by arguing the primer claims are limited to single-stranded DNA.

Thus, Plaintiffs attempt to avoid the "isolated DNA" subject matter in its asserted primer claims by declaring them to be amorphorous "synthetic" DNA. This is clearly unconvincing. Claim 29 encompasses the very subject matter of chemically-synthesized isolated DNA (primers) used in genetic testing that Plaintiffs contended was patentable subject matter, which the *Myriad* Court rejected 9-0. *Myriad*, 133 S. Ct. at 2114 and 2117 ("isolation is necessary to conduct genetic testing"). Moreover, the claims contain subject matter directed to DNA primers that are identical to the natural DNA sequence, as Plaintiffs depicted to this Court in their moving papers.

The *Myriad* court held that the information (sequence) in DNA was the key. The genetic information (nucleotide sequence) gives the DNA primer its ability to bind to the genomic DNA according to the natural law of Watson-Crick base pairing. Pribnow Decl., ¶¶ 28-38. The

primers are not sufficiently different to fall outside of a product of nature – as the prior *Myriad* proceedings determined. And the act of chemically synthesizing the isolated primer does not change the function of the primer, which is tied to the nucleotide sequence. Pribnow Decl., ¶¶ 52-54; *AMP*, 702 F.Supp.2d at 231. Claim 29 encompasses patent ineligible subject matter –a product of nature – and therefore is invalid under *Myriad*. *AMP*, 702 F.Supp.2d at 230, n. 52 (*citing Titanium*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("To the extent a claim reads on unpatentable subject matter, the entire claim must be deemed invalid.").

Dependent claim 30 of the '492 Patent fares no better. It refers to the cDNA sequence for a primer as short as 15 nucleotides. Plaintiffs contend that Ambry's and Gene by Gene's primers have a nucleotide sequence to "only exons in the BRCA2 gene" and that such primer pairs will produce a nucleotide sequence "to *only part of an exon* in the BRCA2 gene." *See, e.g.*, Plaintiffs' Ambry PI Br. at 20. Plaintiffs' infringement contention is an express admission of the scope of claim 30. It reaches, according to Plaintiffs, just one part of a single BRCA2, naturally-occurring exon sequence, and thus claims DNA segments to a single natural DNA sequence found in nature. Justice Thomas declared such short DNA sequence subject matter may "be indistinguishable from the natural DNA" sequence and thus unpatentable. *Myriad,* 133 S. Ct. at 2119. That is the case here for the BRCA2 gene, where short 15-nucleotide primers will be identical to the naturally-occurring sequence in a single genomic exon. *See* Pribnow Decl., ¶¶ 59-63. This dependent claim is thus invalid under *Myriad* as encompassing a product of nature.

Claims 17 and 18 of the '282 patent for BRCA1 primers are similar in scope and language, except that claim 17 says that the DNA is "derived from" chromosome 17 (where the BRCA1 gene is located). That is a distinction without a difference, as "derived from" includes

within its subject matter an "isolated DNA" primer that contains the same sequence as found in the BRCA1 gene. Indeed, Plaintiffs admit as much by arguing that the claim's primers have "complementarity," *i.e.*, follow the natural law rule of Watson-Crick base pairing and thus are identical to the natural DNA sequence. *See, e.g.,* Plaintiffs' Ambry PI Br. at 17 [Dkt # 5]. Plaintiffs further admit that the primer DNA's sequence tracks exactly the natural sequence as depicted in their briefs. *Id.*

Plaintiffs repeatedly emphasized that "isolated DNA" comprised a primer that was a segment of DNA synthesized from the BRCA genes, and the Supreme Court rejected that subject matter as providing a point of patentability. Plaintiffs cannot resuscitate the same subject matter through the artifice of different claims. Ambry and Gene By Gene have clearly and convincingly shown that the claims are invalid under Section 101 and/or at a minimum raised a substantial question.

### B. THE SUPREME COURT'S UNANIMOUS DECISION IN *MAYO* PROHIBITS THE PATENTING OF LAWS OF NATURE, NATURAL PHENOMENA AND ABSTRACT IDEAS AND THEIR APPLICATION USING WELL-UNDERSTOOD, ROUTINE, CONVENTIONAL ACTIVITY

Plaintiffs next attempt to bootstrap their flawed synthetic DNA primer argument into a broader argument to save their patent ineligible method claims by arguing these are applications of synthetic subject matter. But Plaintiffs' generic laboratory method claims are invalid under *Mayo* and both the Supreme Court's and the Federal Circuit's *Myriad* decisions. Plaintiffs' argument rests on the fundamentally-flawed proposition that (1) the DNA primers used in the molecular diagnostic methods claimed are synthetic and (2) the exact copies of the genomic DNA produced as part of the broad amplification methods are synthetic. As just shown, (1) "primers" encompass unpatentable subject matter of "isolated DNA" under *Myriad*, and (2)

exact DNA copies of a portion of a BRCA genomic sequence is nothing more than the "isolated DNA" subject matter that the Supreme Court found unpatentable.

More importantly, the method claims amount to nothing more than an artifice of patent drafting to capture the patent-ineligible subject matter of comparing or reading BRCA genes that the *Myriad* Federal Circuit opinion held unpatentable. In fact, of the method claims asserted: (1) many depend from method claims the Federal Circuit declared invalid under Section 101 and (2) all add no additional patentable limitations. *See AMP,* 689 F.3d at 1334-35 (holding invalid method claims 1 and 2 of the '857 Patent and claim 1 of the '441 Patent of those two asserted patents). Plaintiffs' asserted method claims effectively preempt the ability to read and compare the natural BRCA DNA. To understand why Plaintiffs' method claims are clearly and convincingly unpatentable under Section 101 requires a further discourse of the Supreme Court's *Mayo* decision.

**1. The Unanimous *Mayo* Court Holds Routine or Well-Known Applications of a Law of Nature Constitute Ineligible Subject Matter**

In *Mayo*, a unanimous Supreme Court reversed the Federal Circuit and held that the claims at issue constituted patent-ineligible subject matter under Section 101. *Mayo,* 132 S. Ct. at 1294. In doing so, the Supreme Court articulated principles for assessing when a method claim purporting to apply a law of nature or abstract mental process could constitute patentable subject matter.

The claim at issue was directed to a method for optimizing the use of a thiopurine drug to treat autoimmune diseases that included the steps of "administering" and "determining" the level of a metabolite of the drug in the body and adjusting the dosage. The law of nature being

"applied" was that certain concentrations of metabolites in the blood resulted in a likelihood that a dosage of a thiopurine drug would prove ineffective or cause harm. *Id*. at 1296.

The Court held that the steps purporting to *apply* the law of nature by "administering" and "determining" "*involve[d] well-understood, routine, conventional activity previously engaged in by researchers in the field*." *Mayo*, 132 S.Ct. at 1294 (emphasis added). As such, protecting the method "would risk disproportionately tying up the use of the underlying natural laws." *Id*. The Supreme Court required that a process purporting to apply a natural law must have other elements or combinations that themselves are inventive for the claim to be patentable subject matter:

> [A] process that focuses on the use of a natural law [must] also contain other elements or a combination of elements, sometimes referred to as an "***inventive concept***," sufficient to ensure that the patent in practice amounts to ***significantly more*** than a patent upon the natural law itself."

*Id*. (*citing Parker v. Flook*, 437 U.S. 584, 590, 98 S.Ct. 2522, 57 L.Ed.2d 451 (1978) and *Bilski*, 130 S.Ct. at 3230 (emphasis added).) The Court further warned that attempting "to limit the use to a particular technological environment" could not "circumvent[ ]" the prohibition against patenting abstract ideas or phenomena of nature. *Mayo*, 132 S. Ct. at 1297. Accordingly, the claim was patent-ineligible.

*Mayo* relied upon the Court's earlier decisions in *Diamond v. Diehr* and *Flook* to reinforce its conclusion of unpatentability and to highlight the type of subject matter that could satisfy the "inventive concept." In *Diehr*, a new and novel process for molding uncured rubber into cured, molded products involved specific and new inventive steps in addition to the mathematical equation cited in the claims. *Diamond v. Diehr*, 450 U.S. 175, 177-79, 101 S. Ct. 1048, 67 L. Ed.2d 155 (1981). The *Mayo* Court stated: "[The] decision nowhere suggested that

all these steps, or at least the combination of those steps, were in context *obvious*, already in use, or purely conventional." *Mayo*, 132 S.Ct. at 1299.

The *Mayo* Court then turned to *Flook*. In *Flook*, the Court held unpatentable subject matter a method claim for adjusting "alarm limits" in the catalytic conversion of hydrocarbons. The Court found that that alarm values that must be recalculated and recomputed and the use of computers for "automatic monitoring-alarming" were all "well known, to the point where, putting the formula to the side, there was no 'inventive concept' in the claimed application of the formula." *Mayo*, 132 S.Ct. at 1299 (*quoting Flook*, 437 U.S. at 586, 98 S.Ct. 2522.) "[P]ost-solution activity that is purely 'conventional or obvious,' the [Flook] Court wrote 'can[not] transform an unpatentable principle into a patentable process." *Mayo*, 132 S. Ct. at 1299 (*quoting Flook*, *Id*., at 589-590, 98 S.Ct. 2522).

The *Mayo* Court further recognized the central role of Section 101 "in evaluating the significance of additional steps" over Section 102 and 103's anticipation or obviousness inquiries. *Id*. at 1304. This is because "one could suppose" that a law of nature would not be unpatentable under Section 102 and 103 because it was unknown, while of course the other steps would be. *Id*. *Mayo's* Section 101 inquiry is not limited to just applications of obvious subject matter in the prior art that effectively applied *a known law of nature*. *Mayo's* inquiry extends to methods applying a previously *unknown law of nature* using "well-understood, routine, conventional activity already engaged in by the scientific community." *Id.* at 1298.[8]

Each of the asserted method claims contain the patentable ineligible law of nature, mental process, or product of nature along with steps that use routine and well-known activity already

[8] *See, also,* Section V.C., *infra*, where the obviousness of the method claims is fully addressed under Section 103.

"engaged in by the scientific community" of sequencing, screening, amplification or hybridization. *Id*. at 1298. Whether viewed separately or as a whole, the asserted method claims do not contain the "inventive concept" that is required to pass muster under *Mayo, Myriad* and their progeny.

**2. Plaintiffs' Method Claims Are Unpatentable Applications of a Law of Nature Because They Claim Routine and Well-Known Uses of the Unpatentable BRCA Isolated DNA to Compare the BRCA Sequences.**

Plaintiffs argue that the asserted method claims represent a "method of applying Plaintiffs newly discovered knowledge." *See, e.g*., Plaintiffs' Ambry PI Br. at 14. They point in particular to the "synthetic DNA" that allegedly constitute their primers, and the "amplified DNA" – copies of segments of genomic DNA − which Plaintiffs wrongly characterize as synthetic and not subject to the Supreme Court's *Myriad* decision. Plaintiffs then argue that their method claims are like the sole method claim (claim 20) that was upheld by the Federal Circuit in the prior *Myriad* case. Plaintiffs are clearly wrong in their arguments for the reasons that follow.

*First*, as discussed above, under *Myriad* the BRCA primers, *i.e*., the isolated DNA segments identical to the natural sequence, are unpatentable products of nature. *See* Section IV.A.1, *supra*. The claimed BRCA DNA primers in the method steps clearly contain patentable ineligible subject matter. Notably, Plaintiffs do not contend that either the sequence information or the chemical structure of their primers differs so as to produce something other than isolated DNAs with the same DNA nucleotide sequence that nature made first. Pribnow Decl., ¶¶ 60 - 76; *see also* Kay Decl., ¶¶ 136-38 (Plaintiffs' expert in *Myriad* litigation declaring that chemically-synthesized primers constitute "isolated DNA") (Gaede Decl., Ex. D).

*Second*, amplified DNA (amplicons) includes subject matter that is nothing more than an exact copy of a segment of genomic DNA generated in the routine PCR process. Pribnow Decl., ¶¶ 55-59. An amplified DNA segment from a genomic template consists of an identical nucleotide sequence to natural DNA's nucleotide sequence and is not patentable subject matter. *Myriad*, 133 S. Ct. at 2118-19. As an exact copy of genomic DNA, it is indistinguishable from the segment of genomic DNA. *Id.;* Pribnow Decl., ¶ 58. Plaintiffs acknowledged that fact before the *Myriad* Supreme Court, where they stated that the primers used in the PCR process "serve[] as a starting point for PCR to *synthesize a* ***copy*** *of the target DNA*. The reaction is repeated to 'amplify' – exponentially duplicate – *DNA copies* of the target." Myriad S. Ct. Br at 8 n.3 (Gaede Decl., Ex. J).

*Third*, Plaintiffs argue that the claims are patent eligible because they do not contain naturally-occurring composition subject matter. *See, e.g.,* Plaintiffs' Ambry PI Br. at 13 [Dkt. No. 5]. Plaintiffs further claim their asserted claims are analogous to the very different subject matter of using a non-natural cell in a method, relying upon claim 20 of the '282 Patent addressed by the Federal Circuit in the prior litigation. *Id.* These arguments lack any merit.

Claim 20 of the '282 Patent addresses uses of only a non-naturally occurring composition – a human transformed cell – that does not exist in nature. *See AMP*, 689 F.3d at 1336 ("The cells, like the patent-eligible cells in *Chakarbarty*, are not naturally occurring."); Pribnow Decl., ¶¶ 92-93. Here, by contrast, the method claims include *patent-ineligible* compositions, namely the unpatentable primers and copies of the genomic DNA (amplicons) that are products of nature under *Myriad*. Pribnow Decl., ¶¶ 58, 93. The method claims that recite the use of such primers, therefore, contain patent-ineligible subject matter subject to the *Mayo* analysis. *AMP*, 702

F.Supp.2d at 230, n. 52 (*citing Titanium*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("To the extent a claim reads on unpatentable subject matter, the entire claim must be deemed invalid.").[9]

### 3. Plaintiffs' Method Claims Are Unpatentable Under *Mayo* and the Federal Circuit's *Myriad* Decisions

*Mayo*, the *Myriad* Federal Circuit Opinions, and their progeny are fatal to any contention by Plaintiffs that their method claims are a proper application of an unpatentable law or product of nature or mental process. The method claims lack the necessary and hallmark "inventive concept" to the additional steps. They claim "processes that too broadly preempt the use of the natural law," and the "steps in the claimed processes (apart from the natural laws themselves) involve well-understood, routine, conventional activity previously engaged in by researchers in the field." *Mayo*, 132 S.Ct. at 1294.

The *Myriad* Supreme Court recognized that it was "undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes. *Myriad*, 133 S. Ct. at 2116. It was further undisputed that "the location and order of the nucleotides existed in nature before *Myriad* found them." *Id*. Plaintiffs' "principal contribution was uncovering the precise location and genetic sequence" of the BRCA genes. *Id*. "But the processes used by Myriad to isolate DNA were well understood by geneticists at the time of Myriad's patents 'were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach.'" *Id*. at 2119-20 (*quoting AMP*, 732 F. Supp.2d at 202-03).

[9] Plaintiffs reference Judge Bryson's comment in his dissent in *Myriad*. Judge Bryson did not address the claims asserted here and, in any event, provides no full analysis of the method claims.

Those well-understood processes patentees used here consisted of (1) creating copies of portions of the natural DNA (amplifying), (2) reading (sequencing), (3) probing (hybridization) and (4) screening (identifying) to identify the "location and order of the nucleotides that existed in nature." *Id*. at 2116; Tait Decl., ¶¶ 19-39. Indeed, Plaintiffs' patents admit this. *See, e.g.,* '441 Patent at col. 14, ll. 9-16 (detection can be accomplished by molecular techniques that are well known in the Court) col. 15, ll. 17-22 (*citing* prior art for standard hybridization techniques), col. 17, ll. 20-25 (amplification methods are well known in the art).

Plaintiffs' asserted method claims do no more. They generically patent the process of identifying the natural location and order of nucleotides in a human's BRCA gene through the routine steps of amplification, sequencing, screening, *etc.* They then perform the abstract mental process of comparing that sequence to another "normal" BRCA sequence to identify any mutations that exist naturally. This process subject matter to compare sequences depends vitally on maintaining the fidelity of the patient's natural DNA sequence as copies of it are made (amplified) in order to be read (sequenced or screened), effectively preempting the use of one's own genes. *Id*.

In effect, these claims confer a monopoly upon Plaintiffs to be the exclusive owner of the right to read and compare human BRCA1 and BRCA2 sequences, the genetic information of which the Supreme Court ruled is not patent eligible. The claims merely append routine steps to the patent claims – steps that would necessarily be conducted while assessing the biological relationships between mutations in the BRCA1 and or BRCA2 genes and the predisposition to cancer. The claim strategy is an overt attempt to convert these natural biological phenomena that

Plaintiffs claims they harnessed into patentable inventions through the abstract patent language of a 'method' or 'process.' *Mayo*, 132 S. Ct. at 1294.

Consider claim 8 of the '441 Patent that contains patent-ineligible subject matter and then simply appends the generic steps of amplification and sequencing that are necessary to perform the ineligible comparison.

| **CLAIM 1 OF THE '441 PATENT [NOT ASSERTED] PRIORITY DATE: AUGUST 12, 1994 (FILING DATE OF APPLICATION NO. 08/289,221)** | **BASIS OF SECTION 101 INVALIDITY** |
|---|---|
| 1. A method for screening germline of a human subject | Claim declared to be unpatentable subject matter by Judge Sweet and affirmed by the Federal Circuit. *AMP,* 689 F.3d at 1309, 1334-35. |
| for an alteration of a BRCA1 gene which comprises | |
| comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject | |
| or a sequence of BRCA1 cDNA made from mRNA from said sample | |
| with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, | |
| wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject. | |

| **CLAIM 8 OF THE '441 PATENT PRIORITY DATE: AUGUST 12, 1994 (FILING DATE OF APPLICATION NO. 08/289,221)** | **BASIS OF SECTION 101 INVALIDITY** |
|---|---|
| 8. The method of claim 1 wherein a germline nucleic acid sequence is compared by | Claim 1's subject matter is unpatentable |
| amplifying all or part of a BRCA1 gene from said sample | Amplification is a routine step as acknowledged by, *e.g.,* '441 Patent at col 17, ll. 20-25; Tait Decl., ¶¶ 27-31. |
| using a set of primers to | Primers' subject matter includes unpatentable "isolated DNA" under Judge Sweet's construction, the Supreme Court *Myriad* decision, Myriad's admissions before the Supreme Court that "isolated DNA" comprised primers, and primers are a DNA that is indistinguishable from the order of nucleotides of the natural sequence. Pribnow Decl, ¶¶ 60-76. |
| produce amplified nucleic acids | Subject matter includes copies (amplified) |

| CLAIM 8 OF THE '441 PATENT PRIORITY DATE: AUGUST 12, 1994 (FILING DATE OF APPLICATION NO. 08/289,221) | BASIS OF SECTION 101 INVALIDITY |
|---|---|
| | of portions of BRCA natural sequence using well known amplification process. Pribnow Decl., ¶¶ 55-58. |
| and sequencing the amplified nucleic acids. | Well known and routine step necessary to read the human gene as acknowledged by Myriad's patent specification. Pribnow Decl, ¶ 76. |

Claim 8's steps all either contain either patent-ineligible subject matter or routine, well-known and obvious steps of amplification and sequencing to access the gene's information that violate *Mayo*. Tait Decl., ¶¶ 19-39.

Consider as well Claim 4 of the '857 Patent, which merely requires "screening" and depends from a comparison claim the Federal Circuit declared invalid:

| CLAIM 4 OF THE '857 PATENT[10] | BASIS OF SECTION 101 |
|---|---|
| 4. The method of claim 2 wherein the detection in the alteration in the germline sequence is determined by an assay selected from the group consisting of: | Method Claim 2 declared invalid in *AMP*, 689 F.3d at 1334-35. Also Federal Circuit declared as unpatentable abstract processes for claim 1 of '441 patent directed to a "method for screening." *Id*. |
| (j) *screening* for a deletion mutation in said tissue sample, | Screening as Plaintiffs admitted in the *Myriad* litigation, means simply "using ***any method*** to survey a large number of subjects" to identify a mutation. Kay Decl., ¶ 144 (Gaede Decl., Ex. D). Screening scope violates *Mayo* and shows is not a patent eligible application of a law of nature or mental process. *AMP*, 689 F.3d at 1334-35. S*ee also* Tait Decl., ¶¶ 19-21 |
| (k) *screening* for a point mutation in said tissue sample, | *Id*. |
| (l) *screening* for an insertion mutation in said tissue sample, | *Id*. |

[10] Claim 4 is known as a Markush claim, which means that any of the listed elements may be satisfied to infringe, and therefore constitutes, the subject matter of the claim. As discussed above, if a claim contains any patent-ineligible subject matter, the entire claim is unpatentable.

The remaining method claims similarly append routine, well-known or data gathering steps to read a gene sequence.

- Dependent claim 7 of the '441 patent depends from an invalid method claim 1 directed to gene sequence comparison claim. AMP, 689 F.3d at 1334-35. Claim 7 requires simply applying the steps that there be hybridization and "detection" of a difference between the wild type DNA sequence and an allele (mutation). A broad "detecting" step is insufficient under Mayo, and appending the well-known hybridization of a probe is a routine step. Tait Decl., ¶¶ 19-22.
- Claims 2 and 4 of the '155 Patent are likewise unpatentable because they require "detection" of a naturally occurring mutations by amplifying, sequencing, and comparing the sequences. Such routine steps are no more than an instruction to apply "determining" to the natural law the presence of such mutations in the patient's DNA. Bowcock Decl., ¶¶ 102-108.
- '721 patent, claim 5, requires the unpatentable law of nature or abstract mental step of determining a specific type of naturally-occurring mutation known as an omni haplotype, and appends the routine step of amplifying the BRCA1 gene or fragment prior to sequencing. Tait Decl., ¶¶ 19-21; Bowcock Decl., ¶¶ 102-108. Plaintiffs' motion effectively admits the sweeping scope of the claim when it asserts that any sequencing, which happens to sequence this BRCA natural phenomena, is infringement, underscoring that the claim is nothing more than a patent-ineligible claim on the natural phenomena. Plaintiffs' Ambry PI Br. at 21 [Dkt. 5].

- Plaintiffs' haplotype (claim 5 of the '721 patent) and polymorphism (claims 2 and 4 of the '155 patent) claims are directed to population-based statistical information about patient DNA. For each claim, the information is inherent in the patient's (or collectively, patients') own genetic information. Bowcock Decl., ¶¶ 102-108. Modern sequencing equipment simply cannot exclude reading a single nucleotide base in a gene sequence. Because of this limitation, and not because of any true inventive effort, Myriad has simply found an alternative, inventive way to draft patent claims to exclude scientists from reading patients' genetic information using well-known and standard techniques.

Defendants have not only raised a substantial question; Defendants have shown that the claims are invalid as a matter of law. Several further grounds support this conclusion.

*First*, Judge Sweet's District Court opinion effectively addressed the issue. There, Plaintiffs argued that claim 1 of the '441 Patent was effectively saved because the claim included the necessary transformations of *amplifying* and *sequencing* the DNA. Judge Sweet rejected this argument without even the benefit of *Mayo*. He correctly held: "Even if the challenged method claims were read to include the transformations associated with isolating and sequencing human DNA, these transformations would constitute no more than 'data gathering steps' that are not central to the purpose of the claim process." *Myriad*, 702 F.Supp.2d at 236.

*Second*, to the extent there are transformations involved, the machine or transformation test does not trump the Section 101 exclusions created by the law. "[W]e have neither said nor implied that [machine or transformation] test trumps the 'law of nature' exclusion." *Mayo*, 132 S. Ct. at 1303.

*Third*, the district courts following *Mayo* are in accord. Consider *Aria Diagnostics, Inc. v. Sequenom, Inc.*, where Judge Illston denied a motion for preliminary injunction on the following claim, finding substantial issues, *inter alia*, under Section 101:

> A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises:
>
> ***amplifying*** a paternally inherited nucleic acid from the serum or plasma sample and
>
> ***detecting*** the presence of a paternally inherited nucleic acid of fetal origin in the sample.

2012 U.S. Dist. LEXIS 93124, at *39 (N.D. Cal. July 5, 2012), *rev'd on other grounds*, No. 2012-1531, Slip Op. (Fed. Cir. Aug. 9, 2013).

Judge Illston stated: "[T]he steps Sequenom used to enable their method claims . . . namely fractionation (separating blood into cells and plasma), amplification and detection – are described as 'standard' in the patent itself." *Aria Diagnostic*s, 2012 U.S. Dist. LEXIS 93124, at *39 (N.D. Cal. July 5, 2012). So too here, Plaintiffs' patents described the steps in the method claims as "standard" and or in the "prior art." Tait Decl., ¶¶ 19-39; *see, e.g.*, '441 Patent at col. 17, ll. 20-25; *see also Smartgene Inc. v. Advanced Biological Laboratories*, 852 F. Supp. 2d 42 (D.D.C. 2012) (canvassing the Supreme Court's Section 101 case law including *Mayo* and finding no patentable subject methods for using computers to guide election of therapeutic treatment regimens for complex disorders).

*Fourth*, Judge Alsup's opinion in *Tessenderlo Kerley v. Or-Cal, Inc.*, 2012 U.S. Dist LEXIS 78044, at *16 (N.D. Cal. June 25, 2012), correctly applies *Mayo*. There, Judge Alsup quoted the *Mayo* "inventive concept" requirement discussed above. He then wrote: "That is, the natural law's application must not be "well-understood, routine, conventional activity previously

engaged in by researchers in the field." *Id*. He ordered more discovery on the issue, but no such discovery is necessary here where Plaintiffs' patents, the Supreme Court, and experts have all described the claims as merely appending the well-known and routine steps that lack the inventive concept as a whole that "risk disproportionately tying up the use of the underlying natural laws. *Mayo,* 132 S. Ct. at 1294. Tait Decl., ¶¶ 19-39. Plaintiffs' method claims are invalid under Section 101.

## V. THE ASSERTED CLAIMS ARE INVALID BECAUSE THEY ARE ANTICIPATED OR RENDERED OBVIOUS UNDER THE PRIOR ART

### A. LEGAL STANDARDS

A patent may be awarded to an inventor only if, *inter alia*, a claimed invention is directed to patent-eligible subject matter, 35 U.S.C. § 101, is new under 35 U.S.C. § 102, is non-obvious under 35 U.S.C. § 103, and meets other disclosure requirements of 35 U.S.C. §112. [11] For the reasons that follow, Plaintiffs' asserted claims are anticipated and/or obvious under the prior art and/or fail to meet the disclosure requirements of Section 112.

#### 1. Summary of Section 102, 103 and 112 Requirements

An invention is invalid as "anticipated" if it does not meet the standard for novelty under Section 102, which defines four categories of prior art that are relevant here:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent, or
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States, . . . .

[11] All of the asserted patents in Plaintiffs' motion for preliminary injunction were filed prior to the enactment of the America Invents Act (AIA). As a result, the pre-AIA law governing patentability applies in this case.

> (e) the invention was described in - (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent . . . . [or]
>
> (g)(2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

Even if a claimed invention is not anticipated, it may be deemed invalid as obvious under Section 103, which states:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Section 112 mandates certain disclosures requirements so as to adequately put the public on notice as to the nature and scope of the claims which are known as the written description requirement and the definiteness requirement:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.
>
> The specification shall conclude with one or more claims *particularly pointing out and distinctly claiming* the subject matter which the applicant regards as his invention.

**2. Priority**

A continuation-in-part (CIP) application is a patent application that claims priority to a previously filed parent document, but that also adds new material to the disclosure and/or claims. In CIP applications, priority date is determined on a claim-by-claim basis. Under 35 U.S.C.

§ 120, a claim is entitled to the priority date of the parent application only if the parent application has disclosed the claimed invention in a manner that meets the enablement and written description requirements under the first paragraph of 35 U.S.C.§ 112. When a claim is based in whole or in part on the new material added in the CIP, the priority date for that claim will be the filing date of the CIP. *See, e.g., Chiron Corp. v. Genentech, Inc*., 363 F.3d 1247 (Fed. Cir. 2004) (claims from a later filed patent cannot claim priority to the filing dates of earlier applications because the definition of the term "monoclonal antibody" was revised).

For reasons described below, Defendants assign the following priority dates, for purposes of this opposition, to the claims asserted by Plaintiffs in their Preliminary Injunction motion. These dates differ from Plaintiffs' claimed dates for the claims italicized below:

| Claims | Priority Date | Basis |
|---|---|---|
| Claims 16<br>U.S. Patent No. 5,747,282 | August 12, 1994 | U.S. Patent App. Ser. No. 08/289,221 |
| Claims 7 and 8<br>U.S. Patent No. 5,753,441 | August 12, 1994 | U.S. Patent App. Ser. No. 08/289,221 |
| *Claim 17*<br>*U.S. Patent No. 5,747,282* | *March 24, 1995* | *U.S. Patent App. Ser. No. 08/409,305*[12] |
| Claims 29<br>U.S. Patent No. 5,837,492 | December 18, 1995 | U.S. Patent App. Ser. No. 08/573,779 |
| Claim 4<br>U.S. Patent No. 6,033,857 | December 18, 1995 | U.S. Patent App. Ser. No. 08/573,779 |

[12] Claim 17 of the '282 Patent is directed to a BRCA1 gene with a specific DNA sequence, SEQ ID NO:1. The complete DNA oligonucleotide sequence described by SEQ ID NO:1 was first described in its entirety in a U.S. Patent App. No. Ser. No. 08/409,305, which is a March 24, 1995 continuation-in-part application that claims priority to the '221 application. As SEQ ID NO:1 was "new matter" as of the filing of the March 25, 1995, claim 17 is entitled to a March 25, 1995, priority date. *See* 35 U.S.C §§ 112 ("written description" requirement), 132 (prohibiting "new matter").

| | | |
|---|---|---|
| *Claims 30*<br>*U.S. Patent No. 5,837,492* | *January 11, 1996* | *U.S. Patent App. Ser. No. 08/585,391*[13] |
| Claims 2 and 4<br>U.S. Patent No. 5,654,155 | February 12, 1996 | U.S. Patent App. Ser. No. 08/598,591 |
| Claim 5<br>U.S. Patent No. 6,951,721 | February 12, 1996 | U.S. Patent App. Ser. No. 08/598,591 |

**B. ANTICIPATION UNDER SECTION 102**

**1. Claims 16 and 17 of U.S. Patent No. 5,747,282 Are Invalid (BRCA1 Primers)**

**a. Claim 16 of the '282 Patent (August 12, 1994) Is Anticipated Under 35 U.S.C. §§ 102(a) and 102(g)**

**(1) Claim 16 is Anticipated by Abel et al. (1993) Under Sections 102(a) & (g)**

The article, Abel *et al*., "A Radiation Hybrid Map of the BRCA1 Region of Chromosome 17q12-q12" Genomics, vol.17:632-641 (September 1993) (Bowcock Decl., Ex. C) anticipates claim 16 of the '282 Patent (priority August 12, 1994) under both 35 U.S.C. §§ 102(a) and 102(g)(2). Bowcock Decl., ¶ 64; Gregory Decl., ¶¶ 59-66, Ex. A. Claim 16 states that it is directed to a composition of a pair of single-stranded DNA primers derived from chromosome 17q and which function in pcr to amplify all or part of the BRCA1 gene. The Michigan-based authors of the Abel reference submitted their article to the *Genomics* journal on December 28, 1992 (p. 632) evidencing that it was "known or used by others in this country…before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a).

Abel *et al*. describes a pair of 21-nucleotide long primers that corresponds to a genetic marker identified as Locus D17S855 (7th from top in Table 1 at Bowcock Decl., Ex. C, p. 637),

[13] Claim 30 of the '492 Patent is directed to a BRCA2 gene with a specific DNA sequence, SEQ ID NO:1. The complete DNA oligonucleotide sequence described by SEQ ID NO:1 was first described in its entirety in a U.S. Patent App. No. Ser. No. 08/585,391, which is a January 11, 1996 continuation-in-part application that claims priority to the '779 application. As SEQ ID NO:1 was "new matter" as of the filing of the January 11, 1996, claim 30 is entitled to a December 18, 1995, priority date. *See* 35 U.S.C §§ 112, 132.

that produces a DNA amplification product (*i.e.*, a polymerase chain reaction (PCR) product) that is 145 base pairs of DNA having "all or part of the sequence of the BRCA1 gene" (as required by claims 16 and 17 and detailed further below). Bowcock Decl., ¶ 65; Gregory Decl., ¶¶ 59-60.

The genetic marker D17S855 is intragenic[14] (occurring within) to the BRCA1 gene. Plaintiffs' '282 Patent admits this fact. *See* '282 Patent, col. 58, ll. 57-61. ("Three highly polymorphic, simple tandem repeat markers were used to assess LOH: D17S1323 and *D17S855, which are*_intragenic *to BRCA1*, and D17S1327, which lies approximately 100 kb distal to BRCA1."(emphasis added).) Fig.1 of the '282 Patent further admits that the D17S855 sequence is in the BRCA gene. As the below figure shows, the Abel primers correspond exactly to BRCA and will amplify a portion of the BRCA gene. The claim is invalid under Section 102(a):

**Abel's Prior Art Primers are Identical to the BRCA1 Sequence and Amplify a Portion of the BRCA1 Gene**


[14] Webster's defines "intragenic" as "being or occurring within a gene"

Plaintiffs cannot defeat this anticipation by claiming that it was not known in 1993 that the composition primers could be used to amplify a portion of th BRCA1 gene. A prior art disclosure for a composition need neither describe nor appreciate the intended, later use for the composition. *See Kubin*, 561 F.3d at 1347-58 (*citing Gen. Elec. Co. v. Jewel Incandescent Lamp Co*., 326 U.S. 242, 249, 66 S. Ct. 81, 90 L. Ed. 43 (1945) (''It is not invention to perceive that the product which others had discovered had qualities they failed to detect.''); *In re Wiseman*, 596 F.2d 1019, 1023 (CCPA 1979) (rejecting the notion that ''a structure suggested by the prior art, and, hence, potentially in the possession of the public, is patentable…because it also possesses an inherent, but hitherto unknown, function which [patentees] claim to have discovered. This is not the law. A patent on such a structure would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art.'').

Claim 16 is further invalid under Section 102(g). The December 28, 1992, submission date for publication and the September 1993 date of publication from this Michigan group confirm that "before such person's [(Plaintiffs' claim 16)] invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it." 35 U.S.C. § 102(g)(2). *Id*. ¶ 69; Gregory Decl., ¶ 63, Ex. A.[15]

**(2) Claim 16 (August 12, 1994 priority) is Anticipated by Anderson et al. (September 1993) Under Sections 102(a) & (g)**

The article Anderson et al., High-Density Genetic Map of the BRCA1 Region of Chromosome 17q12-21. Genomics 17:618-623 (Sept. 1993) (Bowcock Decl., Ex. B; Gregory Ex. B) anticipates claim 16 of the '282 Patent under both 35 U.S.C. §§ 102(a) and 102(g).

[15] A Claim Chart for each ground of invalidity under Section 102 and 103 is attached to the Gregory Declaration as Appendix 1, filed herewith.

Bowcock Decl., ¶ 71. Table 1 of the Anderson paper describes the D17S855 Locus as one of the "Ordered Polymorphisms in the BRCA1 Region of Chromosome 17q12-21." As in Abel, Anderson identifies a pair of "Primers for PCR-based systems" in Table 1 corresponding to the D17S855 Locus, *i.e.*, a portion of the BRCA gene found in chromosome 17q. *Id.* Table 2 of Anderson reports the "Fragment Sizes (in bp), Frequencies of Alleles, and Representative Genotypes from the CEPH Families for Five Polymorphic Markers at 17q21." This includes PCR products of various lengths for amplified DNA section of the D17S855 Locus (part of the BRCA1 gene) from different patient samples and reporting 7 Alleles (mutations). Bowcock Decl., ¶ 72, Ex. B at 620. Like Abel, the polymerase chain reaction resulted in the synthesis of DNA having all or part of the sequence of the BRCA1 gene. Bowcock Decl., ¶ 72; Gregory Decl., ¶¶ 67-74. The primers hybridize to and amplify the D17S855 gene marker sequence, which falls within nucleotide numbers 165107-165257 of the BRCA1 gene. Bowcock Decl., ¶ 76.

The California- and Texas-based authors of the Anderson article submitted the publication to the *Genomics* journal on December 28, 1992 evidencing that it was "known or used by others in this country…before the invention thereof by the applicant for patent" and was described in a "printed publication" before the August 1994 priority date. 35 U.S.C. § 102(a); Bowcock Decl., ¶¶ 73-74; Gregory Decl., ¶ 67-74. The December 28, 1992, and September 1993 dates evidence also that "before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it." 35 U.S.C. § 102(g)(2). Bowcock Decl., ¶ 75; Gregory Decl., ¶¶ 67-74. Anderson invalidates claim 16 under Sections 102(a) and (g).

**b. Claims 16 (August 12, 1994) and 17 (March 24, 1995) of the '282 Patent Are Anticipated Under Section 102(b) by Deposit of the D17S855 and DS17932 Gene Markers in a Publicly-Available Database**

Researcher Dr. Jean Weissenbach published the sequence of the D17S932 genomic DNA marker through direct submission to a public, genomic database on July 12, 1993. Bowcock Decl., ¶¶ 79-81; Gregory Decl., ¶¶ 75-93. This means that the lower-numbered D17S855 marker described above was deposited to the same database on or before July 12, 1993 because the "D17S" nomenclature was based on numerically sequential issuance upon chronologically ordered deposit by a public database at the time. *See id.*, ¶ 82.

The double stranded DNA of both D17S932 and D17S855 may both be used as primer pairs to amplify part of the BRCA1 gene. *Id.*, ¶ 83. Their publication more than one year prior to the Aug. 12, 1994, priority date of claim 16 of the '282 Patent and the March 24, 1995 priority date of claim 17, anticipates under Section 102(b).

**c. Claim 17 (March 24, 1995) of the '282 Patent Is Invalid**

**(1) Claim 17 Is Anticipated Under Section 102(b)**

Abel and Anderson were published more than one year prior to the March 24, 1995, priority date of claim 17 of the '282 Patent. Claim 17 is invalid under 35 U.S.C. § 102(b) for the reasons stated above in reference to claim 16 with respect to both the Abel and Anderson references. The pairs of primers directed to D17S855 can be used to amplify a DNA molecule where the corresponding cDNA of the BRCA1 gene "has the nucleotide sequence set forth in SEQ ID NO:1," which results in the synthesis of DNA having "all or part of the sequence of the BRCA1 gene." Gregory Decl., ¶¶ 75-82, 85-91. Disclosure of the D17S855 and DS17932 gene

markers also anticipate claim 17 under Section 102(b) for the reasons described above. *Id*. ¶¶ 75-82, 85-91.

**2. Claims 29 and 30 of U.S. Patent No. 5,837,492 Are Invalid (BRCA2 Primers)**

**a. Claim 29 (December 18, 1995) is Anticipated under Sections 102(a) and 102(g) by Schutte et al. (Oct. 15, 1995)**

The article, Schutte, *et al*., "An Integrated High-Resolution Physical Map of the DPC/BRCA2 Region at Chromosome 13q12." *Cancer Res*. 55:4570-4574 (15 Oct. 1995) anticipates claims 29 and 30 of the '492 Patent under Sections 102(a) and 102(g)(2). Gregory Decl., ¶¶ 233-244, Ex. L.

Schutte discloses at least two pairs of primers--pairs 886s186 and 886s239--each over 15 nucleotides. Gregory Ex. L at 4571 (Table 1). The primer pairs are isolated from chromosome 13 (as claim 29 requires) and produce DNA amplification products (*i.e*., PCR products) comprised of 91 and 76 DNA oligonucleotides, respectively, having "all or part of the sequence of the BRCA2 gene" (as required by the claim and detailed further below). Gregory Decl., ¶ 236. The pair of "886s186" primers each hybridize within an intron of the BRCA2 gene, thereby anticipating and invalidating claim 29. *Id*. One of the primers in the "886s239" primer pair hybridizes within Exon 2 of BRCA2, while the other hybridizes within the neighboring intron such that a portion of the amplified PCR product comprises "part of the sequence of the BRCA2 gene," thereby invalidating claim 30 of the '492 Patent. Gregory Decl., ¶¶ 239-240.

**b. Claim 30 of the '492 Patent is Invalid**

**(1) Claim 30 (January 11, 1996) is Anticipated Under 102(a) and 102(g) by Schutte et al. (October 15, 1995)**

Claim 30 is invalid under Sections 102(a) and (g) for the reasons stated above in reference to claim 29. That is, the two primer pairs--886s186 and 886s239--each over 15 nucleotides, can be used to amplify a DNA molecule where the corresponding cDNA of the BRCA1 gene "has the nucleotide sequence set forth in SEQ ID NO:1," which results in the synthesis of DNA having "all or part of the sequence of the BRCA1 gene." Gregory Decl., ¶¶ 239-240.

**C. PLAINTIFFS' ASSERTED METHOD CLAIMS ARE OBVIOUS UNDER SECTION 103**

Plaintiffs asserted method claims are obvious. The subject matter set forth in Plaintiffs' method claims is directed merely to well-known laboratory tools or procedures available at the time of the claimed invention(s), with the only "hook" being that steps are performed in conjunction with a BRCA1 gene or gene sequence, or a BRCA2 gene or gene sequence. But, although the sequences of BRCA1 and BRCA2 may have been "new" in the sense of having been finally characterized fully, this does not mean that (i) the gene compositions themselves are not obvious, or (ii) that the primers derived or isolated from the genes and sequences themselves are not obvious, or (iii) that the predicable laboratory and well-known laboratory procedures generically claimed, such as sequencing or amplification, were not also obvious – as the patents' specifications readily admit they were at the time. The evidence shows that the method claims are obvious, particularly in view of the "(1) scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the art at the time the invention as made" and the lack of "any [relevant ] (4) objective evidence of non-

obviousness." *See Graham v. John Deere Co*., 383 U.S. 1, 17-28 (1966); *KSR v. Teleflex*, 550 U.S. 398, 127 S. Ct. 1727 (2007).

**1. Isolation and Identification of the Natural Gene Sequences of BRCA1 and BRCA2 Was Obvious as the Scope and Content of the Prior Art Teaches**

In the early 1990's, multiple highly-motivated groups of scientists were working toward locating the *BRCA1* gene, which had been indisputably linked to both breast cancer in 1990, and ovarian cancer in 1991. Bowcock Dec., ¶¶ 18, 21, 22. Plaintiffs admit as much. *See* U.S. Pat. No. 5,753,441 ("Intense efforts to isolate the BRCA1 gene have proceeded since it was first mapped in 1990 (Hall et al., 1990; Narod et al., 1991).") The research community's dedication using known gene-sequencing mapping techniques was with good reason—as of 1990, breast cancer was the leading cause of death among woman, afflicting over 170,000 individuals per year in the United States. *Id*. at ¶ 19.

In 1988, an international consortium of scientists had banded together to tackle the known but extensive work of locating the gene by iteratively refining genetic linkage maps to narrow the range of locations where the BRCA1 gene would be found on human chromosome segment 17q. *Id*., ¶ 20. Similar to finding the proverbial needle in the haystack, it required scientists to examine the larger volume of straw chromosome 17q to find the needle of the BRCA1 gene. By 1994, at least fifteen different research groups had helped to significantly narrow the range for the location of the BRCA1 gene so that it could be isolated. *Id*. at ¶¶ 23-24. The significance and the necessity of completing the tedious, but straightforward task of the gene mapping of human traits, was readily understood—to move from a known chromosomal location to identification of the gene and characterization of its natural alterations. *Id*., ¶¶ 25-26.

By 1993, researchers independent of Plaintiffs had significantly narrowed the range of genomic material from which the BRCA1 gene would be isolated. Bowcock Decl., ¶ 27. Even Plaintiffs scientists acknowledged that the previous work performed by the Breast Cancer Linkage Consortium and its individual members "ha(d) provided an excellent base for characterizing the BRCA1 locus," and expressed an expectation that the BRCA1 gene would be found on that locus. *Id*., ¶ 29. By the start of 1994, it was clear to those in the field what steps and techniques would be employed in order to discover the location and sequence of the BRCA1 gene, building on the iterative work that others had already completed to home in on the gene. *Id*., ¶¶ 30-34.

At the point where a "brute force" approach could be employed to locate the BRCA1 gene, Plaintiffs used the resources they garnered from both corporate sponsors and taxpayer funding to conduct a data processing "surge" to find the *BRCA* genes. Plaintiffs did this to make sure that they were the first to "discover," and patent, the BRCA genes and every reasonably conceivable use for same. Having stood on the shoulders of giants, Plaintiffs sought to claim the kingdom. But, despite their push to be first, Plaintiffs' scientists employed conventional techniques that were well-understood, widely-used, and fairly uniform insomuch that any scientist engaged in the search for genes, like BRCA1 and BRCA2, would almost certainly have utilized the same techniques. *Id*., ¶¶ 14, 35, 37-49.

Indeed, as the *Myriad* Supreme Court stated, "***the processes used by Plaintiffs to isolate DNA were well understood by geneticists at the time of Plaintiffs' patents 'were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for***

***a gene would likely have utilized a similar approach***,'" *Myriad*, 133 S. Ct. at 2119-20 (emphaisis added). Plaintiffs' patents make this clear when they admit:

> The practice of the present invention employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, and immunology. *See, e.g.*, Maniatis et al., 1982; Sambrook et al., 1989; Ausubel et al., 1992; Glover, 1985; Anand, 1992; Guthrie & Fink, 1991. A general discussion of techniques and materials for human gene mapping, including mapping of human chromosome 17q, is provided, e.g., in White and Lalouel, 1988.")

'441 Patent, col. 25, ll. 49-57; *see also* '492 Patent, col. 24, ll. 29-37 (similar). Bowcock Decl., ¶¶ 50-54. These admissions alone are compelling evidence that Plaintiffs claimed invention is obvious. *See In re Kubin*, 561 F.3d 1351, 1356 (Fed. Cir. 2009) ("Kubin and Godwin cannot represent to the public that their claimed gene sequence can be derived and isolated by 'standard biochemical methods' discussed in a well-known manual on cloning techniques, which at the same time discounting the relevance of that very manual to the obviousness of their claims.") As further described in the Declarations of Drs. Bowcock and Gregory, the techniques Plaintiffs used and admitted were known in their patents track the same gene-location techniques that the prior art taught. Bowcock Decl., ¶¶ 34-54; Gregory Decl., ¶¶ 96-216.

Armed with a business plan, Plaintiffs set out to capitalize on the work of the international consortium of mostly academic scientists that had revealed fundamental and tangible *i*nformation about the genetic cause of breast cancer and the genomic location of its source. Bowcock Decl., ¶¶ 55-63. The sizeable investment by Plaintiffs' corporate partners and the federal government evidences Plaintiffs' reasonable expectation of success in isolating the *BRCA* genes. "Obviousness does not require absolute predictability of success… *all that is required is a reasonable expectation of success."* *Kubin*, 561 F.3d at 1360 (*quoting In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988) (emphasis in *Kubin*)).

Plaintiffs did not discover or execute an inventive concept worthy of a patent *in isolating* the *BRCA* genes; they merely pursued known options from a "finite number of identified, predictable solutions" to identify an unpatentable gene with an expansive, exclusive market potential in genetic testing. *Id*. ¶ 58; *Kubin*, 561 F.3d at 1359 (*quoting KSR*, 550 U.S. at 421). "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress." *KSR*, 550 U.S. at 419. With nearly 170,000 individuals afflicted with breast cancer per year in the United States in 1990 (Bowcock Decl., ¶ 19), it is indisputable that "other researchers in the field had every motivation to seek and every reasonable expectation of success in achieving the sequence of the claimed invention," particularly given the high level of research involvement and steady progress in tracking the BRCA genes. *Kubin*, 561 F.3d at 1361.

Once Plaintiffs determined the sequence of the BRCA genes through routine methods, they sought to patent well-known and obvious uses of such genes in methods. The list of well-known biotechnological and medical procedures incorporated into the claims has one common theme—the inclusion of the unpatentable BRCA1 or BRCA2 gene or gene sequence as part of the "invention." The Patent Act addresses such obvious permutations of the same unpatentable subject matter: "(a) A patent may not be obtained… if the differences between the subject matter sought to be patented and the prior art are *such that the subject matter as a whole* would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a).

As further supported in the Bowcock and Gregory Declarations, the prior art teaches the obviousness of the BRCA genes and their use in routine diagnostic tests that the patents wrongfully claim. Defendants turn to the specific claims.

**2. Claim 5 of U.S. Patent No. 6,951,721 Is Invalid Under Section 103**

Plaintiffs have asserted dependent Claim 5 as the only claim of U.S. Patent No. 6,951,721 against Defendants. Claim 5 depends from claim 1:

> 1. A method for determining an omi haplotype of a human BRCA1 gene comprising: (a) determining the nucleotide sequence of the BRCA1 gene or fragment thereof from at least one female individual with a family history which indicates a predisposition to breast cancer, (b) comparing the determined nucleotide sequence from said female individual to SEQ ID NO: 263, and (c) determining the presence of the following nucleotide variations: thymine at nucleotides 2201 and 2731, cytosine at nucleotides 2430 and 4427, and guanine at nucleotides 3232, 3667 and 4956, wherein the presence of the nucleotide variations in the determined nucleotide sequence indicates the omi1 haplotype

Independent claim 1 is not as complex as it sounds.

- According to Webster's Dictionary, a haplotype is "a group of alleles [(nucleotide differences)] of different genes on a single chromosome that are closely enough linked to be inherited usually as a unit."
- Although the '721 Patent does not state in clear terms what the "omi" haplotype is, the inventors' corresponding European patent does: "*It is an object of the invention to provide the most commonly occurring coding sequence of the BRCA1 gene*," (EP 1126034), that is, the "omi haplotype." In other words, the omi haplotype is the most commonly naturally occurring gene sequence for the BRCA1 gene in the human population.
- SEQ ID NO: 263 is the cDNA sequence of the omi haplotype, and the nucleotide positions referred to in the claim (2201, 2731, etc.) merely describe the

nucleotides at those respective potions in the BRCA1 gene that make up the omi haplotype.

Claim 1 thus reduces to the following: (1) determine the nucleotide sequence of the BRCA1 gene or part of a BRCA1 gene from an at-risk woman (by any means at all—no method is specified); and (2) compare the sequence to a known sequence to see if the woman has the (3) most commonly occurring coding sequence of the BRCA1 gene. (The coding sequence is the portion of a gene comprised of exons, *i.e.*, a cDNA sequence.)

Plaintiffs choose to assert claim 5 against the Defendants instead of claim 1. Defendants posit that Plaintiffs know that claim 1 is invalid in view of the previous *Myriad* and *Mayo* cases. Merely observing and comparing a naturally occurring genetic sequence (no matter how technically it is described) to a known reference is simply not patentable. Asserted claim 5 does not add much more, and certainly nothing inventive.

Asserted claim 5 reads: "The method of claim 1 wherein the BRCA1 gene or fragment thereof is amplified prior to nucleotide sequencing." Thus, claim 5 simply adds: (1) amplify the DNA sample prior to sequencing. As discussed in Section IV addressing patent-ineligible subject matter, such techniques were well-known and obvious at the time the 1996 '721 application was filed as the specification admits. The specification states of amplification: "Preferably, the method of amplifying is by PCR, as described herein and as is commonly used by those of ordinary skill in the art." '721 Patent, col. 11, ll. 54-56. The '721 Patent further describes why scientists use PCR: "The steps of denaturing, annealing, and extension product synthesis can be repeated as often as needed *to amplify the target polymorphic locus nucleic acid sequence to the extent necessary for detection.* The amount of the specific nucleic acid sequence

produced will accumulate in an exponential fashion. Amplification is described in PCR. A Practical Approach, ILR Press, Eds. M. J. McPherson, P. Quirke, and G. R. Taylor, 1992." '721 Patent, col. 11, ll. 18-25 (emphasis added).

If sequencing is a required element of the method (all the claim expressly requires is amplification prior to sequencing), that too makes the claim no more inventive or nonobvious, as plaintiffs' patents admit. *See, e.g.*, "A number of methods well-known in the art can be used to carry out the sequencing reactions. Preferably, enzymatic sequencing based on the Sanger dideoxy method is used. Mass spectroscopy may also be used. The sequencing reactions can be analyzed using methods well-known in the art, such as polyacrylamide gel electrophoresis." '721 Patent, col. 12, ll. 62-col. 13, l. 1. Defendants turn to the specific art

**a. Claim 5 of U.S. Patent No. 6,951,721 (February 12, 1996) Is Obvious in View of Miki et al. (1994)**

Miki *et al*., discloses a method for determining a predisposing haplotype of human BRCA1, including the steps of amplifying (using PCR) and sequencing. Gregory Decl., Ex. Z. Miki publishes the BRCA wild-type sequence. Miki does not specifically disclose or claim an omi haplotype (most commonly occurring) with a "thymine at nucleotides 2201 and 2731, cytosine at nucleotides 2430 and 4427, and guanine at nucleotides 3232, 3667 and 4956" within the sequence of a patient's BRCA1 gene. However, while Miki does not disclose these specific cites of nucleotide variation (polymorphic), Miki discloses the methods for determining the presence or absence nucleotide variations (polymorphic) in general, and also discloses several "neutral polymorphisms." Simply put, with Miki disclosing a BRCA1 sequence, it would have been a simple and obvious step to use the Miki methods to sequence more samples and identify the additional specific sequence variations (neutral polymorphism) of the claim, rendering the

claim obvious. Bowcock Decl., ¶¶ 109-114; Gregory Decl., ¶¶ 198-204. (Notably, this claim is also unpatentable Section 101 subject matter under *Mayo* and *Myriad*, as discussed, *supra*, as it simply asserts ownership over human BRCA sequences for comparison purposes.) Merely reciting specific variations (polymorphisms) of natural DNA sequences does not make claim 5 nonobvious. Bowcock Decl, ¶¶ 109-114; Gregory Decl., ¶¶ 198-204.

**b. Claim 5 of U.S. Patent No. 6,951,721 (February 12, 1996) Is Obvious in View of Friedman et al. (1994)**

The article Friedman *et al*., *Confirmation of BRCA1 by analysis of germline mutations linked to breast and ovarian cancer in ten families*, Nature Genet. Dec.1994; 8(4):399-404, invalidates claim 5 of the '721 Patent for the same reasons that Miki (1994) invalidates claim 5 of the '721 Patent. Gregory Decl., Ex. CC. Friedman discloses using Miki's BRCA1 sequence to design primers to look for mutations and polymorphisms of individuals having a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer. Bowcock Decl., ¶¶ 115-116; Gregory Decl., ¶¶ 205-210. Friedman performs every limitation, including the well-known steps of "hybridizing," "amplifying" "sequencing," and "comparing" the results of the sequencing data to a known reference sequence, which are not inventive steps as the patent's specification acknowledges. Bowcock Decl., ¶¶ 115-116; Gregory Decl., ¶¶ 205-210. Like Miki, Friedman does not disclose the specific nucleotide variations (polymorphisms) that exist in a population, however, Friedman does disclose a series of "neutral polymorphisms" that are not associated with breast or ovarian cancer, as well as predisposing mutations that are linked to breast and ovarian cancer. Bowcock Decl, ¶¶ 115-116; Gregory Decl., ¶¶ 205-210. It would have been obvious to use the methods disclosed in Friedman *et al*. to identify additional polymorphisms, including those most common polymorphisms. *Id*.

**c. Claim 5 of U.S. Patent No. 6,951,721 is obvious in view of U.S. Patent No. 5,747,282 (1994) Which is Section 102(e) Prior Art**

The '282 Patent discloses a method of identifying individuals having a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer. Gregory Decl., Ex. DD. The '282 Patent (Plaintiffs' original patent disclosing a BRCA1 sequence) describes every limitation of claim 5 of '721 Patent. This includes the well-known steps of "hybridizing," "amplifying" "sequencing," and "comparing" the results of the sequencing data to a known reference sequence. Bowcock Decl., ¶ 117; Gregory Decl., ¶¶ 211-216. All of the foregoing steps, either together or alone, are not inventive.

While the '282 Patent does not disclose the specific (nucleotide) polymorphic variations described in claim 5, the '282 Patent discloses the methods for determining the presence or absence polymorphic variations in general, and also discloses "neutral polymorphism." For example, the '282 Patent disclosed 11 neutral polymorphism (nucleotide variation at a certain site/position in the gene) that are not associated with breast or ovarian cancer, as well as predisposing mutations that are linked breast and ovarian cancer (Tables 11 and 12, '282 Patent). It would have been obvious to use the methods disclosed in the '282 Patent to identify additional polymorphisms that are not associated with breast or ovarian cancer. Bowcock Decl., ¶ 117; Gregory Decl., ¶¶ 211-216.

**3. Claims 2 and 4 of U.S. Patent No. 5,654,155 (February 12, 1996) are Likewise Invalid over Miki, Friedman and the '282 Patent**

Claims 2 and 4 of the '155 Patent are similar to the '721 Patent, claim 5 as "determining" certain specific nucleotide variations (polymorphisms). Like the '721 Patent, claim 2 and 4 of the '155 Patent are invalid because Miki (1994), Friedman (1994) and the '282 Patent (1994) all

disclose a BRCA1 sequence, variations in the sequence, and methods for amplifying and sequencing. Gregory Decl., ¶¶ 129-189. The references also disclose some of the specific variations claimed in the '155 Patent, claims 2 and 4 (or lack thereof). Claims 2 and 4 simply append the well-known steps of amplifying and sequencing an individual's BRCA1 sequence (1994) to create a population of sequences, and then comparing to a known BRCA1 sequence and determining whether certain "polymorphisms" (nucleotide variations at a specific position) are or are not in the population and are associated with an increased risk or lack of increased risk of breast or ovarian cancer. While this subject matter is plainly invalid under Section 101 because it clams only the comparison of natural information (sequence), it is likewise invalid under Section 103. *See* Bowcock Decl., ¶¶ 122-126; Gregory Decl., ¶¶ 129-189.

**4. Claims 7 and 8 of U.S. Patent No. 5,753,441 (August 1994) Are Obvious**

The structure of the asserted method claims in U.S. Patent No. 5,752,441 is similar to those described for the '721 Patent, although the claim is even more broad in that it does not require any particular sequence or haplotype (common sequence). Claims 7 and 8 are dependent on claim 1, which the Federal Circuit already confirmed was invalid under Section 101, affirming Judge Sweet:

> 1. A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

*AMP*, 689 F.3d at 1309, 1334-35. This patent ineligible claim directs a person merely to compare the sequence of BRCA1 DNA from a tissue sample of a human subject against the

sequence of a wild-type sequence to see if there is an "alteration." Dependent claims 7 and 8 merely append obvious steps:

> 8. The method of claim 1 wherein a germline nucleic acid sequence is compared *by amplifying all or part of a BRCA1 gene from said sample using a set of primers to produce amplified nucleic acids and sequencing the amplified nucleic acids*.

Claim 7 requires even less:

> 7. The method of claim 1 wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 *gene probe which specifically hybridizes* to a BRCA1 allele to genomic DNA isolated from said sample and *detecting* the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.

Claim 7's limitations may be met simply by performing the PCR process and observing whether amplification occurred or not based on the primer sequence through well-known laboratory methods—determining the sequence is not even required. To the extent Plaintiffs raise the argument that the gene sequence must be known, locating the gene was obvious, as explained in the Bowcock and Gregory Declarations and art of the time, *e.g.*, Kelsell *et al*., Genetic analysis of the BRCA1 region in a large breast/ovarian family: refinement of the minimal region containing BRCA1, Hum. Mol. Genet. 1993 Nov;2(11):1823-8 and Bowcock, A, *Molecular cloning of BRCA1: A gene for early onset familial breast and ovarian cancer*. Breast Can. Res. Tr., vol. 28:121-135 (1993). Bowcock Decl.,¶¶ 91-101; Gregory Decl., ¶¶ 96-128, Exs. E-I. Under *Kubin* and *KSR* as discussed above, the BRCA1 subject matter is obvious – rendering these two claims obvious. *Id*.[16]

[16] Claim 8 of the '441 Patent is anticipated under Section 102(b) by Bowcock (February 1993). Bowcock Decl., Ex. G. Bowcock discloses a method of isolating a BRCA1 gene (which were used by Myriad) and then performing diagnostic screening for genetic mutations using well-known laboratory techniques available at the time (which is now claimed by Myriad). The Bowcock meets all limitations of claim 8.

**5. Claim 4 of U.S. Patent No. 6,033,857(December 18, 1995) is Obvious**

Claim 4 of the '857 Patent is similar in scope to the claims of the '441 Patent, but is directed to the *BRCA2* gene instead of *BRCA1*. However, claim 4 is even broader. The Federal Circuit confirmed Judge Sweet's judgment that claim 2 of the '857 Patent is invalid under Section 101. *AMP*, 689 F.3d at 1309, 1334-35. That invalid claim states:

> 2. A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer.

This claim requires "comparing the germline sequence of a BRCA2 gene from a tissue sample…with the germline sequence of the wild-type BRCA2 gene… wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer." That is, compare sequence A with sequence B to arrive at an answer.

The additional appended steps in claim 4[17] include, for example, amplification only using amplification primers directed to a BRCA2 sequence (claim 4(e)) or amplification and sequencing (claim 4(d)), or detecting mere hybridization of a DNA probe to a sample containing BRCA2 (where no amplification is even required)(claim 4(b)), or simply screening (claim 4 (i)-(k). None of that subject matter is novel. As with the '441 Patent, the only remotely "new" aspect of these claims is the use of the patent ineligible BRCA2 gene in the list of standard lab procedures. To the extent Plaintiffs raise that issue, locating the gene was obvious, as explained in the Gregory Declaration and art of the time. Gregory Decl., ¶¶ 263-292, Exs. L and P. Under *Kubin* and *KSR* as discussed above, this subject matter is obvious in view of the scope and content of the prior art, and the claim is invalid. Gregory Decl., ¶¶ 263-292.

[17] Claim 4 of the '857 Patent reads: The method of claim 2 wherein the detection in the alteration in the germline sequence is determined by an assay selected from the group consisting of: (a) observing shifts in electrophoretic mobility of single-stranded DNA on non-denaturing polyacrylamide gels, (b) hybridizing a BRCA2 gene probe to genomic DNA isolated from said tissue sample, (c) hybridizing an allele-specific probe to genomic DNA of the tissue sample, (d) amplifying all or part of the BRCA2 gene from said tissue sample to produce an amplified sequence and sequencing the amplified sequence, (e) amplifying all or part of the BRCA2 gene from said tissue sample using primers for a specific BRCA2 mutant allele, (f) molecularly cloning all or part of the BRCA2 gene from said tissue sample to produce a cloned sequence and sequencing the cloned sequence, (g) identifying a mismatch between (1) a BRCA2 gene or a BRCA2 mRNA isolated from said tissue sample, and (2) a nucleic acid probe complementary to the human wild-type BRCA2 gene sequence, when molecules (1) and (2) are hybridized to each other to form a duplex, (h) amplification of BRCA2 gene sequences in said tissue sample and hybridization of the amplified sequences to nucleic acid probes which comprise wild-type BRCA2 gene sequences, (i) amplification of BRCA2 gene sequences in said tissue sample and hybridization of the amplified sequences to nucleic acid probes which comprise mutant BRCA2 gene sequences, (j) screening for a deletion mutation in said tissue sample, (k) screening for a point mutation in said tissue sample, (l) screening for an insertion mutation in said tissue sample, (m) in situ hybridization of the BRCA2 gene of said tissue sample with nucleic acid probes which comprise the BRCA2 gene.

As discussed above, this is a Markush claim. If any of the options are invalid, the entire claim is invalid.

## D. SECTION 112 INVALIDITY

### 1. Claim 17 Is Indefinite Under Section 112

Claim 17 of the '282 Patent is invalid as indefinite because it does not particularly point out and distinctly claim the subject matter which the applicant regards as his invention as required by section 112. Claim 17 recites: "The pair of primers of claim 16 wherein said BRCA1 gene has the nucleotide sequence set forth in SEQ ID NO:1." The specification of the '282 Patent specifically makes clear that the "BRCA1 gene" is a gene with both introns and exons. Bowcock Decl., ¶¶ 84-88. As a result, the claim is internally inconsistent with the patent specification because there is no BRCA1 gene that has the composite (cDNA) sequence of SEQ ID NO:1. *Id*. at ¶ 89. As a result, the claim is insolubly ambiguous and, therefore, invalid. *Exxon Res. and Eng'g v. United States*, 265 F.3d 1371, 1375 (Fed. Cir. 2001) ("If a claim is insolubly ambiguous, and no narrowing construction can properly be adopted, we have held the claim indefinite.")

### 2. Claim 30 Is Indefinite Under Section 112

Claim 30 of the '492 Patent is invalid as indefinite because it does not particularly point out and distinctly claim the subject matter which the applicant regards as his invention as required by section 112. Claim 30 recites: "The pair of primers of claim 29 wherein said BRCA2 gene has the nucleotide sequence set forth in SEQ ID NO:1." The specification of the '492 Patent makes clear that the "BRCA2 gene" is a gene with both introns and exons. As a result, the claim is internally inconsistent with the patent specification because there is no BRCA2 gene that has the composite (cDNA) sequence of SEQ ID NO:1. Gregory Decl., ¶ 241. The claim is insolubly ambiguous and, therefore, invalid. *Exxon*, 265 F.3d at 1375.

### 3. Claim 4 of the '155 Patent Violates the Written Description Requirement

A claim of a patent is invalid when the patent does not contain an adequate description of the invention of the scope of the claim. In *Ariad Pharmaceuticals Inc. v. Eli Lilly and Company*, 598 F.3d 1336 (2010), the Federal Circuit held that a sufficient description of a genus requires the disclosure of (i) either a representative number of species falling within the scope of the genus, or (ii) structural features common to the members of the genus so that one of skill in the art can "visualize or recognize" the members of the genus. According to the Federal Circuit, "adequate written description requires a precise definition, such as by structure, formula, chemical name, physical properties, or other properties, of species falling within the genus sufficient to distinguish the genus from other materials." *Id*.

Claim 4 of the '155 patent is directed to a method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual that is attributed to a BRCA1 mutation, wherein the mutation is not one of the seven neutral (harmless) mutations list in claim 4. The claim encompasses a genus of nucleotide mutations – as long as the mutation is not one of the seven recited in claim 4, then it is within the scope of the claim. However, the specification neither disclosed "a representative number of species falling within the scope of the genus," nor "structural features common to the members of the genus."

In particular, the specification discloses only seven neutral (harmless) genetic variations that ***do not*** affect a person's risk for developing breast or ovarian cancer. The specification, however, does not teach mutations ***that do*** lead to an increased susceptibility. No exemplary species are given to represent the genus. Further, other than a functional limitation that the mutation leads to "an increased genetic susceptibility to breast and ovarian cancer," no structural

features common to the members of the genus are disclosed. Claim 4 violates the requirement of adequate written description. Gregory Decl., ¶¶ 186-189.

## VI. PLAINTIFFS HAVE NOT SHOWN LIKELIHOOD OF SUCCESS OF INFRINGEMENT

Patent infringement analysis involves two steps: (1) the Court must determine the scope and meaning of the claims, and (2) the fact-finder must compare properly construed claims to the accused process or composition. *See Markman v. Westview Instrs., Inc.*, 517 U.S. 370, 384 (1996). Plaintiffs bear the burden of demonstrating infringement. *E.g.*, *Meyer Intellectual Props. Ltd v. Bodum, Inc.*, 690 F.3d 1354, 1370 (Fed. Cir. 2012).

At this stage, just as before trial, the Court is required to construe any disputed terms, even if the Court's constructions are "temporary" and not intended to be binding in later stages of the case. *O2 Micro Int'l Ltd. v. Beyond Innovation Tech. Co., Ltd.*, 521 F.3d 1351, 1361-63 (Fed. Cir. 2008); *Outside The Box Innovations, LLC v. Travel Caddy, Inc.*, 695 F.3d 1285, 1302 (Fed. Cir. 2012); *Aria*, --- F.3d ---, 2013 WL 4034379 at *2. Claim terms are to be given their ordinary meaning, as informed by the following sources in decreasing order of importance: the claim language itself, the patent specification, the prosecution history (if in evidence), and extrinsic evidence such as technical dictionaries. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1314-19 (Fed. Cir. 2005). A specific definition for a claim term set forth by the patentee controls. *Id.* at 1319. As do descriptions in the specification of "the present invention" as a whole. *E.g.*, *Verizon Servs. Corp. v. Vonage Holdings Corp.*, 503 F.3d 1295, 1308 (Fed. Cir. 2007). Claim terms also are to be construed in light of the surrounding claim language. *IGT v. Bally Gaming Int'l, Inc.*, 659 F.3d 1109, 1116-17 (Fed. Cir. 2011).

To demonstrate infringement, Plaintiffs must "pinpoint" to specific evidence clearly demonstrating that every limitation of the asserted claims appears in the accused products. *See Intellectual Sci. & Tech., Inc. v. Sony Elecs., Inc.*, 589 F.3d 1179, 1184 (Fed. Cir. 2009) (upholding summary judgment of noninfringement where patentee's expert failed to "pinpoint" to specific evidence); *Lucent Techs., Inc. v. Gateway, Inc.*, 580 F.3d 1301, 1317 (Fed. Cir. 2009) ("To infringe a method claim, a person must have practiced all steps of the claimed method."); *Cross Medical Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1310 (Fed. Cir. 2005) ("Literal infringement requires that each and every limitation set forth in a claim appear in an accused product."). Neither opaque identifications of aspects of the accused products purportedly covered by the elements of the asserted claims nor unsupported conclusions of infringement are sufficient. *See, e.g., Dynacore Holdings Corp. v. U.S. Philips Corp.*, 363 F.3d 1263, 1277-78 (Fed. Cir. 2004).

### A. PLAINTIFFS HAVE NOT DEMONSTRATED A LIKELIHOOD OF SUCCESS ON THE MERITS OF INFRINGEMENT OF THE COMPOSITION CLAIMS

Plaintiffs have not carried their burden to demonstrate a likelihood of succeeding at demonstrating infringement at trial for the reasons set forth below.

#### 1. Plaintiffs Do Not Pinpoint To Specific Evidence

Plaintiffs have failed to carry their burden because they have not pinpointed to specific evidence of alleged infringement contentions. In prose, Plaintiffs generally characterize the accused products or the technology used therein. Myriad Ambry P.I. Br. at 16-20; Myriad GBG P.I. Br. at 16-20. Plaintiffs provide infringement charts for four claims, but in those charts Plaintiffs merely characterize their previous characterizations and speculations about Defendants' tests and the technology at issue. Myriad Ambry P.I. Br. at 19, 20; Myriad GBG P.I.

Br. at 19, 20. This is not sufficient to demonstrate a likelihood of success that Defendants infringe every limitation of the composition claims at issue. *See Intellectual Sci.*, 589 F.3d at 1184; *Lucent,* 580 F.3d at 1317; *Cross Medical*, 424 F.3d at 1310; *Dynacore*, 363 F.3d at 1277-78.

**2. Defendants' Noninfringement Arguments Have Substantial Merit**

**a. U.S. Patent No. 5,747,282 Claim 16**

Plaintiffs have not provided any proof that that either Ambry or Gene by Gene infringe the first limitation of claim 16, when that claim is properly construed. Claim 16 recites,

> A pair of single-stranded DNA primers for determination of a nucleotide sequence of a *BRCA1* gene by a polymerase chain reaction,
>
> **the sequence of said primers being derived from human chromosome 17q,**
>
> wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the *BRCA1* gene.

'282 Patent cl. 16 (emphasis added).

The Court should construe "derived from" to mean "derived wholly from." The plain language of the claim limitation indicates that the sequence of the DNA primers of this claim contain only DNA sequence present in chromosome 17q.

So, too, does the specification. The patentees defined "amplification of polynucleotides," the subject matter of this claim, as utilizing primers "complementary" and which "hybridize to" regions of chromosome 17q:

> "Amplification of polynucleotides" utilizes methods such as the polymerase chain reaction (PCR), ligation amplification (or ligase chain reaction, LCR) and amplification methods based on the use of Q-beta replicase. These methods are well known and widely practiced in the art. … **Primers useful to amplify sequences from the BRCA1 region are preferably complementary to, and hybridize specifically to sequences in the BRCA1 region or in regions that flank a target region therein.**

'282 Patent at col. 17 ll. 15-32 (emphasis added). The inventors also described that the "primers of the present invention" used for amplification should exhibit **perfect base pair complementarity** with the DNA sequencing flanking the target, *i.e.*, is the same as a portion of the sequence of chromosome 17q. *Id.* at col. 16 ll. 23-35.

The lone description in the specification of primers having a few nucleotides that are not wholly derived from chromosome 17q (in addition to the vast majority being derived from chromosome 17q) applies only to claims covering cloning of DNA. Claims 1 through 15 recite cloning DNA coding for the BRCA1 peptide into a vector for expression in host cells. The definition of "amplification of polynucleotides" discusses the subject matter of these claims: "Alternatively, but less desirably, the amplified sequence(s) may be cloned prior to sequence analysis." *Id.* at col. 17 ll. 15-32.[18] This use is applicable only to other claims involving cloning, a process not present in claim 16. Rather, claim 16 expressly requires that the primers for amplification be the same as a portion of chromosome 17q. Defendants' construction is correct.

Finally, Defendants' proposed construction also is correct in light of the patentees' decision not to use open-ended claim language, such as "comprising," to describe the sequence of the primers of claim 16. *See, e.g.*, *Genentech, Inc. v. Chiron Corp.*, 112 F.3d 495, 501 (Fed. Cir. 1997) (describing "comprising" as a term of art that means that other elements may be added

[18] The specification teaches that for these "cloning" claims, the primers may include sequence that is not derived wholly from chromosome 17q – namely, restriction enzyme sites. '282 Patent at col. 16 ll. 36-48; Pribnow Decl., ¶¶ 71, 72. However, this description pertaining to the cloning claims supports the proposed construction for the first limitation of claim 16, because this description provides that "derived from" should be construed consistent with Defendants' construction: "Thus, all nucleotides of the primers are **derived from** *BRCA1* sequences or sequences adjacent to *BRCA1*, except for a few nucleotides necessary to form a restriction enzyme site." '282 Patent at col. 16 ll. 36-48 (emphasis added). In other words, any sequence "derived from" *BRCA1* sequences are derived wholly from *BRCA1* sequences. No claim other than claim 16 uses the term "derived from."

to the claim language). Instead, the patentees chose to use the phrase "derived from" - which, unlike commonly used phrases such as "comprising" and "consisting of" that are almost invariably construed as open- and closed-ended, respectively - has no well-accepted meaning and therefore must be construed in light of the specification just as any other claim term. *Cf. AFG Indus., Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1244-45 (Fed. Cir. 2001) (construing "composed of," which had "little" definitional precedent, according to teachings of specification).

Plaintiffs' "evidence" of Ambry's infringement fails to demonstrate the likelihood that Ambry's primers literally infringe this limitation. In contrast to the requirements of the claim, Ambry's DNA PCR primers and sequencing primers contain sequences other than the natural sequence of chromosome 17q. Specifically, Ambry's PCR primers contain "adaptor" and "bar code" sequences that are not derived from the sequence of chromosome 17q. Elliott Decl., ¶¶ 15-19. Further, Ambry's sequencing primers contain no sequence whatsoever derived from chromosome 17q and thus cannot literally infringe. *Id.* ¶ 26. Ambry's literal noninfringement is established from the very "evidence" Plaintiffs contend supports infringement. *Id.* ¶¶ 15-19.

Likewise, none of the "evidence" cited by Plaintiffs demonstrates that the primers utilized in Gene by Gene's tests contain sequences wholly derived from chromosome 17q. The fact of the matter is that Plaintiffs **can't** demonstrate that Gene by Gene infringes, because its accused services are still under development, and Gene by Gene intends to utilize primers containing sequence that is not derived from chromosome 17q. Mittelman Decl., ¶ 16.

Even were the Court to find that "derived" allowed for some modification of the sequence from that found on chromosome 17q, the claim still requires that the sequence be

derived from chromosome 17q. The adaptors, barcode sequences, and "tags" are in no way derived from chromosome 17q sequence. Elliott Decl., ¶¶ 15-19; Mittelman Decl., ¶ 16. On this separate ground, there is no infringement.

In sum, Plaintiffs have not carried their burden to show a likelihood of literal direct infringement of claim 16 of the '282 Patent by either Defendant.

**b. U.S. Patent No. 5,747,282 Claim 17**

Claim 17 of the '282 Patent requires the pair of primers recited in claim 16 generate all or part of the nucleotide sequence of SEQ ID NO: 1, which Plaintiffs point out is a contiguous cDNA sequence of *BRCA1*. *E.g.*, Myriad Ambry P.I. Br. at 19; *see also* '282 Patent at col. 67 (identifying SEQ ID NO:1 as cDNA). Claim 17 also is not a "comprising" claim, indicating that Plaintiffs intended for the claim to cover only amplicons containing all or part of the contiguous *BRCA1* cDNA sequence specifically identified as SEQ ID NO:1.

Plaintiffs have not carried their burden to demonstrate the likelihood of success on the merits of literal infringement, because they have not shown that the amplicons generated by Ambry's and Gene by Gene's products contain only contiguous *BRCA1* cDNA sequence. As noted above, Ambry's primers – and the resulting amplicons – contain sequences that are not wholly derived from *BRCA1*, as demonstrated by the "evidence" cited by Plaintiffs. Elliott Decl., ¶¶ 15-19. Furthermore, amplicons generated by Ambry's and Gene by Gene's tests contain intronic sequences, which are not, of course, contained in cDNA. *E.g.*, Elliott Decl., ¶ 8; Mittelman Decl., ¶ 16. For these reasons, Defendants do not literally and directly infringe claim 17 of the '282 Patent.

**c. U.S. Patent No. 5,837,492 Claims 29 and 30**

The same reasons why Ambry and Gene by Gene do not infringe claims 16 and 17 of the '282 Patent apply to claims 29 and 30 of the '492 Patent as well. Claim 29 of the '492 Patent is essentially the same as claim 16 of the '282 Patent, except that claim 29 of the '492 Patent is drawn to *BRCA2* and substitutes "isolated from" for "derived from," making even clearer that the primer sequence may not deviate from the sequence of human chromosome 13.[19] Likewise, claim 30 of the '492 Patent is essentially the same as claim 17 of the '282 Patent, except that claim 30 recites a contiguous *BRCA2* cDNA sequence. *E.g.*, Myriad Ambry P.I. Br. at 20.

The term "isolated from" in claim 29 should be construed to mean "isolated wholly from" for the same reasons why "derived from" in claim 16 of the '282 Patent should be construed to mean "derived wholly from." The teachings of the '492 Patent specification pertaining to the design of primers for use in amplification are the same as in the '282 Patent specification. *Compare* '282 Patent at col. 16 ll. 23-35 (describing "the primer pairs of the present invention") *with* '492 Patent at col. 15 ll. 10-23 (same); '282 Patent at col. 17 ll. 23-26 (explaining that "primera hybridize specifically to sequences in the *BRAC1* region") *with* '492 Patent at col. 16 ll. 11-14 (same for *BRCA2*); '282 Patent at col. 16 ll. 36-48 (explaining that restriction sites used in cloning) *with* '492 Patent at col. 15 ll. 23-36 (same). Furthermore, the patentees defined "isolated nucleic acid" to include primers and other chemically synthesized DNA that are "substantially

[19] "A pair of single-stranded DNA primers of at least 15 nucleotides in length for determination of a nucleotide sequence of a *BRCA2* gene by a polymerase chain reaction, the sequence of said primers being **isolated from** human chromosome 13, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA comprising all or at least 15 contiguous nucleotides of the *BRCA2* gene." '492 Patent cl. 29 (emphasis added).

separated from other cellular components," *i.e.*, the sequence in the primers is the same as in the naturally occurring DNA. '492 Patent at col. 17 ll. 62-18:5.

Thus, to show likelihood of success on infringement, Plaintiffs must demonstrate that Ambry's and Gene by Gene's primers are "isolated wholly from" the sequence of chromosome 13. For the same reasons explained above in connection with the '282 Patent, Plaintiffs have not met this burden. Defendants have also affirmatively shown that the primer sequences do not track a *BRCA2* natural sequence, defeating any claim of literal, direct infringement. Elliott Decl., ¶¶ 15-19; Mittelman Decl., ¶ 16.

Even if the Court were to find that some deviation in sequence may be permitted, the undisputed fact is that a portion of the primers used in no way was isolated or derived from the chromosome 13 sequence

### B. PLAINTIFFS HAVE NOT DEMONSTRATED A LIKELIHOOD OF SUCCESS ON THE MERITS OF INFRINGEMENT OF THE METHOD CLAIMS

#### 1. Plaintiffs Do Not Pinpoint to Specific Evidence and Rely Solely on Offers to Sell and Announcements to Launch

Plaintiffs' infringement contentions for the method claims fail for lack of specificity in evidence supporting infringement, instead choosing to vaguely characterize Defendants' products or the technology at issue (including citing Wikipedia for support). Myriad Ambry P.I. Br. at 23 (citing Wikipedia entry for "germline"); Myriad GBG P.I. Br. at 22 (same).

In addition, Plaintiffs' infringement analysis also fails because it amounts only to a demonstration that Ambry has offered to sell, and GBG has announced its intentions to sell, accused products. *See, e.g.*, *Meyer*, 690 F.3d at 1366 ("Where, as here, the asserted claims are method claims, the sale of a product, without more, does not infringe the patent. Instead, direct

infringement of a method claim requires a showing that each and every step of the claimed method has been practiced.") (citation omitted.)

**2. Defendants' Noninfringement Defenses Have Substantial Merit**

**a. U.S. Patent No. 5,753,441 Claim 8 and U.S. Patent No. 6,033,857 Claim 4**

These claims cover comparisons of patient germline *BRCA1* gene sequences - either in the form of a "*BRCA1* gene," "*BRCA1* mRNA," or "*BRCA1* cDNA" - to "wild-type" germline *BRCA1* sequences to identify alterations, where the patients' *BRCA1* sequences are amplified and sequenced. Myriad Ambry P.I. Br. at 22-23; Myriad GBG P.I. Br. at 22. Defendants do not utilize patient mRNA or cDNA obtained from patient mRNA. Elliott Decl., ¶ 8; Mittelman Decl., ¶ 16.

"*BRCA1* gene" as used in claim 8 of the '441 Patent (and claim 1 from which claim 8 depends) means the "genomic *BRCA1* gene" and does not include any other region of genomic DNA. The patentee defined "*BRCA1* gene" to refer to "polynucleotides" that include "RNA, cDNA, [or] genomic DNA" of *BRCA1*:

> "BRCA1 Locus," "BRCA1 Gene," "BRCA1 Nucleic Acids" or "BRCA1 Polynucleotide" each refer to **polynucleotides**, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancers…. **The polynucleotide compositions of this invention include RNA, cDNA, genomic DNA, synthetic forms, and mixed polymers, both sense and antisense strands, and may be chemically or biochemically modified or may contain non-natural or derivatized nucleotide bases, as will be readily appreciated by those skilled in the art.**

'441 Patent at col. 19 ll. 30-60 (emphases added). The patentees also pointed out in the specification that "the present invention" involves discovering mutations in all regions of the *BRCA1* gene. *E.g.*, *id.* at col. 7 ll. 23-37 ("a discovery of the present invention" involved

identifying "mutational events" in *BRCA1* that "can involve deletions, insertions and point mutations within the coding sequence and the non-coding sequence"), col. 12 ll. 34-44 (describing in the context of "the present invention" that "'[a]lteration of the wild-type gene' encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions."). In other words, when the patentees said, "*BRCA1* gene," they meant only the *BRCA1* gene region. *See, e.g.*, *Phillips*, 415 F.3d at 1314-19; *Verizon*, 503 F.3d at 1308.

Plaintiffs have not showed that Defendants perform the steps of a claim where *"BRCA1* gene" has been properly construed, *i.e.*, that Ambry and Gene by Gene compare patient samples only to genomic, wild-type *BRCA1* gene sequence. And, in fact, both Ambry and Gene by Gene compare patient sequences to the sequence of the entire human genome. Elliott Decl., ¶ 32-34; Mittelman Decl., ¶ 20.

Plaintiffs' infringement arguments are not saved by the fact that these claims utilize the transition word "comprising," because Defendants do not practice all of the recited steps as claimed. "Comprising" is synonymous with "including," "containing," or "characterized by" and is inclusive or open-ended such that infringement of a method claim utilizing "comprising" cannot be defeated by adding to the accused method steps not recited in the claim. *E.g.*, *Mars, Inc. v. H.J. Heinz Co., L.P.*, 377 F.3d 1369, 1376 (Fed. Cir. 2004). However, the steps **as claimed** (plus any other steps) must be performed in order to find infringement. *See, e.g.*, *Dippin' Dots, Inc. v. Mosey*, 476 F.3d 1337, 1343 (Fed. Cir. 2007) ("Those six enumerated steps must, however, all be practiced as recited in the claim for a process to infringe. The presumption raised by the term ''comprising'' does not reach into each of the six steps to render every word

and phrase therein open-ended—especially where, as here, the patentee has narrowly defined the claim term it now seeks to have broadened.").

This noninfringement analysis also applies to uncharted claim 4 of the '857 Patent. *See, e.g.*, Myriad Ambry P.I. Br. at 23 (contending that claim 4 of the '857 Patent is similar to claim 8 of the '441 Patent in relevant aspects); Myriad GBG P.I. Br. at 22 (same).

**b. U.S. Patent No. 6,951,721 Claim 5 and U.S. Patent No. 5,654,155 Claims 2 and 4**

Defendants do not infringe any of these claims, because they do not compare patient sequences to contiguous cDNA sequences, as explicitly recited by the claims. Claim 5 of the '721 Patent requires comparing a female patient's DNA sequence to a sequence called "SEQ ID NO: 263." This sequence is a contiguous cDNA sequence of *BRCA1*. '721 Patent at col. 109 (identifying SEQ ID NO: 263 as "cds," or cDNA sequence). Likewise, the recited "SEQ ID NO: 1" in claims 2 and 4 of the '155 Patent also is a contiguous cDNA sequence of *BRCA1*. '155 Patent at col. 19 (identifying SEQ ID NO:1 as cDNA). Ambry and Gene by Gene do not literally infringe because neither compares patients' amplified sequences to a contiguous cDNA sequence of *BRCA1*. Elliott Decl., ¶¶ 32-34; Mittelman Decl., ¶ 20.

**c. U.S. Patent No. 5,753,441 Claim 7 and U.S. Patent No. 6,033,857 Claim 4**

Plaintiffs do not provide charts for claim 7 of the '441 Patent or claim 4 of the '857 Patent at all, instead relying on general characterizations of the processes utilized by Defendants. For the reasons stated above, this is insufficient.

In addition, Plaintiffs cannot demonstrate a likelihood of success on the merits of infringement of these two claims. Claim 7 of the '441 Patent requires the use of allele-specific probes:

> The method of claim 1 wherein a germline nucleic acid sequence is compared by hybridizing a ***BRCA1* gene probe which specifically hybridizes to a *BRCA1* allele** to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the said subject.

The Court should construe "a *BRCA1* gene probe which specifically hybridizes to a *BRCA1* allele" to mean "a *BRCA1* gene probe that hybridizes either to the wild-type *BRCA1* allele or a sequence of a known mutation of the *BRCA1* gene sequence which predisposes to certain cancers."

The specification defines "*BRAC1* allele" as including "normal alleles" as well as known variants that "predispose individuals to develop cancer." '441 Patent at col. 19 ll. 24-30. The specification teaches that each probe is specific for a particular variant (allele), and, to identify whether a patient has such an allele, his or her sample is incubated with a panel of allele-specific probes. *E.g., id.* at col. 21 ll. 35-41 (defining "probe" as "Polynucleotide polymorphisms associated with *BRCA1* alleles which predispose to certain cancers or are associated with most cancers are detected by hybridization with a polynucleotide probe which forms a stable hybrid with that of the target sequence, under stringent to moderately stringent hybridization and wash conditions."), col. 15 ll. 29-43 (describing "allele-specific probes" that are "nucleic acid oligomers, each of which contains a region of the *BRCA1* gene sequence harboring a known mutation…By using a battery of such allele-specific probes, PCR amplification products can be screened to identify the presence of a previously identified mutation in the *BRCA1* gene.").

Defendants do not literally infringe because they do not use or intend to use probes specific for any known variations of *BRCA1* that predispose a patient to certain cancers. Elliott Decl., ¶ 49; Mittelman Decl., ¶ 21. That is, the probes that Ambry and Gene by Gene uses or will use will only identify *BRCA1* and are not specific for any particular allele, as required by the claim.

Both claim 7 of the '441 Patent and claim 4 of the '857 Patent depend from independent claims that recite "*BRCA1* gene" and "*BRCA2* gene," respectively, requiring that the entire genes (including all of the introns and exons) are screened. Plaintiffs have not demonstrated that the large rearrangement tests that Ambry has offered for sale, or the tests that Gene by Gene are developing, literally screen for rearrangements in all portions of the *BRCA1* and *BRCA2* genes.

## VII. PLAINTIFFS HAVE NOT MET THEIR BURDEN THAT THEY WILL SUFFER IRREPARABLE HARM, THAT THE BALANCE OF HARDSHIPS TIPS IN THEIR FAVOR, AND THAT THE PUBLIC INTEREST WILL BE SERVED IF INJUNCTIVE RELIEF IS GRANTED AGAINST AMBRY AND GENE BY GENE

### A. PLAINTIFFS HAVE NOT ESTABLISHED THAT THEY WILL SUFFER IRREPARABLE HARM[20]

"The essence of showing irreparable harm is demonstrating an injury that money damages cannot sufficiently remedy." *Voilé Mfg. Corp. v. Dandurand*, 551 F. Supp. 2d 1301, 1307 (D. Utah 2008) (citing *High Tech Med. Instrumentation, Inc. v. New Image Indus., Inc.*, 49 F.3d 1551, 1557 (Fed. Cir. 1995)). To support such a finding, courts require more than conclusory affidavits and unsupported factual conclusions. *Id.*; *LL&L Innovations, LLC, et al. v.*

[20] Although the Federal Circuit used to apply a presumption of irreparable harm upon finding that a plaintiff was likely to succeed on the merits, the Supreme Court's decision in *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388 (2006), jettisoned this presumption. *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1148-49 (Fed. Cir. 2011).

*Jerry Leigh of Cal., Inc.*, No. 2:10-CV-829-TC, 2010 U.S. Dist. LEXIS 108173, at *25-*26 (D. Utah Oct. 8, 2010).

**1. Plaintiffs Cannot Establish That Any Alleged Price Erosion Is Either Immediate or Irreparable**

Plaintiffs offer no evidence that money damages are inadequate to redress any injury from future sales of the accused BRCA1/2 tests. Plaintiffs only offer the conclusory declaration of Alexander Ford, Myriad's Chief Commercial Officer, who asserts that Myriad may suffer immediate price erosion but offers no examples of a single reduction in price Myriad has made as a result of Ambry's or Gene by Gene's entry into the market some two months ago.

Myriad contends that if it does drop its prices during this lawsuit, it would be impossible to later restore prices to current levels due to pressure against raising prices. But for years, Myriad has kept its prices high despite widespread criticism and pressure to reduce prices and despite even acknowledging that its prices should be reduced. Indeed, six years ago, when Myriad's founder Dr. Skolnick was confronted about why Myriad's tests continued to be so expensive, he acknowledged that prices should come down:

> Q: "And you [Myriad] said, when the test came out, that this is going to be a less expensive test. This test will one day be hundreds of dollars. So why is it still $3,000? Why is it increasing?"
>
> A: "That's a good question. And I think there's a point at which we have to start looking at decreasing the cost of the test."

J. Rudnick interview of Dr. Skolnick, In the Family: A Visit to Myriad Genetics (Kartemquin Films) (documentary film aired on PBS on Oct. 8, 2008), *available at* http://inthefamily.kartemquin.com/content/great-news-myriad-genetic-patenting-case (3:37 mark). Six years later, despite earning billions in revenue and recouping its alleged investment several times over, Myriad's prices have only continued to go up. Hampton Decl., ¶¶ 23-24, 62.

Not surprisingly, as a monopolist, Myriad has the ability to set prices wherever it wants. Even if Myriad were to drop its prices in response to competition during the pendency of this lawsuit, there is no evidence that Myriad will be prevented from restoring its prices to current levels if it prevails at trial. *Id.* ¶ 25. If Myriad somehow revives its patent rights and once again becomes the only company to offer BRCA1/2 testing, insurance companies, HMOs, and other third party payors will have no choice but to accept Myriad's prices if those third parties want to provide such testing in their insurance offerings. *Id.* Under these circumstances, Myriad cannot establish that any alleged price erosion is irreparable.

A number of mitigating factors further demonstrate that Plaintiffs will not suffer irreparable harm. First, any such price erosion, if it were to occur at all, would likely be slow in view of Myriad's setting of prices through insurance contracts. *Id.* This is not a market where prices fluctuate quickly. Rather, such contracts often include fixed terms of a year or more, during which it is difficult for a third party payor to demand a lower price. *See id.* ¶ 28. In addition, Myriad's financial position, including its more than $400 million in cash and cash equivalents, will allow it to maintain its current pricing structure during the pendency of this suit if it chooses to do so. *Id.* ¶ 27. Myriad also has the competitive advantage of having had exclusivity for so many years, such that it is unlikely its customer base and revenue growth will disappear. *Id.* ¶¶ 25-27, 29. Indeed, as recently as yesterday, Myriad forecast 14% to 18% revenue growth for Fiscal Year 2014 and emphasized that this projection takes into consideration the fact that Myriad faces new competition and is still in line with Myriad's prior revenue forecast, pre-Supreme Court ruling. *Id.* ¶¶ 52-53, Ex. R.

Finally, any claim for price erosion here is quantifiable; it is not an impossible task, as asserted by Plaintiffs. *Id.* ¶ 31. *See Eli Lilly & Co. v. Am. Cyanamid Co.*, 82 F.3d 1568, 1578 (Fed. Cir. 1996) (affirming denial of preliminary injunction motion where district court determined that any damages computation necessary was readily determinable should infringement be found).

**2. Instead of Causing Loss of Market Share, Ambry and Gene By Gene Are Expanding the Market for BRCA1/2 Testing**

Plaintiffs assert that Ambry and Gene by Gene will cause Myriad to lose market share. What Plaintiffs ignore is that Defendants will expand the market in several ways:

- Defendants can provide *meaningful* second opinion testing, which has not been available to patients under Myriad's monopoly. Chao Decl., ¶¶ 65-66; Hampton Decl., ¶ 46.
- Defendants offer testing at prices that were previously out of reach for many patients. Chao Decl., ¶¶ 26-28; Hampton Decl., ¶¶ 44-46.
- Defendants will offer testing under health plans that currently do not cover Myriad testing – for example, Ambry is in-network with certain plans where Myriad is out-of-network. Chao Decl., ¶ 29.
- For those who want more transparency in the data collected and received, Defendants' tests offer an option that has not been available under Myriad. Chao Decl., ¶¶ 50-51, 58-59; Hampton Decl., ¶¶ 46.
- For those who want multi-gene breast and ovarian cancer panel tests, Ambry offers an option that, so far, has not been available under Myriad. Chao Decl., ¶¶ 16-21; Hampton Decl., ¶¶ 46.
- For those who want full sequencing and large rearrangement testing for one price (because insurance typically only covers one test), Ambry offers an option that has not been available under Myriad. Chao Decl., ¶¶ 17-18.

This market expansion is relevant because it shows that Myriad and Ambry and Gene by Gene are not always going to be competing for the same customers. And Myriad is not damaged

by the loss of sales it never would have realized. Hampton Decl., ¶ 46. Myriad still argues that alleged market losses are difficult to disentangle. But "neither the difficulty of calculating losses in market share, nor speculation that such losses might occur, amount to proof of special circumstances justifying the extraordinary relief of an injunction prior to trial." *Nutrition 21 v. United States*, 930 F.2d 867, 871 (Fed. Cir. 1991). Such losses can be quantified.

**3. Myriad Cannot Establish Any Reputational Harm as a Result of Ambry's and Gene By Gene's Entry Into the Market**

Plaintiffs' argues that Ambry's and Gene by Gene's offering of BRCA1/2 testing somehow will harm *Myriad's* reputation. Myriad offers no support for its conclusory statement that that those who order the such testing – *i.e.*, highly sophisticated and knowledgeable genetic counselors and insurance providers – "are not well-informed" and will be confused as to whether the test they might order from Ambry or Gene by Gene originated from Myriad. Pl.'s Ambry Br. at 38. To the contrary, in the two months since Ambry began offering its BRCA1/2 test, no such confusion has occurred, and it is doubtful that such confusion would occur. Hampton Decl. ¶ 50. Plaintiffs also make unfounded allegations about the accuracy and reliability of Ambry's and Gene by Gene's tests, insinuating that Defendants' tests will produce a high rate of false positives or false negatives. As explained below in the public interest discussion, these statements are wrong and misleading. *See infra* part VII.C.3. The Court should reject Plaintiffs' reputational harm argument as unsubstantiated. *See Chrysler Motors Corp. v. Auto Body Panels of Ohio Inc.*, 908 F.2d 951, 954 (Fed. Cir. 1990) (rejecting reputational harm argument where patentee asserted consumers would see faulty accused products and mistakenly attribute the poor quality to patentee; "No objective, empirical information – surveys, interviews, or other material – was provided in support.").

Defendants in fact have undergone rigorous certification and accreditation processes, they operate state-of-the-art laboratories, and their tests result in exceedingly high accuracy and detection of genetic variants. *Id.* Moreover, Myriad recently announced that it is soon launching a multi-gene panel, myRisk, that is essentially a copy of Ambry's multi-gene cancer panel. Chao Decl., ¶¶ 45-47. This change follows years of widespread criticism of Myriad's BRCA1/2 test as substandard. *See infra* part VII.C.2. Undoubtedly, Myriad's reputation has suffered, but that harm is due to its own actions. None of Myriad's self-inflicted reputational damage can be attributed to Defendants.

**4. Plaintiffs' Inconsistently Enforce Their Patents**

Myriad states that it does, in some instances, license its patents. Ford Decl. ¶ 6. So too, in some instances, Myriad chooses not to assert its patents. There are at least five other laboratories – the University of Washington, GeneDX Inc., Quest Diagnostics Inc., Pathway Genomics Inc., and Ethigen, LLC – who are either currently offering BRCA1/2 testing or who have publicly announced they will soon offer such testing. Hampton Decl., ¶ 30. None of these entities has been sued by Plaintiffs, thus indicating an indifference to their use of the same technology. *Id.* ¶¶ 30, 47. Such circumstances, especially in view of the speculative nature of Plaintiffs' supposed irreparable harm, the other mitigating circumstances discussed above, and the fact that the alleged harm is ultimately compensable with a monetary award for damages, demonstrate that Plaintiffs have not met their burden of a clear showing of irreparable harm. *Id.* ¶¶ 25-43. *Cf. T.J. Smith & Nephew Ltd. v. Consolidated Medical Equip., Inc.*, 821 F.2d 646, 648 (Fed.Cir.1987) (holding that licensing is "incompatible with the emphasis on the right to exclude" and is a basis for finding lack of irreparable harm).

### B. PLAINTIFFS HAVE NOT ESTABLISHED THAT THE BALANCE OF HARDSHIPS TIPS IN THEIR FAVOR

The Court must balance the harm an injunction would inflict on Ambry and Gene by Gene, by ordering them to cease offering BRCA1/2 testing, with the harm to Plaintiffs, of allowing Ambry and Gene by Gene to continue with their business. For this factor, Plaintiffs rely on the same arguments they proffered for irreparable harm. Pl.'s Ambry Br. at 41; Pl.'s GBG Br. at 36-37. But just as a plaintiff cannot rely on conclusory statements to establish irreparable harm, a plaintiff likewise cannot rely on those same conclusory statements to show that the balance of hardships tips in its favor. *LL&L Innovations*, 2010 U.S. Dist. LEXIS 108173, at *26-*28. Thus, the Court should give little weight to Plaintiffs' alleged harm.

More importantly, the Court should consider the fact that Myriad kept others out of the market for 17 years based on patents that were invalidated by the Supreme Court. During this time, Myriad reaped billions of dollars through monopoly pricing. In the last three years alone, Myriad has earned more than $1 billion through sales of its BRACAnalysis test. Hampton Decl., ¶ 62. As a result, Myriad currently holds over $400 million in cash and cash equivalents. *Id.* ¶ 66. Myriad claims that it spent $500 million developing the BRCA1/2 test market (Ford Decl., ¶ 4), and while this claim is unsupported and highly questionable (Hampton Decl., ¶ 54; Ledbetter Decl., ¶ 30), one thing is clear: Myriad has already earned a return on any such investment by several orders of magnitude. Hampton Decl., ¶ 65. Myriad's strong financial position also means that it faces no existential threat by the entry of new competitors into the

market. *Id.* ¶ 27.[21] As noted above, just yesterday, Myriad forecast 14% to 18% revenue growth for 2014 fully aware of this new competition. *Id.* ¶¶ 52-53.

Plaintiffs assert that Ambry and Gene by Gene "will suffer no harm to [their] current business should an injunction issue" because they have "no established presence." Pl.'s Ambry Br. at 41; Pl.'s GBG Br. at 37. To the contrary, Ambry and Gene by Gene will suffer substantial hardship if Myriad's unlawful monopoly over human DNA sequences is extended. They would lose their valuable headstart of being among the first to announce that they would offer BRCA1/2 testing after the Supreme Court cleared the way to do so. Hampton Decl., ¶¶ 58-61. Being the first in the market to offer a BRCA1/2 testing alternative to Myriad provides a distinct advantage in terms of initial market penetration and the ability to eventually obtain a strong market position. *Id.* A preliminary injunction would eviscerate this accelerated entry to market and would negate Ambry's and Gene by Gene's significant time, resources, and investment to earn this competitive advantage. *Id.* Once lost, a headstart cannot be regained. *Id.*

Indeed, leading up to its June 13, 2013 launch, Ambry invested an estimated $46.7 million in preparing to offer the first comprehensive multi-gene hereditary test for breast and ovarian cancer that included BRCA1 and BRCA2. *Id.* ¶ 57. To this end, and in anticipation of the invalidation of Myriad's patents, Ambry procured expensive equipment, conducted extensive validation testing, obtained necessary certifications and regulatory approvals, added more than 100 employees, and devoted the majority of its workforce to accelerate its entry into this market. *Id.*

[21] The licensor Plaintiffs have equally strong endowments and financial positions, and there is no indication that any of them are dependent in any significant way upon a revenue stream from Myriad. *Id.* ¶¶ 34-39.

An injunction would wipe out all of this investment. With Myriad soon to compete head-to-head with Ambry on multi-gene panel cancer testing, if Ambry were enjoined from offering its current test options that include BRCA1 and BRCA2, then Ambry likely would be pushed out of the market and lose the bulk of its revenue stream. *Id.* This would further result in idling of a substantial laboratory operation and most if not all of Ambry's 180 employees losing their employment. *Id.* In balancing the hardships, it is proper for courts to consider that an injunction could put the non-moving party out of business. *See Bell & Howell Document Management Prods. Co. v. Altek Sys.*, 132 F.3d 701, 704, 708 (Fed. Cir. 1997) (approving district court's consideration of the parties' relative size in determining that the balance of hardships favored the accused infringer, a smaller, fledgling company whose existence would be threatened by an injunction, versus the patentee, which was "a subsidiary of a large corporation that . . . enjoys annual sales of $800 to $900 million"); *Illinois Tool Works, Inc. v. Grip-Pak, Inc.*, 906 F.2d 679, 683 (Fed. Cir. 1990) (affirming preliminary injunction denial where injunction would have devastating impact on small accused infringer "while a denial would leave [the patentee] a going concern").

Plaintiffs also wrongly allege that Ambry has "no established presence." Although it took the *Myriad* decision to open the door to offering BRCA1/2 testing, Ambry is by no means a newcomer to the hereditary cancer testing market. Since 2003, Ambry has been building what is now the most comprehensive hereditary cancer testing menu available. Chao Decl., ¶ 70. And although it may be true that Ambry and Gene by Gene are smaller companies than Myriad, that fact tips the balance of hardships in their favor, as they are more likely to suffer harm from an

injunction that Myriad. *Bell & Howell*, 132 F.3d at 704, 708; *Illinois Tool Works, Inc. v. Grip-Pak, Inc.*, 906 F.2d at 683.

In sum, the alleged harm to Myriad, which has already earned windfall profits from invalid patents for 17 years, is speculative, conclusory, and ultimately reparable. By sharp contrast, the loss of investment and head start advantage caused by enjoining Defendants, who already have been unlawfully deprived of entering the BRCA1/2 testing market for years, is significant and irreparable. Ambry, in particular, would doubtfully survive an injunction. The balance of harms tips decidedly in Defendants' favor.

### C. THE PUBLIC INTEREST WILL BE HARMED IF DEFENDANTS ARE ENJOINED

This case involves access to life-saving technology. This is precisely the kind of case where consideration of the public interest compels denial of injunctive relief. Indeed, courts have rejected injunctive relief on public interest grounds where removal of the accused product or process could have serious consequences on public heath – even when the patentee has satisfied its burden as to the other factors. *See, e.g.*, *Hybritech, Inc. v. Abbott Labs.*, 849 F.2d 1446, 1458 (Fed. Cir. 1988) (affirming carve-out of preliminary injunction as to cancer and hepatitis test kits on public interest grounds even though patentee established likelihood of success on the merits and irreparable harm).[22]

The stakes here are high. Breast cancer is the most common cancer in women, affecting about 1 in 8 women. Swisher Decl., ¶ 19. There will be approximately 232,340 new cases of

[22] *Compare Dippin' Dots v. Mosey*, 44 U.S.P.Q.2d 1812, 1818-19 (N.D. Tex. 1997) (finding public interest not affected by injunction because "[t]he process and product at issue involve ice cream, not heart valves, medical catheters, drug therapies or the cure for the common cold.").

breast cancer and approximately 39,620 deaths in the U.S. in 2013.[23] *Id*. About 5% of breast cancer is a result of an inherited mutation in *BRCA1/2*. *Id.* ¶ 20. Women with inherited *BRCA1/2* mutations have a 45-87% risk of breast cancer by age 70. *Id.* Similarly for ovarian cancer, which causes more deaths in the U.S. than any other gynecologic cancer, inherited *BRCA1/2* mutations dramatically increase a woman's risk of ovarian cancer by age 70. *Id.* ¶¶ 21-22. And because treatment options for ovarian cancer remain extremely limited, early detection of risk is imperative to saving lives through timely preventative measures. *Id.* ¶ 23. One can only conclude that an injunction in this case will deny patient access to proper care and lives will likely be lost. *Id.* ¶ 12.

Regardless of the outcome of the first three preliminary injunction factors, public interest considerations alone support denial of Myriad's motion for at least the following reasons. *First*, Ambry's and Gene by Gene's BRCA1/2 tests are vital to patient care. *Second*, Myriad has a history of providing substandard BRCA1/2 testing and continues to lag behind standards of care. *Third*, Myriad's claims about Ambry's and Gene by Gene's VUS rates are unfounded, and Myriad's claims specifically directed at Ambry's accuracy are not only wrong, but show a fundamental disregard for basic principles of genetic testing. *Fourth*, Myriad's patents have hindered, rather than incentivized innovation.

[23] A small percentage of men also have hereditary breast cancer and the *BRCA1/2* genes are also implicated.

### 1. The Tests Ambry and Gene By Gene Provide Are Critical to Patient Care

Defendants' BRCA1/2 tests (i) provide critically needed testing options that patients have not had under Myriad's monopoly, (ii) bring much needed transparency in the reporting and sharing of variant data, and (iii) provide much needed changes in pricing and access.

#### a. Vital Testing Options Not Offered by Myriad

Patients, physicians, clinicians, and providers prefer Defendants' testing over Myriad's testing. Courts have denied injunctive relief in such circumstances where the medical community has expressed a preference for the accused infringer's product based on public health concerns. *See, e.g.*, *Kimberly-Clark Worldwide, Inc. v. Tyco Healthcare Group LP*, 635 F. Supp. 2d 870, 881-82 (E.D. Wis. 2009) (denying preliminary injunction where "nontrivial number of patients would not be able to receive the treatment their physician preferred"); *Advanced Cardiovascular Sys. v. Medtronic Vascular, Inc.*, 579 F. Supp. 2d 554, 560 (D. Del. 2008) (finding public interest favored denial of preliminary injunction where evidence showed physician preference for accused stents and "strong public interest in maintaining diversity in the coronary stent market"); *Ethicon Endo-Surgery v. U.S. Surgical Corp.*, 855 F. Supp. 1500, 1517 (S.D. Ohio 1994) (finding public interest disserved by enjoining accused infringer's surgical devices which were strongly preferred by surgeons); *Am. Cyanamid Co. v. U.S. Surgical Corp.*, 833 F. Supp. 92, 134 (D. Conn. 1993) (finding public interest favors access to accused infringer's product, which "has spurred interest from numerous hospitals and doctors, who see it potentially as an innovative product with advantage over the previously existing products"); *Cordis Corp. v. Medtronic Inc.*, 2 U.S.P.Q.2d 1845, 1855 (D. Minn. 1986), *aff'd*, 835 F.2d 859

(Fed. Cir. 1987) (granting provisional remedy in favor of accused infringer where patent related to life-saving technology).

Ambry offers a much more comprehensive hereditary cancer menu surrounding *BRCA1* and *BRCA2* than Myriad. In addition to offering a test for the BRCA1/2 genes as Myriad does, Ambry offers a number of multi-gene panels that include BRCA1/2 along with scores of other genes also associated with hereditary cancer risk. Myriad has to date never offered a multi-gene panel with BRCA1/2. Multi-gene panels are critical to patient care because the BRCA1/2 genes do not account for all the hereditary risk of cancer. Swisher Decl., ¶¶ 102, 106, 110; Ledbetter Decl., ¶¶ 18-20. For breast cancer, BRCA1/2 account for up to 50% of the risk, but there are 14 other genes that combined account for up to another 20% of the risk (some risk remains because not all the genes associated with breast cancer are known). Swisher Decl., ¶ 104.

In March 2012, Ambry launched BreastNext, a test that would have covered all 14 genes plus BRCA1/2, so that a patient could assess as much as 70% of her hereditary risk of breast cancer in a single test, but for Myriad's monopoly. Thus, for over year, patients who needed this comprehensive testing were forced to order two separate tests, one from Myriad for the BRCA1/2 genes, and one from Ambry for the other 14 genes. Chao Decl., ¶¶ 11, 23-24. This artificial division of gene testing harms patients because many insurance companies cover only one test and those patients fortunate enough to obtain the second test have to provide multiple blood samples, wait longer, and pay more. *Id.*, ¶¶ 105, 125-26; Chao Decl., ¶¶ 11, 21. If other genes were all covered by patents owned by different companies who held monopolies, multi-gene panels could simply never exist, to the great detriment of patients. *See* Swisher Decl., ¶ 106. Fortunately for patients, on June 13, 2013, Ambry was finally able to include BRCA1/2 in

BreastNext, as well as in four other multi-gene panels, including CancerNext, which in addition to BRCA1/2 covers 22 additional genes related increased risk for breast, colon, ovarian, uterine and other cancers. Chao Decl., ¶¶ 13, 16-20; Swisher Decl., ¶¶ 107-09.

Also critical to patient care is the option to obtain comprehensive testing of the BRCA1/2 genes themselves in a single test. Many mutations are point mutations or small mutations involving ten or so bases, but there are also large genomic rearrangements, *i.e.*, mutations involving the deletion or insertion of hundreds or thousands of bases. Thus, including large rearrangement testing is a necessary part of the standard of care because large rearrangements account for about 10% of all BRCA1/2 mutations and, without it, patients will get false negatives. Swisher Decl., ¶¶ 72-82, 95-96; Morris Decl., ¶ 7; Matloff Decl. ¶ 7; Ledbetter ¶¶ 15-17, 20. All of Ambry's tests automatically cover point or small mutations, as well as large rearrangements. Chao ¶ 17. Myriad may claim that it now provides large rearrangement testing automatically, but in fact it continues to bill BRCA1/2 testing as two separate tests – one for the point and small mutations (BRACAnalysis) and another one for the large rearrangements (BART) – and, as discussed below, many Myriad patients continue to get incomplete, substandard BRCA1/2 testing. Swisher Decl., ¶¶ 48, 97-98, Ex. G; Matloff Decl., ¶ 7.

The option of a second opinion is likewise critical to patients who are facing life altering decisions, such as whether to have a preventive mastectomy or ovarian surgery. Swisher Decl., ¶ 116-17; Gaede Decl. Ex. C (Girard Decl., ¶¶ 3-7); Ledbetter Decl., ¶¶ 31-34; Morris Decl., ¶ 5. Under Myriad's monopoly, however, only Myriad could provide full sequencing of the BRCA1/2 genes, without which there is no meaningful second opinion. Swisher Decl., ¶¶ 117-

21; Chao Decl. ¶¶ 65, 67-68. With Ambry and Gene by Gene, Myriad patients can now obtain independent and meaningful second opinions.

**b. Transparency of Variant Data Not Offered by Myriad**

Transparency in the reporting and sharing of variant data is critical for patient care. When reporting the results of a BRCA1/2 test, the mutation or variant detected is identified (usually some insertion or deletion of a base) and classified to indicate whether it is benign or pathogenic. Nussbaum Decl., ¶¶ 27-40. The classification must be based on evidence, such as the clinical outcome for others with the same variant. The strength or reliability of the classification depends on that evidence, which is why when physicians or genetic counselors are advising their patients about the reliability of the classification, they need to know what that evidence is. SwisherDecl., ¶¶ 40-49. With Ambry's and Gene by Gene's test reports, that underlying evidence is included. *Id.* ¶¶ 45-49; Chao Decl., ¶¶ 58-59; Mittelman Decl., ¶ 32. Not so with Myriad, which reports classifications based on undisclosed "Myriad internal data," forcing patients to make difficult course of treatment decisions without access to all the relevant information. Swisher Decl., ¶ 49, Ex. E; Morris Decl. ¶¶ 8-9.

Sharing data about BRCA1/2 variants, including the underlying evidence used to make classifications, is vital to advancing patient care. Comprehensive public databases of BRCA1/2 data allow genetic testing laboratories and researchers to better understand and classify more variants with more reliability. Nussbaum Decl., ¶¶ 27-40; Ledbetter Decl., ¶¶ 35-44; Swisher Decl., ¶¶ 26-32. This is due to the synergies of pooling data and the independent verification and cross-checking that open databases allow. Ledbetter Decl., ¶¶ 38-40. On the other hand, when BRCA1/2 data is sequestered, as Myriad has done since 2004 in an attempt to claim trade secret

protection of this data, all those synergies are lost, and our ability to understand BRCA1/2 is impeded. Nussbaum Decl., ¶¶ 27-35, 40; Ledbetter Decl., ¶ 36; Swisher Decl., ¶¶ 33-38; Matloff Decl., ¶ 8. Classifications made based on Myriad's database cannot be independently verified, which leads to substandard patient care. Nussbaum Decl., ¶ 32; Ledbetter Decl., ¶ 36; Swisher Decl., ¶ 37.

**c. Access and Affordability Not Offered by Myriad**

Affordable and accessible testing is critical for patient care. Ambry is offering more inclusive testing at a much lower price than Myriad. For $2,200, Ambry offers comprehensive BRCA1/2 testing that always includes large rearrangement testing, as compared to $4,040 for Myriad's BRACAnalysis ($3,340) plus its large rearrangement test BART ($700). Gene by Gene is offering BRCA1/2 testing that includes large rearrangement testing for only $995.

Myriad claims that notwithstanding its high price tag, its test is accessible. The reality is that Myriad has and continues to turn away patients whose insurance does not cover its testing, and those patients have to pay Myriad's high prices out of pocket. Swisher Decl., ¶¶ 122-24; Gaede Decl., Ex. H (Raker Decl., ¶¶ 6-10), Ex. I (Thomason Decl., ¶¶ 6-9).[24] Since Ambry started providing its test at least one genetic counselor has already had several patients "who chose to pay for Ambry's testing out of pocket, which they were unable or unwilling to do at Myriad's higher price point." Matloff Decl., ¶ 10. Patients who have high deductibles or who

[24] Pursuant to Federal Rule of Evidence 201, Defendants request that the Court take judicial notice of the declarations of Harry Ostrer, Arupa Ganguly, Genae Girard, Haig Kazazian, Shobita Parthasarathy, Kathleen Raker, and Vicky Thomason, which were filed in the case *Association for Molecular Pathology v. USPTO*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) and relied upon by Judge Sweet in his March 29, 2010 summary judgment opinion. Defendants also request that the Court take judicial notice of the declarations submitted in that case by Professor Stiglitz, Dr. Swisher, Ms. Matloff , Dr. Ledbetter, Dr. Cho, Dr. Leonard and Dr. Nussbaum, who have provided updated declarations in this case. These declarations are attached to the Declaration of William G. Gaede as Exhibits B-I.

have to pay a percentage of the cost will also have greater access with Ambry's and Gene by Gene's more affordable prices. Myriad makes much ado about its insurance contracts, but Ambry is already in-network with many insurers, which just means more patients have access now. Chao Decl., ¶ 29. In addition, Myriad's policy of capping out-of-pocket costs to $375 for the underinsured is brand new. It was announced on July 15, 2013, just at the start of this litigation. In contrast, Ambry limits out-of-pocket costs to $100 for the underinsured. But more importantly, Ambry is committed to finding a way, case by case, to get patients tested whether for BRCA1/2 or any other genetic test it offers. *Id.*, ¶ 28.

**2. Myriad Has Failed to Provide the Standard of Care During the Period of Its Unlawful Monopoly**

Myriad has a long-standing history of providing substandard BRCA1/2 testing, and absent competition, it cannot be counted on to provide the BRCA1/2 testing that patients need. First, in the early 2000s, as it became increasingly clear that, absent comprehensive large rearrangement testing, patients would receive false negatives, Myriad refused to provide a complete test and additionally refused to allow others to provide large rearrangement testing. Swisher Decl., ¶¶ 75-84; Matloff Decl., ¶ 7; Ledbetter Decl., ¶¶ 15-18, 20. In 2006, when it finally added its large rearrangement test (BART), it did so only after its failure was made public in a peer-reviewed study in the *Journal of the American Medical Association* and then further publicized in the *New York Times*. Swisher Decl., ¶¶ 85-87. Even then, however, Myriad only added BART as an additional test to its standard BRACAnalysis test and instituted strict criteria as to who qualified for BART testing so that hundreds of thousands of women who should have gotten large rearrangement testing under accepted standards of care did not receive it. *Id.* ¶¶ 90-96. Not until 2012 did Myriad introduce "integrated BRACAnalysis," which is Myriad's version

of a comprehensive BRCA1/2 test. But Myriad bills integrated BRACAnalysis as two separate tests – one for the point and small mutations (BRACAnalysis) and another one for the large rearrangements (BART) – such that patients in 2013 continue to receive incomplete BRCA1/2 testing from Myriad. *Id.* ¶¶ 97-98.

In addition, in the latter part of the 2000s, so-called "next-generation (or next-gen) sequencing" became the state-of-the-art sequencing methodology, enabling more sensitive, cost-effective, and efficient testing. But Myriad simply continued to use a 1980s sequencing method known as "Sanger sequencing" and has not provided any next-generation multi-gene panel tests. In contrast, Ambry was an early adopter of next-generation sequencing in 2007 and has become a leader in this technology. Chao Decl., ¶¶ 31-36. Its current next-generation multi-gene panels, including BreastNext and CancerNext, were the first of its kind to be offered by any commercial laboratory in the United States. *Id.*, ¶ 36.

Now that it is facing competition, Myriad has announced that it, too, finally intends to use next-generation sequencing and offer a multi-gene panel. Myriad's proposed myRisk test, if actually ever implemented, is essentially a copy of Ambry's CancerNext test, down to using the same third party, RainDance Technologies, Inc., to aid in the design of primers for next-generation sequencing. *Id.*, ¶¶ 45-47. Per Myriad, "myRisk represents a scientific advancement that will revolutionize hereditary cancer testing for appropriate patients" and is a "significant improvement of BRACAnalysis." *Id.*, ¶ 45, Exs. I, J.

**3. Myriad Has Resorted to Unfounded Claims About the Quality of Ambry's and Gene By Gene's Tests**

Ignoring its implicit endorsement of Ambry's methodology by copying Ambry's CancerNext test, Myriad has resorted to wrong and unfounded claims about the quality of

Ambry's and Gene by Gene's tests. Myriad claims that both Ambry and Gene by Gene have a 25-30% VUS rate (*i.e.*, how often a variant is classified as a variant of unknown significance). Mr. Ford's declarations, which supposedly provide support for ascribing the same high rate to both Ambry and Gene by Gene, simply state the same without more. In fact, Ambry's VUS rate is presently only 4.5%, and Gene by Gene estimates an initial VUS rate less than 12-13%. Chao Decl., ¶¶ 52-53, Mittelman Decl., ¶ 28. Neither Ambry nor Gene by Gene are starting from scratch because they are tapping into a number of existing public databases of BRCA1/2 data, including the data that Myriad contributed up until 2004, as well as ongoing efforts to pool data, even including collecting Myriad reports from patients willing to share them. Swisher Decl., ¶¶ 52-55; Matloff Decl., ¶ 11; Chao Decl., ¶¶ 54-55; Mittelman Decl., ¶ 25-26; Nussbaum Decl., ¶¶ 17-21, 29-30. Further, as Ambry and Gene by Gene perform more and more tests, their respective VUS rates will decrease, and they will lower even more rapidly as other laboratories share and pool their data in public databases. Swisher Decl., ¶ 53; Ledbetter ¶ 37.

Importantly, while VUS rates can be a measure of success in classifying variants, they are not actually a measure of the quality of the classifications themselves. For instance, a laboratory may have a policy of keeping its VUS rate low and as a result classify variants as benign or deleterious (to avoid classifying them as variants of unknown significance) when in fact there is not enough evidence to determine whether the variant is benign or deleterious. Swisher Decl., ¶ 56. Myriad, while it reports a 3% VUS rate, does not disclose the internal data upon which it relies to make its classifications. Swisher Decl., ¶¶ 43-49; Chao Decl., ¶¶ 59-60. Unverifiable classifications can contain misclassifications, and Myriad's VUS rate is suspect. Swisher Decl., ¶ 44; Ledbetter ¶ 36. The difference between Ambry's 4.5% VUS rate and Myriad's 3% VUS

rate is minimal, and Ambry's transparent classifications meet the standard of care, whereas Myriad's practice of withholding the basis for its classifications is clinically unacceptable. Swisher Decl., ¶ 54.

Myriad also claims that "Ambry's published accuracy rate of 96-99% means that as many as ***4%*** (or 1 in 25) of patients tested with Ambry products will receive either a false negative or a false positive." In fact, Ambry's analytic sensitivity is greater than 99%, with a false negative rate much less than 0.1%. Chao Decl., ¶¶ 37, 41. Ambry's false positive rate is virtually 0% because Ambry confirms any variant it finds by next-gen sequencing with a second Sanger sequencing test. Chao Decl., ¶¶ 42; Swisher Decl., ¶ 65. Thus, Ambry's BRCA1/2 tests are extremely accurate and high quality. Swisher Decl. ¶ 69.

Notwithstanding that Ambry's analytic sensitivity is in fact greater than 99%, Myriad's claim "that as many as ***4%*** (or 1 in 25) of patients tested with Ambry products will receive either a false negative or a false positive" is additionally wrong because it shows a fundamental disregard for basic principles of genetic testing. To make its claim regarding the rate of false *negatives*, Myriad started off by assuming a 96% analytic sensitivity, meaning the test is not sensitive to 4% of variants. To get the false negative rate, one has to ask how many people this would affect. For example, if a variant is rare (as are even the most common deleterious BRCA variants), few people will get a false negative even though the test is not sensitive to that variant. To get the "***4%*** (or 1 in 25)" false negative, Myriad had to assume that 100% of the population carries deleterious mutations – which is scientifically absurd. *Id.*, ¶ 62.

Myriad's representation that there could be as "many as ***4%*** (or 1 in 25)" false *positives*, is equally contrary to basic principles of genetic testing. The frequency of false positives cannot

be determined from analytic sensitivity. Analytic sensitivity measures percent of mutations *not* identified; it does not measure the percent of mutations *incorrectly* identified. *Id.*, ¶ 61.

Myriad's claims as to the accuracy of Gene by Gene's tests are likewise entirely speculative. In fact Gene by Gene's analytic sensitivity is 99% or greater, with an exceedingly small false negative rate. Mittelman Decl. ¶ 30. Gene by Gene also confirms any variants it finds with a second test, and its false positive rate is virtually 0%. *Id.* Thus, Gene by Gene's BRCA1/2 test is also extremely accurate and high quality. Swisher Decl. ¶ 69.

As for the accuracy of Myriad's BRACAnalysis, it is clinically unacceptable. It is less than 90% because BRACAnalysis does not test for large rearrangements, which are known to account for about 10% of all deleterious mutations. Myriad has provided this incomplete test to hundreds of thousands of patients, despite knowing for more than a decade that this test misses an entire class of deleterious mutations. *Id.*, ¶¶ 63, 70-98.

**4. Myriad's Patents on BRCA 1 and BRCA 2 Have Hindered Rather Than Incentivized Innovation**

Myriad argues that the public interest would be served by a preliminary injunction because patent rights incentivize innovation. Pl.'s Ambry Br. at 42. Although patents, as a general matter, may incentivize innovation in other contexts, in the case of Myriad's patents on BRCA1 and BRCA2, that is decidedly not the case. BRCA 1 and BRCA 2 would have been sequenced without Myriad, and efforts to do so were well under way, funded significantly with public monies. Stiglitz Decl., ¶ 36; Ledbetter ¶ 22-30; Gaede Decl., Ex. G (Parthasarathy Decl. ¶¶ 9-19).

Among the many critics of the notion that Myriad's patents incentivize innovation are Professor Joseph Stiglitz, a Nobel Prize winner in economics, Deborah Leonard, M.D., testifying

in part on behalf of the College of American Pathologists, and Mildred Cho, Ph.D., Associate Director of the Stanford Center for Biomedical Ethics, all of whom have submitted declarations in this case and in the *Myriad* litigation. Stiglitz Decl., ¶¶ 2-3, 30-40; Leonard Decl., ¶¶ 26-44; Cho Decl. ¶¶ 17-25. They observe that patents such as Myriad's have blocked important follow-on scientific research, hindered collaborative data collection and sharing, halted patient screenings at cancer diagnostic facilities, and prevented others from developing and/or offering additional, alternative, and more affordable technologies. Stiglitz Decl., ¶¶ 23-40; Leonard Decl., ¶¶ 26-44; Ledbetter ¶¶ 11-21, 35-47.

These not just a hypothetical arguments. These things have happened. *See, e.g.*, Matloff Decl., ¶¶ 6-7 (Yale DNA Diagnostics Lab denied permission by Myriad to conduct large rearrangement screenings, which Myriad was not conducting at the time); Ledbetter Decl., ¶¶ 36-40 (Myriad's withholding of test data from public databases has deprived researchers and clinicians of key information necessary for classifying genetic variants of unknown significance); Gaede Decl. Ex. B (Ganguly Decl., ¶¶ 3-14 (University of Pennsylvania's Genetic Diagnostic Laboratory forced to stop screening patient samples in response to Myriad's threats)), Ex. E (Kazazian Decl., ¶¶ 3-11 (same)), Ex. F (Ostrer Decl., ¶¶ 4-12 (Myriad's actions prevented geneticists at NYU Langone Medical Center from providing BRCA 1/2 screening results to patients)).

Moreover, a 2001 survey of laboratory directors throughout the United States conducted through a grant from the National Human Genome Research Institute of the National Institutes of Health showed that "patents on genes used for clinical diagnostics inhibit the conduct of research to further the development of improvements to genetic tests [and] . . . inhibit clinical diagnostic

laboratories from providing clinical tests and services. Cho Decl., ¶ 24. The survey further showed such "patents are not necessary to incent either the research on initial discoveries or the development of clinical applications and commercializable products." *Id.* ¶ 25. In view of this evidence, Myriad's generalized claim that an injunction here would promote innovation is highly questionable. Public interest considerations strongly compel the denial of Myriad's preliminary injunction motion.

## VIII. CONCLUSION

For all of the foregoing reasons, Defendants respectfully request the Court deny Plaintiffs' Motions for Preliminary Injunction.

Respectfully Submitted,

MCDERMOTT WILL & EMERY LLP

DATED: August 14, 2013 By: */s/ William G. Gaede, III*
William G. Gaede, III

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**CERTIFICATE OF SERVICE**

On August 14, 2013, I served a copy of the foregoing, by electronic case filing (ECF), by e-filing the above-referenced document(s) utilizing the United States District Court, District of Utah's mandated Electronic Case Filing service, which service automatically e-served a copy of the document(s) upon confirmation of e-filing to all counsel in this case registered to receive e-filing notice, and additionally by electronic transmission by attaching the referenced documents or link to the referenced documents to an electronic mail and transmitting the same to the e-mail addresses indicated below as follows:

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