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

UNIVERSITY OF UTAH RESEARCH FOUNDATION, a division of the University of Utah, a Utah nonprofit corporation; TRUSTEES OF THE UNIVERSITY OF PENNSYLVANIA, a Pennsylvania nonprofit corporation; HSC RESEARCH AND DEVELOPMENT LIMITED PARTNERSHIP, a Canadian limited partnership organized under the laws of the Province of Ontario; ENDORECHERCHE, INC., a Canadian corporation organized under the laws of the Province of Quebec; and MYRIAD GENETICS, INC., a Delaware corporation, Plaintiffs, vs. AMBRY GENETICS CORPORATION,	**MOTION FOR PRELIMINARY INJUNCTIVE RELIEF AND MEMORANDUM IN SUPPORT** Case No. 2:13-cv-00640-RJS Judge Robert J. Shelby

Defendant.	

Plaintiffs University of Utah Research Foundation, Trustees of the University of Pennsylvania, HSC Research and Development Limited Partnership (an affiliate of The Hospital for Sick Children), Endorecherche, Inc., and Myriad Genetics, Inc., submit their Motion for Preliminary Injunctive Relief and Memorandum in Support against Defendant Ambry Genetics Corporation ("Ambry").

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INTRODUCTION

In 1992 and 1994, Plaintiffs prevailed in one of the most widely contested technology races of the last century, discovering the genetic sequences of two human genes, BRCA1 and BRCA2 linked to hereditary breast and ovarian cancer. At the time, this discovery was universally hailed. Since that time, Plaintiff Myriad Genetics, Inc., has invested over $500 million dollars to implement this discovery and create a molecular diagnostic test for hereditary breast and ovarian cancer related to the BRCA1 and BRCA2 genes that has revolutionized patient care and provided medical diagnosis and treatment options never thought possible. This investment has yielded a test of superior reliability and accuracy. Simply put, Myriad's BRCA testing has saved, and continues to save, countless lives.

As of the morning of June 13, 2013, Plaintiffs collectively had 24 patents containing 520 claims concerning two genes (BRCA1 and BRCA2), and methods of use and synthetic compositions of matter related thereto. On June 13, the Supreme Court of the United States ruled that five patent claims covering isolated naturally occurring DNA were not patent-eligible, thereby reducing the overall patent estate to 24 patents and 515 patent claims. This case involves none of those five rejected claims.

While the Court invalidated a small number of claims, it clearly affirmed the patent eligibility of synthetic DNA and underscored the importance and applicability of method-of-use patents for gene-based diagnostic tests. The Court found that, unlike isolated human genes, synthetic DNA is man-made and is not a product of nature. Plaintiffs' remaining patent claims covering BRCA1 and BRCA2 gene testing, including those at issue here, pertain to synthetic DNA or methods-of-use, which were not affected by the Court's decision, and remain valid and enforceable.

Unfortunately, the Supreme Court's ruling has been misunderstood and misreported in many media outlets. As a result, the validity and significance of Plaintiffs' remaining patent estate covering BRCA1 and BRCA2 testing has been largely ignored.

Indeed, before the ink on the Supreme Court's decision was dry, Ambry publicly announced and put an order form on its web site offering BRCA1 and BRCA2 genetic testing. Plaintiffs filed this lawsuit for patent infringement because such testing requires use of methods and synthetic DNA over which Plaintiffs have exclusive patent rights. Plaintiffs seek a preliminary injunction because they will be immediately and irreparably damaged by Ambry's infringement pending final judgment on the merits and during the remaining life of the patents.

The Plaintiffs are likely to prevail on the merits of their claims against Ambry for the reasons detailed below. Additionally, Plaintiffs will be immediately and irreparably harmed in the interim if the status quo is not maintained and Ambry's infringement enjoined, and the balance of the harms and public interest strongly supports granting this motion.

STATEMENT OF FACTS

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.

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.

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.

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.

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.

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.

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.

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.

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).[1]

[1] The Supreme Court decision represents the culmination of four years of litigation. After the District Court granted summary judgment to plaintiffs based on its conclusion that Myriad's claims were invalid because they purportedly covered products of nature (*Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F.Supp.2d 181 (S.D.N.Y. 2010)), the Federal Circuit affirmed in part and reversed in part. *Association for Molecular Pathology* v. *United States Patent and Trademark Office*, 653 F. 3d 1329 (2011). The Supreme Court granted certiorari, vacated the judgment, and remanded the case in light of *Mayo Collaborative Services* v. *Prometheus Laboratories, Inc.*, 132 S.Ct. 1289 (2012). *See Association for Molecular Pathology* v. *Myriad Genetics, Inc*., 132 S.Ct. 1289 (2012). On remand, the Federal Circuit again affirmed the District Court in part and reversed in part, holding that both isolated DNA and synthetic DNA were patent eligible under §101, noting that "each of the claimed molecules represents a non-naturally occurring composition of matter". *Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 689 F.3d 1303, 1309 (Fed. Cir. 2012). The case then proceeded to the Supreme Court for a second time.

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.

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).

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.

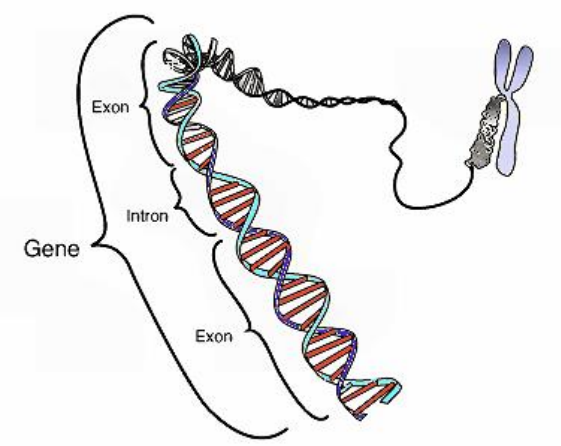
13. Ambry is able to offer testing at this discounted price by unfairly and improperly "free-riding" off of the hundreds of millions of dollars invested by Myriad Genetics in developing the science and market for clinical diagnostic testing for hereditary cancers. *See supra* at ¶¶ 6-8.

BACKGROUND OF THE TECHNOLOGY AT ISSUE

A human gene is a small region of DNA, or deoxyribonucleic acid, which is contained within the chromosomes of the nucleus of human cells. In cells, DNA has the form of a double-stranded helix linked by cross-bars. The cross-bars consist of chemically joined molecules on each strand known as "nucleotides." There are four types of nucleotides—adenine, thymine, guanine and cytosine—commonly identified in a shorthand way by their first letters A, T, G, and C. The nucleotides on each strand are "bound" to a corresponding or complementary nucleotide

on the other strand in a very specific manner. In particular, adenine (A) can bind only to thymine (T) and guanine (G) can bind only to cytosine (C), and vice versa, and thus the nucleotides on each strand "complement" each other in this manner. A human gene is a section of DNA that contains a set of instructions or the "coding" for creating a string of amino acids used to build a protein.

The precise order of the nucleotides within a given gene varies depending upon the protein that is being coded. While science is increasingly revealing new layers of function for genomic regions previously thought to be inert, in humans only parts of the gene "code" for protein-building amino acids. The portions of the gene that code for amino acids are called "exons," and the portions that do not have such coding are called "introns." The exons are separated within the gene by introns.



As mentioned earlier, one DNA molecule can have nucleotides that correspond to, or are "complementary" to, another DNA molecule. For example, in the position where the first DNA molecule has an "A" nucleotide, the second DNA molecule has a "T" nucleotide. Given a particular DNA molecule of interest, scientists can create in a laboratory strands of synthetic molecules that are complementary to the original DNA. This synthetic, man-made DNA can be made through a variety of methods, including but not limited to using naturally occurring mRNA

or naturally occurring genomic DNA as a base or reference material. Examples include synthetic "primers" and "probes" that are complementary to a particular genomic target sequence. Synthetically created complementary DNA molecules are different from genomic DNA because they are not naturally occurring. Rather, they are synthetic, laboratory-created DNA carefully designed by man to achieve specific performance metrics. Creating synthetic DNA sharing sequence similarity with any particular gene requires an application of detailed knowledge from the discovery of that gene's structure.[2]

A genetic variant is a change in the gene sequence. Any change, even one nucleotide, can constitute a variant. Some variants are harmless, but some—termed "mutations"—can cause disease or increase the risk of disease. The patents-in-suit involve synthetic DNA molecules and methods of testing for mutations in the BRCA1 and BRCA2 genes that are known to result in a significantly increased risk of breast and/or ovarian cancer.

[2] Chromosomes in a human cell are made up of two complementary strands of DNA molecules—one strand is on one side of the double helix and the second strand is on the other side. For any given gene, only one molecule strand (the "template strand") is actually transcribed into mRNA and ultimately used to produce a protein, while the other strand is, for purposes of that gene, simply a space-filling molecule to provide the other side of the double helix. This space-filling strand is sometimes referred to as the "coding strand" because its sequence is similar to that of the mRNA (simply by virtue of being complementary to the template strand). However, from a biological standpoint, the "coding strand" is not an actively transcribed part of the gene. When engineering primers for a specific polymerase chain reaction, scientists give each primer a specific sequence that will be complementary to one strand of the genetic region of interest. The purpose of the primer is to hybridize (attach or bond) to its target sequence in a given DNA molecule and "prime" (cause initiation of) the synthesis of a new synthetic DNA molecule. While a "forward" primer targeting the template strand may include nucleotides chemically arranged in the same order as a small portion of the naturally occurring coding strand, this is purely incidental to the double-strand nature of naturally occurring DNA and does not alter the synthetic, man-made nature of the primer. The same is true for the other primer, the "reverse" primer in a primer pair. That primer is designed to be complementary to the coding strand and, as a result, it will share some incidental similarity to the template strand. Declaration of Benjamin B. Roa ("Roa Decl."), ¶¶ 17-19.

ARGUMENT

I. ENTRY OF A PRELIMINARY INJUNCTION IS WARRANTED TO PREVENT ONGOING INFRINGEMENT PENDING A FULL DETERMINATION ON THE MERITS

Pursuant to 35 U.S.C. § 283, federal courts may grant injunctions "to prevent the violation of any right secured by patent." The standards applied to the grant of preliminary injunctions in patent infringement cases are the same as those in any other area of the law. *High Tech. Med. Instr., Inc. v. New Image Indus., Inc*., 49 F.3d 1551, 1554 (Fed. Cir. 1995). The purpose of a preliminary injunction is to preserve the status quo by preventing future infringement pending a determination on the merits. *Abbott Labs. v. Sandoz*, 544 F.3d 1341, 1344-45 (Fed. Cir. 2008) (citing *University of Texas v. Camenisch,* 451 U.S. 390, 395, 101 S.Ct. 1830, 68 L.Ed.2d 175 (1981)).

Thus, the four factors to be applied in determining whether a preliminary injunction should issue in a patent case are the same as those considered in other suits. They include: "(1) likelihood of success on the merits of the underlying litigation, (2) whether irreparable harm is likely if the injunction is not granted, (3) the balance of hardships as between the litigants, and (4) factors of the public interest." *Abbott Labs*., 544 F.3d at 1344 (citing *Oakley, Inc. v. Sunglass Hut Int'l,* 316 F.3d 1331, 1338-39 (Fed. Cir. 2003). No one element is dispositive; rather, "the district court must weigh and measure each factor against the other factors and against the form and magnitude of the relief requested." *Hybritech, Inc. v. Abbott Labs*., 849 F.2d 1446, 1451 (Fed. Cir. 1988).[3]

[3] Because the question of whether to grant a preliminary injunction involves substantive questions unique to patent law, it is governed by Federal Circuit authority. Procedural issues, such as compliance with Rule 65, are governed by regional authority. *Revision Military, Inc. v. Balboa Mfg. Co*., 700 F.3d 524, 525 (Fed. Cir. 2012) (citing *Hybritech Inc*., 849 F.2d at 1451, n. 12).

A. Myriad[4] Has a High Likelihood of Success on the Merits, as Demonstrated by the Supreme Court's Finding of Patentability of the Type of Claims at Issue and Ambry's Direct Infringement of the Correctly Construed Patent Claims.

The first factor to be considered in determining whether injunctive relief should issue, the likelihood that Myriad will prevail on the merits, pertains to patent validity and patent infringement. *Hybritech Inc.*, 849 F.2d at 1451. The court does not resolve the issue of patent validity at this preliminary stage, but instead must "make an assessment of the persuasiveness of the challenger's evidence, recognizing that it is doing so without all evidence that may come out at trial." *New England Braiding Co. v. A.W. Chesterton Co.*, 970 F.2d 878, 882-83 (Fed. Cir. 1987).

Regarding infringement, the likelihood that the patentee will prevail upon the merits is determined by comparing the properly construed patent claims with the accused product or process. *See H.H. Robertson Co. v. United Steel Deck, Inc.*, 820 F.2d 384, 389-90 (Fed. Cir. 1987), *rev'd in part on other grounds*, *Markman* v. *Westview Instruments, Inc.*, 52 F.3d 967 (Fed. Cir. 1995). Furthermore, "[t]he grant of a preliminary injunction does not require that infringement be proved beyond all question, or that there be no evidence supporting the viewpoint of the accused infringer [citation omitted]. The grant turns on the likelihood that [the patentee] will meet its burden at trial of proving infringement." *Id.* at 390.

1. The Claims Infringed by Ambry Are Presumed Valid and, Indeed, Are of the Type Endorsed by the Supreme Court.

The validity of the claims at issue is demonstrated by the presumption of validity accorded every patent duly issued by the United States Patent & Trademark Office. 35 U.S.C. § 282(a) ("A patent shall be presumed valid. . . . The burden of establishing invalidity of a patent

[4] The Plaintiffs are collectively referred to as "Myriad" herein, other than where context dictates otherwise, such as in section I(B).

or any claim thereof shall rest on the party asserting such invalidity."); *see Microsoft Corp. v. i4i Limited Partnership, et. al*., 131 S.Ct. 2238, 2245 (2011) (holding that "by its express terms, § 282 establishes a presumption of patent validity, and it provides that a challenger must overcome that presumption to prevail on an invalidity defense."). Absent a showing to the contrary, "the very existence of the patent with its concomitant presumption of validity satisfies the patentee's burden of showing a likelihood of success on the validity issue." *Titan Tire Corp. v. Case New Holland, Inc*., 566 F.3d 1372, 1377 (Fed. Cir. 2009).

Here, the validity of Myriad's patent claims is supported beyond the statutory presumption by the fact that Myriad previously has been forced to bring suit against infringers, and all of those actions settled within a year of filing. *See Ass'n for Molecular Pathology*, 133 S. Ct. at 2114 (noting that various entities that were conducting BRCA tests in violation of Myriad's patents agreed to "cease all allegedly infringing activity" upon notification from Myriad, or in settlement of infringement suits). Not one of those infringers raised a serious contention as to the validity of Myriad's patents, and their quick exit from the market is indicative of the validity of those patents.

Indeed, the validity of Myriad's patent claims was not challenged on any grounds until the 2009 declaratory judgment lawsuit filed by the Association for Medical Pathology and other plaintiffs, which resulted in the Supreme Court's June 13, 2013 decision. ***Even then***, the plaintiffs chose only to assert a claim for invalidity pursuant to 35 U.S.C. §101 and expressly disclaimed any other invalidity argument against the claims at issue in that case and repeatedly disclaimed any argument against the specific claims Myriad now asserts against Ambry (*e.g.*, claims to primers and to methods of testing the BRCA genes), thus signaling that there was no other serious challenge to be levied against those patents.

Furthermore, the June 13 Supreme Court decision, which represents the culmination of that lawsuit, endorses the patent claims asserted against Ambry in this action. While the Court did not specifically address every claim asserted here, the very framework that the Court used – the distinction between naturally occurring DNA (which it held unpatentable) and artificially created, synthetic DNA, along with the methods of applying knowledge about the genes – leads to the conclusion that the claims Myriad asserts here, all of which fall into the latter category, are valid and enforceable.[5]

The Supreme Court held that the discovery of "the location of the BRCA1 and BRCA2 genes . . . *by itself*, does not render the BRCA genes 'new . . . composition[s] of matter,' § 101, that are patent eligible." 133 S.Ct. at 2117. It found that "the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a non-naturally occurring molecule" was insufficient to satisfy §101, emphasizing that the claims were not "expressed in terms of chemical composition" and did not rely on chemical changes that result from isolating a particular section of DNA. *Id*. at 2118. However, there was nothing untoward about Myriad having sought and obtained patent protection over these newly discovered and isolated genes. Myriad's actions were consistent with decades of patent practice and patent law, which the Supreme Court refined with its decision.

More importantly, the Court's decision, on balance, vindicated Myriad's patent rights. The Court specifically distinguished claims pertaining to isolated naturally occurring BRCA1 and BRCA2 genes, defined not by chemical changes brought about by isolation but instead by

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[5] The Supreme Court did not specifically address every claim now asserted because the plaintiffs ***did not challenge*** those claims as part of their request for declaratory relief. This decision not to even challenge those claims underscores the conclusion that that they are valid and patentable, or, at an absolute minimum, that Myriad is more likely than not to establish this factor at trial on the merits.

their natural function and informational character, from artificially created synthetic DNA. The Court held that "cDNA is patent eligible because it is not naturally occurring." 133 S.Ct. at 2111. The Court went on to reject the argument that any synthetic DNA sharing any sequence similarity to natural DNA is ineligible for patenting, despite the fact "[t]he nucleotide sequence of cDNA is dictated by nature, not by the lab technician," and held:

> That may be so, but the lab technician unquestionably creates something new when cDNA is made. cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived. As a result, cDNA is not a "product of nature" and is patent eligible under §101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA ***may be*** indistinguishable from natural DNA.

Id. at 2119 (emphasis added). Furthermore, the Court carefully noted that claims pertaining to methods of testing and using isolated DNA for diagnosis were exempt from its decision:

> [T]his case does not involve patents on new *applications* of knowledge about the BRCA1 and BRCA2 genes. Judge Bryson [of the Federal Circuit] aptly noted that, "[a]s the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge. ***Many of its unchallenged claims are limited to such applications***."

Id. at 2120 (citing *Ass'n for Molecular Pathology*, 689 F. 3d at 1349) (emphasis added). Some of the very claims Judge Bryson highlighted as properly limited are asserted in this action.

In so holding, the Supreme Court additionally implicitly adopted the Federal Circuit's explanation that when such claims include physical, transformative steps, such as the use of synthetic DNA, they necessarily encompass patentable subject matter because the method includes more than abstract mental steps. For example, in addressing method claim 20 of the '282 patent (not at issue in this motion), the Federal Circuit held that it was patentable because the method includes more than "abstract mental step[s]" and "does not simply apply a law of nature." *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 689 F.3d 1303, 1336

(Fed. Cir. 2012). The court so held because the method included the use of "cells [that] are not naturally occurring" because they are "man-made." *Id.* The court further noted that the patentability of the method was not affected by the fact that the steps or operations performed with those synthetic cells were well-known. "[O]nce one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is ***not merely applying conventional steps to a law of nature***," and thus such a method claim is "patent eligible" under § 101. *Id.*(emphasis added).[6]

All of Myriad's patent claims asserted in this case either require the use of inventive DNA synthesized in a laboratory based upon knowledge about the BRCA1 and BRCA2 genes (*e.g.*, gene-specific probes, primers and arrays) and thus are patentable under § 101 based on the Supreme Court's and Federal Circuit's analysis, or pertain to such synthetic DNA compositions themselves, which are patentable under the same analysis. As set forth in more detail below in the section discussing Myriad's likelihood of success in proving infringement, claims 16-17 of the '282 patent and claims 29-30 of the '492 patent 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 BRCA1 or the BRCA2 gene.

[6] Furthermore, and as the Supreme Court implicitly recognized, the method claims asserted here by Myriad are distinguishable from the claims at issue in *Mayo Collaborative Services v. Prometheus Laboratories*, 132 S.Ct. 1289 (2012), decided just prior to the *Myriad* decision. There, the process claims merely provided for administering a particular drug, then determining the resulting metabolite level. The drug was known, the analyte was known, numerous methods of testing the analyte were known, the relationship between drug concentration and either efficacy or toxicity for the drug was known, testing the analyte for the exact purpose of determining an optimal dose was known, and even certain optimal dose ranges were known. The patentee merely refined those optimal dose ranges. Thus, they only described a "relevant natural law" (*id*. at 1297-98), and the processes of drug administration and testing of the results involved "well-understood, routine, conventional activity" known in the field. *Id*. at 1294. As such, they added "nothing to the laws of nature." *Id*. at 1298. Myriad's claims are distinguishable, and more clearly involve a patent-eligible invention, on each of these points. Myriad discovered a new biomarker, created new reagents and techniques that could now analyze this new biomarker, and invented new methods of determining a patient's risk of breast and ovarian cancer using these reagents and techniques.

Further, claims 7 and 8 of the '441 patent and claim 4 of the '857 patent are method claims that likewise require the use of synthetic DNA from the BRCA1 or BRCA2 genes and include much more than merely abstract mental steps, including at least the physical, non-abstract steps of using specially engineered synthetic DNA primers (*i.e.*, synthetic DNA laboratory tools) to produce by PCR amplification other synthetic DNA molecules and sequence them. Claim 5 of the '721 patent requires the same process, with a difference in the method of detection. Again, as in the '282 patent, each and every one of these claims pertain not to a law of nature or mere knowledge of that law, but instead to a specific ***method of applying*** Myriad's newly discovered knowledge.

Claims 2 and 4 of the '155 patent also pertain to a method, namely a method for identifying individuals "having a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer." This method consists of synthesis by PCR amplification of artificial DNA molecules using a laboratory-engineered oligonucleotide primer, sequencing the synthetic molecules using a particular technology, comparing this sequence to a reference, and determining the presence or absence of seven specific, highly significant genetic variations. As in the other asserted patents, the claim represents yet another method used to ***apply*** Myriad's characterization of the BRCA1 gene—subject matter which both the Supreme Court and the Federal Circuit have endorsed as valid and patentable. Accordingly, all of the claims at issue in this motion constitute patentable subject matter.

These prior opinions upholding the patentability of the very type of claims asserted by Myriad here, including an opinion from the Supreme Court, amply support that Myriad is substantially likely to prevail on the patentability and validity issues. Indeed, evidence of a prior determination of patent validity is highly relevant to the likelihood of success. *Atlas Powder*,

773 F.2d at 1232 (rejecting defendant's argument that a prior adjudication of validity in a suit involving a different defendant was insufficient to meet the patentee's burden of demonstrating likelihood of success); *H.R. Robertson Co.*, 820 F.2d at 388 (holding that district court properly relied upon determination of validity and infringement in a prior matter involving a different defendant; "[s]ubstantial weight may be given to a patent's litigation history in connection with a motion for relief pendent lite).

2. Ambry Is Infringing a Number of Myriad's Patent Claims.

Ambry began offering BRCA1 and BRCA2 gene sequencing and analysis as of "Thursday, June 13, 2013," and began infringing Myriad's patents at least by that date. Ambry's test requisition form, by which a patient submits a DNA sample, such as blood or saliva, lists a number of test panels or other tests that include testing the BRCA1 and BRCA2 genes. Ambry Website Screenshots, Exh. A; Ambry Test Requisition Form (Ford Decl., Exh. 1) at 2-3. Ambry's actions include at least three areas of infringing activities: (1) preparation of synthetic DNA samples for BRCA1 and BRCA2 sequencing and analysis; (2) sequencing of BRCA1 and BRCA2; and (3) large rearrangement analysis of BRCA1 and BRCA2.

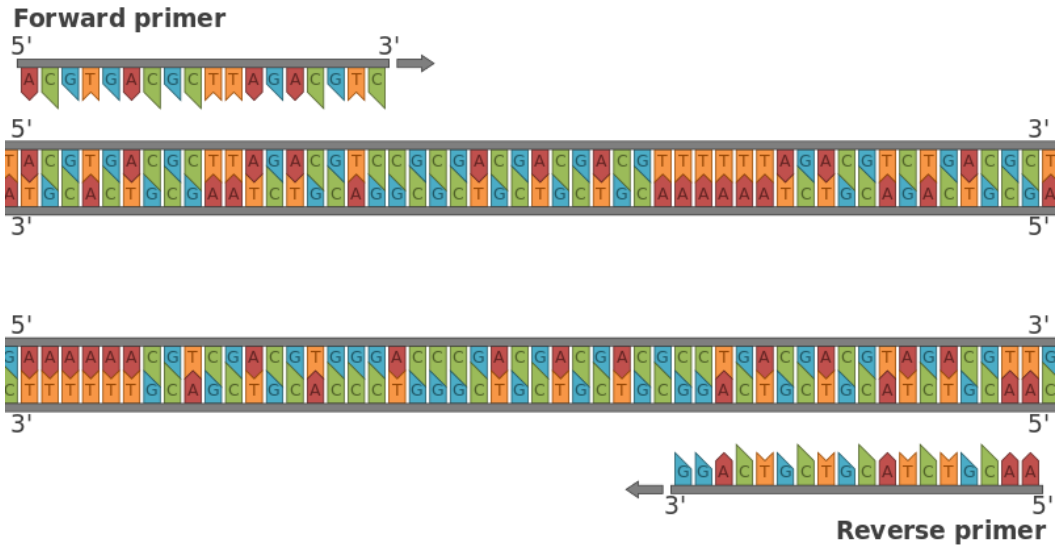
In regard to Ambry's first area of activities—its preparation of synthetic DNA samples for BRCA1 and BRCA2 sequencing and analysis—Myriad is highly likely to prove that Ambry infringes at least claims 16 and 17 of the '282 patent and claims 29 and 30 of the '492 patent. As for Ambry's second area of activities—sequencing of the BRCA1 and BRCA2 genes—Myriad is highly likely to prove that Ambry infringes at least claim 8 of the '441 patent, claim 4 of the '857 patent, claim 5 of the '721 patent, and claims 2 and 4 of the '155 patent. Regarding Ambry's third area of activities—large rearrangement analysis of BRCA1 and BRCA2—Myriad is highly likely to prove that Ambry infringes claim 7 of the '441 patent and claim 4 of the '857 patent.

a. Myriad is Likely to Prove that Ambry's Use of Synthetic DNA Primers for Preparation of Synthetic DNA Samples for BRCA1 and BRCA2 Sequencing and Analysis Infringes Claims 16 and 17 of the '282 Patent and Claims 29 and 30 of the '492 Patent.

Ambry's process starts with DNA "isolated" "from the patient's specimen" that has been "fragmented" into pieces. Ambry NGS Cancer Panels PowerPoint (Exh. B) at 4; Ambry Poster (Exh. C); Ambry Data Sheets for BreastNext (Exh. D) at 4-5, CancerNext (Exh. E) at 6-7, OvaNext (Exh. F) at 5-6, BRCA1 & BRCA2 (Exh. I) at 2; BRCAplus tests (Exh. L) at 3; Ambry NextGen PowerPoint (Exh. J) at 7-8; *see* RainDance Target Sequencing Assay Manual (Exh. K) at 2-2. Ambry then performs "[s]equence enrichment," such as "RainDance PCR Target Enrichment" (or "RDT Enrichment"), on that extracted and fragmented DNA. Ambry NGS Cancer Panels PowerPoint (Exh. B) at 4; Ambry Poster (Exh. C); Ambry Data Sheets for BreastNext (Exh. D) at 4, CancerNext (Exh. E) at 6, OvaNext (Exh. F) at 5, BRCA1 & BRCA2 (Exh. I) at 2, BRCAplus tests (Exh. L) at 3. In the naturally occurring DNA isolated from the patient's cells, every gene will be present in roughly the same proportion to each other. Because a scientist is usually interested in analyzing only a small number of those genes, the rest of the genomic DNA will interfere with efforts to analyze any particular genes of interest, such as BRCA1 or BRCA2. To overcome this issue, scientists "enrich" the sample for the DNA of interest by creating synthetic, laboratory-designed DNA molecules sharing a nucleotide sequence with the selected portions of BRCA1 or BRCA2. The process creates multiple synthetic DNA molecules that correspond to specific parts of the patient's original genomic DNA in the BRCA1 and BRCA2 genes. *See* Roa Decl. ¶¶ 5-12. In Ambry's process, the patient's naturally occurring but isolated DNA is combined with "primer pairs designed to the target breast cancer gene coding exons followed by polymerase chain reaction (PCR)" to produce these synthetic DNA molecules that can then be sequenced. Ambry Data Sheets for BreastNext (Exh. D) at 4,

CancerNext (Exh. E) at 6, OvaNext (Exh. F) at 5-6, BRCA1 & BRCA2 (Exh. I) at 2, BRCAplus tests (Exh. L) at 3; *see* Ambry NextGen PowerPoint (Exh. J) at 8; RainDance Target Sequencing Assay Manual (Exh. K) at A-3 to A-7, 3-2, 4-2, 5-2.

Ambry's process accordingly involves the use of short pieces of synthetic DNA called "primers" that are used in "pairs." While naturally-occurring DNA is double-stranded, primers are single-stranded. Primers are synthetic DNA molecules made in a laboratory. They are man-made, not products of nature. Each primer is specifically engineered to have a sequence of nucleotides designed in the laboratory to be "complementary" to a single strand of a region of the target breast cancer gene to be sequenced, BRCA1 and/or BRCA2. The primers must be engineered that way so that they will "hybridize," or bond or attach, to the corresponding or "complementary" part of a gene fragment after the dual-stranded fragments have been separated in the laboratory. Roa Decl. at ¶¶ 16, 18, 21, 6-7; *see* Ambry NextGen PowerPoint (Exh. J) at 30 An illustration of a primer pair and the DNA fragment to which they are complementary is shown below:



When designing primers (and similar molecules called "probes"), scientists use natural DNA sequences as inspiration. Roa Decl. at ¶¶ 19-20, 31. In that sense, the nucleotide sequence of the

BRCA1 and BRCA2 primers made in the laboratory are "derived" from the nucleotide sequence of those genes in the human chromosomes, which are chromosomes 17q and 13, respectively. Roa Decl. at ¶ 23; Ambry BRCA1 and BRCA2 Data Sheets (Exhs. G at 1 & H at 1). However, the primer molecules themselves are entirely man-made; they are synthesized in a laboratory. Roa Decl. at ¶ 6. After the synthetic primers "hybridize" (*i.e.*, attach or bond) to the fragmented and isolated naturally-occurring DNA pieces, Ambry "amplifies" the BRCA1 and BRCA2 genes piece by synthetic piece through multiple rounds of the polymerase chain reaction ("PCR") process or, in other words, creates many synthetic molecules sharing sequence similarity with the isolated naturally-occurring DNA fragments. *See* Ambry NextGen PowerPoint (Exh. J) at 8, 30; RainDance Target Sequencing Assay Manual (Exh. K) at A-3 to A-7, 3-2, 4-2, 5-2.[7] These DNA molecules are 100% synthetic; that is, they are entirely man-made through the PCR process. Because they are amplified synthetic DNA, they are typically called "amplicons." The synthetic nature (or in other words, the human design) of these amplicons is further evidenced by the fact that the structural dimensions of these amplicons will be different from the original fragmented genomic DNA. Roa Decl. at ¶¶ 6-15.

Myriad is likely to prove that Ambry's use of synthetic primers and creation of synthetic DNA molecules for BRCA1 and BRCA2 sequencing infringes claims 16-17 of the '282 patent and claims 29-30 of the '492 patent. The following comparison of claims 16 and 17 of the '282 patent to Ambry's activities shows infringement of those claims:

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[7] Typical primer pairs used in PCR are between 15 and 30 nucleotides in length. Roa Decl. at ¶ 16. To hybridize well to the patient's DNA, the length of the nucleotide sequence of the primer that matches up to the sample DNA needs to be at least 15 nucleotides long. The part of at least some of the primer pairs that is complementary to the nucleotide sequence in the single strand of an exon of the BRCA1 and BRCA2 genes is generally between 15 and 30 nucleotides long. Some of the exons in each gene are so long that, when the entire gene is fragmented for PCR, some of the resulting fragments consist only of exons (*i.e.*, without any intron fragments). As a result, the entire nucleotide sequence in the primer pairs for those exon fragments, and the resulting amplified DNA molecules, will inevitably share sequence similarity only with part of an exon in the gene. *Id.* at ¶¶ 12-16.

16. A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction	Ambry uses pairs of single-stranded primers in the polymerase chain reaction. Ambry uses the resulting synthetic DNA to determine the nucleotide sequence of the patient's BRCA1 gene.
the sequence of said primers being derived from human chromosome 17q	Ambry's primers are engineered to be complementary to the nucleotide sequence of a region in the BRCA1 gene, which is located on chromosome 17q.[8]
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.	The polymerase chain reaction synthesizes DNA based on primers complementary to regions of the BRCA1 gene, and thus "synthesizes" several DNA molecules having at least part the sequence of the BRCA1 gene.
17. The pair of primers of claim 16 wherein said BRCA1 gene has the nucleotide sequence set forth in SEQ ID NO:1 [*i.e.*, the BRCA1 nucleotide sequence with only the exons from that gene].[9]	At least some of Ambry's primer pairs have a nucleotide sequence complementary to only the exons in the BRCA1 gene. Also, during the PCR process, such primer pairs will act to produce DNA molecules whose relevant nucleotide sequence shares similarity to only part of an exon in the BRCA1 gene.

Claims 29 and 30 of the '492 are virtually the same but are directed at the BRCA2 gene.

The following comparison of those claims to Ambry's activities demonstrates infringement:

[8] Ambry's primers may also contain additional nucleotide sequences, such as "adapter" sequences, that allow for later manipulation of the DNA, such as in a sequencing machine. However, the primer sequence is nevertheless "derived" from chromosome 17 because the structure of the central functional portion of the molecule is designed to be complementary to a small, specific region of the chromosome corresponding to the BRCA1 gene.

[9] As the Supreme Court explained in *Myriad*, 133 S.Ct. 2107, SEQ ID NO:1 is the nucleotide sequence of a synthetic DNA for the BRCA1 gene with only the exons from that gene. *Id*. at 2113.

29. 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,	Ambry uses pairs of single-stranded primers in the polymerase chain reaction. At least some primers must be at least 15 nucleotides long because some of the BRCA2 exons are very large. Ambry uses the resulting synthetic DNA molecules to determine the nucleotide sequence of the patient's BRCA2 gene.
the sequence of said primers being isolated from human chromosome 13,	Ambry's primers each are engineered to be complementary to a nucleotide sequence of a region in the BRCA2 gene, which is located on 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.	The polymerase chain reaction makes a synthetic DNA based on all the pieces of DNA to which the primers have attached, and thus synthesizes at least part of the BRCA2 gene, including those pieces that are at least 15 nucleotides long.
30. The pair of primers of claim 29 wherein said BRCA2 gene has the nucleotide sequence set forth in SEQ ID NO:1 [*i.e.*, the BRCA2 nucleotide sequence with only the exons from that gene].	At least some of Ambry's primer pairs have a nucleotide sequence complementary only to exons in the BRCA2 gene. Also, during the PCR process, such primer pairs will act to produce DNA molecules whose relevant nucleotide sequence shares similarity to only part of an exon in the BRCA2 gene.

b. Myriad is Likely to Prove that Ambry's Next-Generation Sequencing and Sanger Sequencing Infringes Claim 8 of the '441 Patent, Claim 5 of the '721 Patent, and Claims 2 and 4 of the '155 Patent.

After obtaining multiple synthetic DNA molecules, Ambry applies various "sequencing" methods to them. Sequencing is a chemical laboratory process that identifies each nucleotide in the DNA molecules artificially synthesized in the prior PCR process. In other word, it determines at each position in the synthetic DNA molecule which nucleotide—adenine ("A"), thymine ("T"), cytosine ("C"), or guanine ("G")—is located at that position. Ambry NGS

Cancer Panels PowerPoint (Exh. B) at 4 ; Ambry Poster (Exh. C); Ambry NextGen PowerPoint (Exh. J) at 10-12, 26, 32; Roa Decl., ¶ 24.

The first sequencing process Ambry uses is called "Next-Generation sequencing." Ambry Data Sheets for BreastNext (Exh. D) at 4-5, CancerNext (Exh. E) at 6, OvaNext (Exh. F) at 5, BRCA1 & BRCA2 (Exh. I) at 2, BRCAplus tests (Exh. L) at 3; *see* Ambry NextGen PowerPoint (Exh. J) at 10-12, 26; RainDance Target Sequencing Assay Manual (Exh. K) at A-3 to A-7, 3-2, 4-2, 5-2. Ambry performs "sequencing of all coding exons plus at least 5 bases into the 5′ and 3′ ends of all the introns and untranslated regions." Ambry Data Sheets for BreastNext (Exh. D) at 4, CancerNext (Exh. D) at 6, OvaNext (Exh. F) at 5, BRCA1 & BRCA2 (Exh. I) at 2, BRCAplus tests (Exh. L) at 3. The sequence of the exons in the BRCA1 gene includes nucleotide position numbers 2201, 2731, 2430, 4427, 3232, 3667, and 4956. Roa Decl., ¶ 29; *see* NCBI webpages (Exhs. N & O) at final page. Ambry's sequencing thus includes determining the nucleotides at each of these positions in the BRCA1 gene and at every other position of every exon in both the BRCA1 and BRCA2 genes.

Ambry then also performs a second form of sequencing called "Sanger" sequencing as verification of next-generation sequencing to confirm "all identified variants." Ambry NGS Cancer Panels PowerPoint (Exh. B) at 4; Ambry Poster (Exh. C); *see* Ambry Data Sheets for BreastNext (Exh. D) at 5, CancerNext (Exh. E) at 6, OvaNext (Exh. F) at 6, BRCA1 & BRCA2 (Exh. I) at 2, BRCAplus tests (Exh. L) at 3. Sanger sequencing includes, among other things, applying to the patient's DNA not only synthetic primers, but also special nucleotides called "dideoxynucletide" chain terminators. The primers and/or the terminators have labels that can be read during sequencing of the synthetic DNA that identify what type of nucleotide is present at

each position. Roa Decl., ¶ 25; Ambry NextGen Powerpoint (Exh. J) at 10; Wikipedia.com (entry for "Sanger sequencing").

The patient's DNA sequence for BRCA1 and BRCA2 as determined in those sequencing processes is compared using specialized computer software with "reference sequences" or, in other words, the commonly expected sequences, for BRCA1 and BRCA2 to locate "[a]ll identified variants" and thus for "Mutation Detection." Roa Decl., ¶¶ 27-28; Ambry NGS Cancer Panels PowerPoint (Exh. B) at 4. As reference sequences, Ambry uses at least the "NCBI reference sequences: BRCA1 – NM_007294 and BRCA2 – NM_000059." Ambry Data Sheet for BRCA1 & BRCA2 Test (Exh. I) at 2. Those sequences are a "reference standard" and represent the most common forms of variations of those genes, or what is often called the "wild-type." Roa Decl., ¶ 28; *see Myriad*, 133 S.Ct. at 2113, n.1; NCBI webpages (Exh. N at 2 & Exh. O at 2).

Myriad is likely to prove that Ambry infringes claim 8 of the '441 patent by both next-generation and Sanger sequencing, as demonstrated by the following comparison of claim 8 to Ambry's sequencing process:

8. [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	Ambry compares the sequence of a human patient's BRCA1 gene deduced from a patient's sample to "reference sequences" that represent the most commonly occurring sequences for that gene. A "germline" is the genetic material that the human subject inherited through birth (as opposed to genetic sequences created through mutations during the person's lifetime as a result of exposure to toxins or other environmental causes). *See* '441 patent at col. 13, lines 5-10; col. 12, lines 34-46; Wikipedia.com entry for "germline."

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][10]	The differences located in the comparison indicate "variants" or "mutations" ("alterations") in the patient's BRCA1 gene.
wherein a germline nucleic acid sequence is compared by amplifying all or part of BRCA1 gene from said sample using a set of primers to produce amplified nucleic acid and	Ambry uses various pairs or sets of primers in a polymerase chain reaction process that produces many synthetic DNA molecules having (and thereby "amplifies") nucleotides ("nucleic acids") of at least part of a patient's BRCA1 gene from the patient's sample.
sequencing the amplified nucleic acids.	Ambry sequences the parts of the amplified BRCA1 gene both by next-generation sequencing and by Sanger sequencing.

For the same reasons, Ambry's sequencing methods infringe claim 4 of U.S. Patent No. 6,033,857, which requires a similar method but for the BRCA2 gene.[11]

Myriad is also likely to prove that both of Ambry's sequencing methods infringe claim 5 of the '721 patent. The following comparison to claim 5 demonstrates that fact:

5. [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,	For each test Ambry performs for a human female with a family history that indicates a predisposition to breast cancer, Ambry uses next-generation and Sanger sequencing to determine the nucleotide sequence of at least the exon fragments of the BRCA1 gene.

[10] Claim 8 incorporates "[t]he method of claim 1." The bracketed language is the inserted language from claim 1.

[11] Claim 4 recites in pertinent part "[a] method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene … in a tissue sample from [a human] subject with the germline sequence of the wild-type BRCA2 gene … wherein an alteration in the germline sequence of the BRCA2 gene … indicates a predisposition to said cancer" and "wherein the detection in the alteration in the germline sequence is determined by an assay selected from the group consisting of … (d) amplifying all or part of the BRCA2 gene from said tissue sample to produce an amplified sequence and sequencing the amplified sequence."

(b) comparing the determined nucleotide sequence from said female individual to SEQ ID NO: 263, and	Ambry compares the sequence of the exons in the patient's BRCA1 gene to the exons in "reference sequences," and that comparison includes the nucleotides in sequence SEQ ID NO: 263, which are the nucleotides at the seven positions 2201, 2731, 2430, 4427, 3232, 3667, and 4956. *See* '721 patent at col. 4, lines 2-8 (identifying "SEQ ID NO: 263" as the "nucleotide variations" set forth in step (c) of claim 5, illustrating them in Figure 1, and referring to the variations as the "BRCA1$^{(omi1)}$ haplotype").
(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 omil haplotype][12]	Ambry's sequencing determines the specific nucleotide at each position in each exon of the patient's BRCA1 gene, which includes determining whether the nucleotide at each of the seven positions 2201, 2731, 2430, 4427, 3232, 3667, and 4956 is thymine (T), cytosine (C), or guanine (G) or some other nucleotide instead. If the nucleotides listed in step (c) are present at the listed positions, then it indicates the existence of the *omi*1 haplotype in the patient.[13]
wherein the BRCA1 gene or fragment thereof is amplified prior to nucleotide sequencing.	Ambry's process includes using the polymerase chain reaction process to make synthetic DNA molecules that share a nucleotide sequence similar to at least the exon fragments of the patient's BRCA1 gene (*i.e.*, amplify the DNA), and then sequences those synthetically produced DNA molecules both by next-generation and Sanger sequencing.

Similar to that claim, Myriad also is likely to prove that Ambry's Sanger sequencing infringes claims 2 and 4 of the '155 patent. Those claims focus on the same nucleotide variations identified in the claim just discussed. Claims 2 and 4 refer to those variations as

[12] Claim 5 incorporates "[t]he method of claim 1." The bracketed language is the inserted language from claim 1.

[13] About 50% of the testing population that is not of African ancestry will have all of the seven variations required in claim 5. Roa Decl., ¶ 29. As a result, 50% of Ambry's BRCA1 sequencing in patients not of African ancestry will detect the presence of all seven variations.

"polymorphisms," which is a variation in the nucleotide sequence of even one nucleotide. *See generally* '155 patent at col. 11, line 57 to col. 18, line 41. The '155 patent explains that each of the seven variations is considered a "normal variation" rather than a change that indicates an increased susceptibility to breast or ovarian cancer. *See id.* at col. 13, lines 28-56; col. 15, lines 19-47. The following comparison of Ambry's Sanger sequencing demonstrates that it uses the methods recited in claims 2 and 4:

2. A method of identifying individuals having a BRCA1 gene with a BRCA1 coding sequence not associated with breast or ovarian cancer comprising: a) amplifying a DNA fragment of an individual's BRCA1 coding sequence using an oligonucleotide primer which specifically hybridizes to sequences within the gene;	Ambry's Sanger sequencing process uses primers having a number of nucleotides (an "oligonucleotide"). The primers are designed with a sequence of nucleotides that is complementary to single-stranded region of the exons of the BRCA1 gene, and accordingly they specifically hybridize to those exons. Those primers are used with the patient's DNA in the PCR process to make synthetic DNA molecules that share a nucleotide sequence similar to at least the exon fragments of the patient's BRCA1 gene (*i.e.*, amplify the DNA).
b) sequencing said amplified fragment by dideoxy sequencing;	Ambry's use of "Sanger" sequencing by definition means that the sequencing includes the use of dideoxynucleotides and thus also dideoxy sequencing.
c) repeating steps (a) and (b) until said individual's BRCA1 coding sequence is completely sequenced;	Ambry completely sequences all of the coding exons in the BRCA1 gene.
d) comparing the sequence of said amplified DNA to the sequence of SEQ. ID. NO: 1;	Ambry compares the entire determined BRCA1 sequence of the patient to "reference sequences"—the commonly expected BRCA1 sequences.
e) determining the presence or absence of each of the following polymorphic variations in said individual's BRCA1 coding sequence: AGC and AGT at position 2201, TTG and CTG at position 2430,	Ambry's comparison includes each nucleotide in each exon of the entire BRCA1 sequence, and thus includes each of the three groups of nucleotides at the seven positions—2201, 2731, 2430, 4427, 3232, 3667, and 4956—and a determination of presence or absence of each group at each position listed.

CCG and CTG at position 2731, GAA and GGA at position 3232, AAA and AGA at position 3667, TCT and TCC at position 4427, and AGT and GGT at position 4956;	
f) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 wherein the presence of any of the said polymorphic variations and the absence of a polymorphism outside of positions 2201, 2430, 2731, 3232, 3667, 4427, and 4956, is correlated with an absence of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in the BRCA1 coding sequence.	For each BRCA1 test in which Ambry determines the absence of variations outside of the seven variable groups of nucleotides in the seven recited positions, that determination indicates the absence of an increased susceptibility for breast or ovarian cancer.
4. A method of detecting an increased genetic susceptibility to breast and ovarian cancer in an individual resulting from the presence of a mutation in the BRCA1 coding sequence, comprising: [steps (a), (b), (c), and (d) are the same as in claim 2]	*See* claim 2, steps (a) to (d) above.
(e) determining any sequence differences between said individual's BRCA1 coding sequences and SEQ. ID. NO: 1 to determine the presence or absence of polymorphisms in said individual's BRCA coding sequences wherein a polymorphism which is not any of the following: AGC and AGT at position 2201, TTG and CTG at position 2430, CCG and CTG at position 2731, GAA and GGA at position 3232, AAA and AGA at position 3667, TCT and TCC at position 4427, and AGT and GGT at position 4956; is correlated with the potential of increased genetic susceptibility to breast or ovarian cancer resulting from a BRCA1 mutation in	Ambry's comparison includes each nucleotide in each exon of the entire BRCA1 sequence, and thus includes each of the three groups of nucleotides at the seven positions—2201, 2731, 2430, 4427, 3232, 3667, and 4956—and a determination of presence or absence of each group at each position listed. For each BRCA1 test in which Ambry determines that there are variations outside of the seven variable groups of nucleotides in the seven recited positions, and the existence of those variations leads to a determination of an increased susceptibility for breast or ovarian cancer, then Ambry's test is encompassed by claim 4.

the BRCA1 coding sequence.	

c. Myriad is Likely to Prove that Ambry's Large Rearrangement Analysis Infringes Claim 7 of the '441 Patent.

As additional steps in its BRCA1 and BRCA2 testing, Ambry uses a large rearrangement analysis that looks for large deletions and duplications of nucleotides in the patient's genes. Depending on what test the patient requests, Ambry either uses (1) multiplex ligation-dependent probe amplification ("MLPA") analysis or (2) chromosomal "microarray" analysis. In particular, Ambry uses MLPA kits, developed by MRC Holland, for "comprehensive (full-gene) gross deletion/duplication analysis" as part of at least two of its BRCA1 and BRCA2 tests. Ambry Data Sheet for BRCA1 & BRCA2 Test (Exh. I) at 2.

Ambry's MLPA process uses synthetic BRCA1 and BRCA2-specific probes. The probes are similar to synthetic DNA primers. They each contain a series of nucleotides designed to be complementary to a single strand of a region of the BRCA1 or BRCA2 genes. Like primers, the probes "hybridize" to the corresponding target section of the exon to which they are complementary or, in other words, they hybridize to any BRCA1 and BRCA2 allele or to any synthetic DNA that shares a nucleotide sequence similar to the target sequence. MLPA – an introduction (MRC Holland) (Exh. P) at 1-2; Roa Decl., ¶ 31.[14] MLPA probes that hybridize to adjacent genomic sequences are ligated. The polymerase chain reaction process is then applied, which will amplify (make many synthetic DNA molecules) of each targeted part of the gene where hybridization of the probes has taken place. If a target section of the gene is present, then the probes will hybridize and the hybridization will be detected because the PCR process will create many synthetic DNA molecules having the sequence of the target section for that probe.

[14] An "allele" refers to a form of the gene having a certain sequence, such as variant sequences or mutation sequences of interest, and thus may be called a "wild-type allele" or a "mutated allele." Roa Decl., ¶ 31.

If a target section is not present, then the probes for that section will not hybridize to anything, and the fact that the target section is missing will be evident from the relative lack of synthetic DNA molecules corresponding to that section made during the PCR process. MLPA – an introduction (MRC Holland) (Exh. P) at 1-2; Roa Decl., ¶¶ 31-33. The resulting data allows Ambry to compare the patient's germline sequence to a wild-type sequence. Roa Decl., ¶ 34.

Ambry also uses a "chromosomal microarray" analysis to identify "gross deletions or duplications in all" genes analyzed as part of its BRCAplus test and its BreastNext, CancerNext, and OvaNext tests. Ambry Data Sheets for BRCAplus (Exh. L) at 3, BreastNext (Exh. D) at 5, CancerNext (Exh. E) at 6, and OvaNext tests (Exh. F) at 6. A microarray is a solid surface having a collection of microscopic spots to which different synthetic DNA probes are attached. The probes are similar to the probes used for MLPA. They each contain a series of nucleotides that is precisely complementary to a piece of a single strand of an exon in the BRCA1 or BRCA2 genes and "hybridize" to the corresponding target section of the exon. Roa Decl., ¶¶ 35-37. Ambry's microarray necessarily requires hybridization of the synthetic DNA created from a patient's sample DNA to a BRCA1- or BRCA 2-specific probe, and detection of that hybridization product. *Id.* Microarray analysis typically includes synthesis of different fluorescently labeled products from the patient and from wild-type genomic DNA, followed by competitive hybridization to the immobilized probes on the microarray slide. Deviation from the expected copy numbers of the hybridized products indicates deletion or duplication of the corresponding gene region. *Id.* The resulting data allows Ambry to identify both the existence of the allele and the existence of large base pair mutations in a germline nucleic acid sequence by comparing that sequence to the wild-type allele. *Id.*

Myriad is likely to prove that Ambry's use of MLPA and microarray analysis for BRCA1 infringes claim 7 of the '441 patent. Claim 7 is similar to claim 8 of that patent discussed above. However, rather than requiring the use of a set of primers and amplification to perform the DNA sequence comparison, claim 7 requires that the comparison instead include "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."

As set forth above, Ambry's MLPA and microarray processes include the use of BRCA1-specific gene probes. It also includes the hybridization of those probes either to sample DNA obtained from a patient (in other words, an isolated genomic DNA sample) or to synthetic DNA produced from such a sample. Both processes also include the step of detecting each act of hybridization and, as a result, the detection of the hybridization at each location on the gene. Because each probe hybridizes only to a specific BRCA1 allele, detecting the hybridization thus indicates the presence of each BRCA1 allele corresponding to any probe used.

Next, Ambry's MLPA and microarray analyses also infringe claim 4 of U.S. Patent No. 6,033,857. In pertinent part, that claim requires "comparing the germline sequence of the BRCA2 gene … in a tissue sample from [a human] subject with the germline sequence of the wild-type BRCA2 gene … wherein an alteration in the germline sequence of the BRCA2 gene … indicates a predisposition to said cancer" and "wherein the detection in the alteration in the germline sequence is determined by an assay selected from the group consisting of … (b) hybridizing a BRCA1 gene probe to genomic DNA isolated from said tissue sample" . . . (d) amplifying all or part of the BRCA2 gene from said tissue sample to produce an amplified sequence and sequencing said amplified sequence." As set forth above, Ambry uses BRCA2

gene probes and they hybridization of those probes to a patient's sample DNA. Ambry also uses the polymerase chain reaction process to amplify at least parts of the BRCA2 gene after applying the synthetic probes. Further, the detection of which probes hybridize and which do not includes the claimed comparison of the patient's germline BRCA2 sequence to the wild-type BRCA2 sequence. The composition of each probe is a commonly expected nucleotide sequence within the gene (*i.e.*, the "wild-type"). If a probe hybridizes, then it indicates that the patient's sequence matches that part of the wild-type gene sequence, and thus the comparison is a positive match. If a probe does not hybridize, then it indicates that the patient's sequence is lacking that part of the wild-type sequence, and thus the comparison indicates no match.

B. Myriad Will Suffer Immediate and Irreparable Injury If Injunctive Relief Is Not Granted to Prevent Ongoing Infringement by Ambry.

The second element of the test for injunctive relief is met because Myriad will suffer immediate and irreparable harm if Ambry is not enjoined from its infringing activity.[15] At a minimum, such harm consists of: (1) price erosion and the loss of the benefit of Myriad's established pricing strategy; (2) the loss of market share; (3) reputational injury; and (4) loss of the benefit of the remaining limited term of patent exclusivity and Myriad's business plans for that period, as well as the inability to fully obtain its reliance interest obtained by disclosing its discovery and investing hundreds of millions of dollars to commercialize that discovery in exchange for a limited exclusive right. The Federal Circuit has recognized each of these forms of damage as irreparable harm that warrant the imposition of injunctive relief. *Robert Bosch LLC v. Pylon Mfg. Corp.*, 659 F.3d 1142, 1152-54 (Fed. Cir. 2011) (the district court "committed a clear error in judgment" in denying a motion for a permanent injunction where the record

[15] The references to "Myriad" in this section (B) refer to Plaintiff Myriad Genetics, Inc., except as otherwise noted.

contained "undisputed evidence of direct competition in each of the market segments identified by the parties" and "unrebutted evidence of loss of market share and access to potential customers," and the patentee suffered "irreversible price erosion, loss of market share, loss of customers, and loss of access to potential customers."); *Douglas Dynamics, LLC v. Buyers Products Company*, Nos. 2011–1291, 2012–1046, 2012–1057, 2012–1087, 2012–1088, 2013 WL 2158423 at *5-6 (Fed. Cir. May 21, 2013) ("[i]rreparable injury encompasses different types of losses that are often difficult to quantify, including lost sales and erosion in reputation and brand distinction."); *Pfizer, Inc. v. Teva Pharmaceuticals, USA, Inc*., 429 F.3d 1364, 1380 (Fed. Cir. 2005) (the district court properly considered the fact that "[defendant's] sales of its generic product would cause substantial harm to [patentee] and loss of the statutory right to exclude [defendant] for the remaining life of the '450 patent, which expires in August 2007").

1. If Allowed to Proceed, Ambry's Deeply Discounted Test Panels Will Result in Significant and Irreparable Price Erosion and Loss of the Benefit of Myriad's Pricing Strategy.

A patentee is entitled to practice its right of exclusion by pricing its patented products accordingly, and an infringer may substantially and irreversibly damage that right by offering infringing products at deeply discounted prices. *See, e.g., Robert Bosch LLC* 659 F.3d at 1154 ("Bosch argues that it will continue to suffer irreparable harm due to lost market share, lost business opportunities, and price erosion unless Pylon is permanently enjoined. According to Bosch, money damages alone cannot fully compensate Bosch for these harms. We agree.").

Until a couple of weeks ago, Myriad was the only company that offered a full sequence test for the BRCA1 and 2 genes in the United States.[16] Ambry unambiguously declared its intent

[16] No other entity in the United States has been licensed to perform full sequencing of the BRCA1 and 2 genes. Ford Decl., ¶ 8.

to compete directly with Myriad when it announced on June 13, 2013, mere hours after the United States Supreme Court decision, that it is now offering its own BRCAPlus test that includes BRCA1 and BRCA2 testing. *See* http://ambrygen.com/tests/brcaplus-%E2%80%93-high-risk-breast-cancer-panel. At the same time, Ambry released a Cancer Test Requisition Form that invites members of the public to purchase various tests, four of which (BreastNext, BRCAPlus, CancerNext and OvaNext) offer BRCA1 and/or BRCA2 testing. Ford Decl., ¶ 10; Exh. 1. Ambry further indicated that it will offer its BRCAPlus test for $2,280, significantly below the price for Myriad's competing test, which is priced at $4,040. *Id*., ¶ 11. Thus, Ambry has entered the market not only as a direct competitor of Myriad, but at a significantly discounted price.

If Ambry is allowed to proceed, market prices will decline. This is largely because third-party payors (such as insurers and/or HMO's) are primarily responsible for deciding whether they will reimburse or pay for testing, rather than the physician or the patient. *Id*., ¶¶ 12-13. Those payors will exert pressure on Myriad to lower its prices in response to Ambry, and Myriad would be forced to do so in some instances. *Id*., ¶ 16. This could lead to a competitive response by Ambry and even lower market prices. Additionally, other competitors potentially could enter the market at even lower prices. As a consequence, Myriad's market share will decline to the extent it does not match Ambry's lower price. In either case, Myriad will lose significant amounts of revenue.

This loss will extend to the other Plaintiffs with equal force. Their license royalties are directly dependent upon Myriad's revenue. The loss of significant amounts of revenue by Myriad translates directly to the loss of significant amounts of license revenue by each licensor. This revenue, which to date amounts to approximately $57,000,000, is critical to these

institutions, the majority of which are publicly funded research universities and a children's hospital, the Hospital For Sick Children located in Toronto, Canada. If this revenue stream is reduced for the remaining patent term, it will impact their ability to fund ongoing programs and new endeavors. And, it will be exceedingly difficult, if not impossible, to estimate damages to Myriad and the licensor Plaintiffs with any reliability post-trial because that would require a disentangling of the impact of the change in market prices on each competitor's sales. There will be no way to determine post trial whether a particular consumer switched from Myriad to Ambry as a result of price differences, whether that consumer would have purchased from Myriad absent Ambry, or whether it may not have purchased at all at the current price level.[17]

The Federal Circuit has repeatedly found that such circumstances prove irreparable harm. In particular, in *Sanofi–Synthelabo, Inc. v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006), the Federal Circuit affirmed the district court's grant of an injunction based in part upon evidence of irreversible price erosion. There, the patentee employed a complex pricing scheme that was "directly affected by the presence of the generic product in the market" as the patentee was "forced to offer discounted rates and price concessions to third-party payors, such as health maintenance organizations, in order to keep Plavix® on a favorable pricing tier, which governs what consumers pay for that drug." *Id.* at 1382-83. *See also Merial Ltd. v. Cipla Ltd.*, 681 F.3d 1283, 1306 (Fed. Cir. 2012) (upholding district court's finding of irreparable harm based in part upon "evidence that Velcera's marketing strategy was geared specifically to target Frontline Plus by touting PetArmor Plus as a cheaper but otherwise equal alternative."); *Purdue Pharma L.P. v.*

[17] The foregoing damage to Myriad only will be compounded by the fact that Ambry is not likely to be the only entrant to the market. If other infringers enter, the barriers to obtaining damages will become even more challenging because of the difficulty in tracing the cause of Myriad's lower prices to any single defendant.

Boehringer Ingelheim GmbH, 237 F.3d 1359, 1368 (Fed. Cir. 2001) (likelihood of price erosion and loss of market position are evidence of irreparable harm).

Regardless of how the competitive dynamics play out, Myriad also will suffer the irretrievable loss of the benefit of its current pricing policy. Myriad offers its BRCA1 and BRCA2 testing at $4,040. Myriad sets its prices based on consideration of the present demand conditions and the future post-patent expiration demand a few years from now. And, while nearly all third-party payors offer coverage for the test, many with no out-of-pocket cost to the patient, Myriad's prices are constrained by the ability of employers to opt out of genetic testing in their insurance offerings if they determine that it has become too expensive. Ford Decl., ¶ 15. Myriad has set its prices to reflect the higher quality of Myriad's test, including the significant investments made in discovering the sequences of the BRCA1 and BRCA2 genes, developing necessary technology to perform testing, building the market and analyzing and characterizing variants in a proprietary database that enables Myriad to provide a clinically meaningful result for over 97% of the variants identified, as opposed to approximately 70% using the publicly available database. *Id.*, ¶ 7; *see id.* at ¶¶ 19-20. Myriad's price/quality strategy thus allows Myriad to recoup its investment during the life of the patents, while providing the benefit of BRCA testing to a vast majority of insured individuals. Indeed, over 1,000,000 individuals have been tested to date. *Id.*, ¶ 1. Absent an injunction, the benefit of this pricing strategy will be lost forever. As the *Sanofi-Synthelabo* court noted, a patentee is entitled to enjoy the benefits of its pricing strategy, and intrusion upon those benefits may constitute irreparable harm. 470 F.3d at 1372-73.

These factors, taken as a whole, compel the conclusion that the price erosion damage Myriad would suffer from Ambry's sales would be irreparable. *Abbott Labs. v. Sandoz, Inc.*, 544

F.3d 1341, 1361-62 (Fed. Cir. 2008), *reh'g denied* (in affirming the grant of a preliminary injunction, the Federal Circuit relied in part upon the patentee's argument that "it could not be made whole if it prevails in this litigation, for the added erosion of markets, customers and prices, is rarely reversible."); *Polymer Tech. Inc.*, 103 F.3d at 975-76 ("Competitors change the marketplace. Years after infringement has begun, it may be impossible to restore a patentee's (or an exclusive licensee's) exclusive position by an award of damages and a permanent injunction. Customers may have established relationships with infringers. The market is rarely the same when a market of multiple sellers is suddenly converted to one with a single seller by legal fiat. Requiring purchasers to pay higher prices after years of paying lower prices to infringers is not a reliable business option.").

2. Absent Injunctive Relief, Ambry's Conduct Will Also Result in Significant and Irreparable Loss of Market Share.

Absent an injunction, Myriad is certain to lose market share after Ambry enters. A substantial portion of Myriad's business is based upon BRCA1 and BRCA2 testing covered by the patents. Through its hard work and dedication, Myriad was able to finalize this invention, secure licenses from the patent owners, and develop a superior BRCA1 and BRCA2 test that not only created the market from scratch, but exhibits superior methodology and unparalleled reliability. Ford Decl., ¶ 2, 4; *see infra* at 39-40.

Thus, if Ambry is allowed to free ride into the market with its infringing tests, Myriad will lose significant market share whether it lowers its prices or not. This is because Ambry's significantly discounted prices will result in some third-party payors insisting that patients choose Ambry over Myriad solely because of cost and regardless of the fact that Myriad offers a superior, far more reliable product, and even if patients or physicians prefer to use Myriad. *Id.*,

¶¶ 12-13; 15-17. Indeed, this has already begun to take place. *Id.*, ¶ 16. This loss of market share provides ample basis for finding irreparable harm.

This situation is akin to that recently addressed in *Presidio Components, Inc. v. American Technical Ceramics Corp.*, 702 F.3d 1351 (Fed. Cir. 2012). There, the court specifically addressed a loss of market share argument and found that evidence that the patentee and the defendant "were competing for the same customers in the same markets" favored a finding of irreparable harm. "Direct competition in the same market is certainly one factor suggesting strongly the potential for irreparable harm without enforcement of the right to exclude." *Id.* at 1363. *See also Hybritech*, 849 F.2d at 1456 (in finding irreparable harm, the court considered a list of factors that included the fact that the patentee "has a very large presence" in the field); *Robert Bosch LLC*, 659 F.3d at 1152 (relying upon "unrebutted evidence of loss of market share and access to potential customers," among other things).[18]

3. Myriad Will Suffer Irreparable Reputational Harm Absent Injunctive Relief.

Allowing Ambry to enter the market will result in a third form of irreparable injury to Myriad – non-compensable damage to its reputation. As the discoverer of the sequences of the BRCA1 and BRCA2 genes and the knowledge of their disease association, Myriad has significantly advanced the knowledge in the field of hereditary cancer and improved patient health-care. As the developer of the variant database, the inventor of the synthetic probes, primers and assays, and the developer of the BRCA tests, Myriad has spent the entirety of its time in the market improving the accuracy and reliability of its BRAC*Analysis*® test, and has

[18] The fact that Myriad has not licensed to any other party the rights to the patents at issue to do full BRCA1 and BRCA2 testing further favors a finding of irreparable harm. *Douglas Dynamics, LLC*, 2013 WL 2158423 at * 6 (fact patentee "had never licensed the infringed patents, and intentionally chose not to, so that it could maintain market exclusivity" weighed in favor of entry of injunctive relief).

saved countless lives and improved the quality of life of patients with cancer. Myriad's years of experience and its built-in quality checks, including the fact that it has developed proprietary DNA base calling software, have resulted in a near perfect accuracy rate. Ford Decl., ¶ 5. Ambry's failure rate, in contrast, may be as high as 4%. *Id.*, ¶ 17.[19] This difference is highly significant when translated to real-world numbers. The clinical significance of a 4% error rate means that as many as 1 in every 25 patients could experience an incorrect test result (again, assuming 96% accuracy). *Id.*, ¶ 18.

The reliability of Myriad's test is based not only on its years of experience, but also on Myriad's extensive database of genetic variants developed based on analyzing over 1,000,000 patient samples. *Id.*, ¶ 6; *see supra* at 37. This database was developed in part utilizing extensive research by Myriad, and also consists of phenotypic information from patients and family members of patients who were identified as having a variant that was difficult to determine whether it was harmful or benign (variants of unknown significance). *See* Ford Decl., ¶ 6. By investing in research to characterize these variants and building this database, Myriad has been able to further improve its test quality by ensuring that its percentage of "variants of unknown significance" is less than 3%, compared to 25% to 30% in public databases. *Id.*, ¶ 7; *see id.* at ¶¶ 19-20. This means that over 97% of the patients that Myriad tests will receive a result indicating whether they have a genetic variation that increases her risk of breast or ovarian cancer. Again in contrast, Ambry's percentage of "variants of unknown significance" is between 25-30%. *Id.*, ¶ 19.

[19] While Ambry initially indicated on its website that its sensitivity rate was 96-99%, a mere seven days later (on July 7), it changed that statement to 99%.

If Ambry is allowed to continue selling its tests, which have a higher error rate than Myriad's and will result in many more "variants of unknown significance," consumers will receive inconclusive or even flatly incorrect results from those tests. However, because consumers generally are not well-informed about the different test providers, in part because third-party payors often select the provider based on cost (*id*., ¶¶ 12-13), those consumers are likely to associate those flawed results with Myriad. This is particularly true since Myriad was the only supplier of the BRCA1 and BRCA2 tests before Ambry announced the availability of its tests, meaning that consumers who do pay attention to test providers naturally associate the test with Myriad.

And, Myriad has had no time or opportunity to distinguish its BRAC*Analysis*® test and associated testing quality from competitors as it would if its competitors were barred from entry until the patents' expiration. Myriad is well aware that its patents will eventually expire, and has begun to formulate a marketing strategy to advise the public of the superiority of its BRAC*Analysis*® test. *Id*., ¶ 21. However, Myriad relied on the premise that it still had the benefit of a few years of patent exclusivity to finalize this strategy. It is not prepared to implement those plans immediately, which it would need to do in order to combat the effect of Ambry's testing. *Id*., ¶ 22. Allowing patients to experience the effects of flawed results, absent appropriate education, will damage the reputation of BRCA testing in general, including the test offered by Myriad. This would also indirectly damage the reputation of the other patent owners, several of which are respected research universities or hospitals.[20]

[20] For these reasons, as set forth in section I(D) below, allowing Ambry to market its tests will do far more than injure Myriad's reputation – it will result in a virtually certain and severe public harm resulting from the reporting of flawed and incorrect results.

The foregoing will result in significant harm to Myriad's (and the other patent owners) reputation in the industry, yet another recognized form of irreparable harm. Indeed, the Federal Circuit addressed a similar issue earlier this year in *Douglas Dynamics, LLC*, 2013 WL 2158423. Among other things, the court found that the patentee had established a reputation as a "Mercedes," and would lose some of its "distinctiveness and market lure" if the defendant could market itself as a "Ford," albeit it at a lower price. *Id*. at *5. Similarly, the patentee had established itself as an "innovator," and "[]i]rreparable injury encompasses different types of losses that are often difficult to quantify, including lost sales and erosion in reputation and brand distinction." *Id.* at * 6.

4. Absent Injunctive Relief, Myriad Will Lose the Benefit of the Remaining Term of Patent Exclusivity and its Related Corporate Strategy, as Well as Its Significant Capital Investments in Developing the Market.

Finally, if Ambry is allowed to infringe during the pendency of litigation, Myriad's ability to benefit from its remaining term of patent exclusivity will be irreparably damaged. The patents-in-suit begin to expire in August 2014. This, in itself, provides ample basis for a finding of irreparable harm. *Pfizer, Inc.*, 429 F.3d at 1380; *see also Hybritech*, 849 F.2d at 1456 (noting the fact that "by the time the litigation is finished, it is entirely possible that the value of the patent will be gone and that technology might well bypass it" and the fact that, absent injunction, "other potential infringers will be encouraged to infringe").

Furthermore, Myriad has formulated a corporate strategy for its remaining years of patent exclusivity, including the development and introduction of new and beneficial products, such as Myriad's MyRisk™ hereditary cancer test. This multi-gene panel, which will be introduced later this year, will offer testing of 25 different genes in six different cancers, including the BRCA genes. Ford Decl., ¶ 23. Myriad rightly expected that this advanced test would be brought to

market during the remaining patent term, thus allowing Myriad and its investors the full benefit of market development for that multi-gene panel.

And, the potential harm to Myriad is not limited to the loss of its statutory right of exclusivity. If Ambry is allowed to enter the market now, Myriad also will lose much of the benefit of its significant expenditures (over $500 million) in developing that market. In reliance upon its patent rights, Myriad devoted a substantial amount of effort and capital to creating and cultivating the market for hereditary cancer predisposition testing. Ford Decl., ¶ 4. As discussed above, this effort included developing and continually improving the quality, accuracy and reliability of the BRAC*Analysis*® test, performing extensive clinical testing, educating physicians and patients, and developing an extensive variant database. But, Myriad's efforts were by no means limited to this work. Myriad also created the market structure which was critical to the success of its test. This included the development and promotion of medical industry guidelines pertaining to hereditary cancer predisposition testing. *Id.*

Myriad also dedicated substantial effort to establishing accepted procedures and protocols for insurance reimbursement for such testing, including private third-party payors as well as Medicare and Medicaid reimbursement. *Id*. This process was made possible only by years of work and clinical trials and research studies regarding the importance and efficacy of hereditary cancer testing, and the positive health-economic impact of such testing. *Id*. In other words, Myriad undertook the task of convincing both private and public health insurers that the type of testing performed by BRAC*Analysis*® is not only in the public health interest, but saves the healthcare system money by preventing diseases. The inequity of allowing Ambry to piggy-back off of Myriad's efforts, and reap the benefits of those efforts, provides yet another basis for finding irreparable harm. *EcoNova Inc. v. DPS Utah*, No. 1:12-cv-174-TC, 2012 WL 5944257 at

*15 (D. Utah Nov. 28, 2012) (considering, among other things, fact that defendant "has an unfair advantage because it is able to undercut [patentee's] price by benefitting from [patentee's] investment in the technology. . . .This is something that [patentee] may not be able to reverse.").

C. The Balance of Hardships Weighs Heavily in Favor of an Injunction, as Ambry Will Suffer No Legitimate Hardship from Issuance of an Injunction.

The third factor to be considered in determining whether to grant a preliminary injunction is the relative balance of hardships. This entails consideration of the "harm that will occur to the moving party from the denial of the preliminary injunction with the harm that the non-moving party will incur if the injunction is granted." *Hybritech*, 849 F.2d at 1457. Although the district court is required to consider this factor, there is no requirement that the court expressly find that the balance tips in favor of the patentee to award an injunction. *Id.*

Be that as it may, the balance here clearly weighs heavily in Myriad's favor. As noted above, Ambry first indicated its intention to enter the market for BRCA1 and BRCA2 testing on June 13, 2013. Accordingly, it has no established presence, and such testing is by no means central to its business model. Accordingly, Ambry will suffer no harm to its current business should an injunction issue. This is in stark contrast to Myriad. A significant part of Myriad's business is based on BRCA1 and BRCA2 testing (Ford Decl., ¶ 2), and it will suffer significant hardship if it loses its hard-won patent exclusivity. This will include the economic injuries outlined above, as well as the injury likely to be suffered by the licensor Plaintiffs occasioned by a decrease in license revenue.

D. The Public Interest Favors an Injunction, as there Will Be No Public "Injury" From Such Relief, and the Protection Afforded the Acquisition of New Technology Favors Such Relief.

The Federal Circuit has held that "the focus of the district court's public interest analysis should be whether there exists some critical public interest that would be injured by the grant of

preliminary relief." *Hybritech*, 849 F.2d at 1458. While competition may serve the public interest in the short term, the mere existence of a lower-priced, lower quality option available from an infringer does not necessarily advance the broader public interest. Indeed, "a new "competitor" will often find it easier to avoid the costs and risks of research and development and just "compete" by infringement." *Douglas Dynamics*, 2013 WL 2158423 at *7. For this reason, "[w]hile the general public certainly enjoys lower prices, cheap copies of patented inventions have the effect of inhibiting innovation and incentive. This detrimental effect, coupled with the public's general interest in the judicial protection of property rights in inventive technology, outweighs any interest the public has in purchasing cheaper infringing products. In sum, the public has a greater interest in acquiring new technology through the protections provided by the Patent Act than it has in buying 'cheaper knock-offs'." *Id*. at * 7.

Of particular interest here, the Federal Circuit has considered the public interest in obtaining "less expensive forms of successful medicines." *Abbott Labs*, 544 F.3d at 1362. It found that the district court properly "recognize[d] the public interest in competition in the pharmaceutical market" but also recognized "the public interest in creating beneficial and useful products and the cost involved in that process." *Id*. Thus:

> The district court appreciated that the public interest includes a consideration of whether, by shifting market benefits to the infringer while litigation is pending for patents that are likely to withstand the attack, the incentive for discovery and development of new products is adversely affected. The statutory period of exclusivity reflects the congressional balance of interests, and warrants weight in considering the public interest.

Id.

Therefore, the public interest in recognizing and incentivizing inventive work such as that performed by Myriad often outweighs any purported "interest" in obtaining inexpensive infringing products. Here, however, the public interest at issue goes far beyond incentivizing

invention. Precluding Ambry from selling its less accurate test is critical, as allowing Ambry to proceed results in significant public risk over the status quo where Myriad provides testing of very high quality, accuracy and affordability. Thus, the public interest is currently being served by Myriad's testing.

As discussed above, Myriad used its years in the market to perfect its testing processes. This work resulted in a near-perfect accuracy rate. Ford Decl., ¶ 5. 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. *Id.*, ¶ 18. The false negative result, of course is of the utmost concern. Assuming such an error rate, allowing Ambry into the market will result in more patients believing incorrectly that they are not at elevated risk, and not taking preventative measures that they otherwise would take. Conversely, a patient receiving a false positive may well elect preventative measures such as surgery when in fact there is no elevated risk. This untenable result can and should be avoided by issuance of an injunction.[21]

The public interest is advanced by more patients receiving tests from Myriad because of Myriad's exclusive access to its proprietary and extensive database of known genetic variants when making a comparison with a patient test sample. Ford Decl., ¶ 6. This database allows Myriad to report definitive findings to over 97% of its patients. *Id.*, ¶ 7. Ambry, in contrast, can do this only 70-75***%*** of the time. *Id.*, ¶ 19**.** Thus, Ambry will inform 25-30% of patients tested that they have a genetic variant, but will give them no further information about the clinical implications of that variant. Because insurance will not reimburse for a second, repetitive test, most patients will not be able to be tested again. Thus, those patients and their medical providers

[21] This risk is heightened by the fact that, unlike FDA approved products, a new competitor does not need to prove equivalence of its tests. Therefore, competitors such as Ambry can launch their products without proof of equivalent reliability, thus placing the public at an elevated risk.

will be left to guess at an appropriate course of treatment. Some patients, knowing they have a genetic variant of unknown significance, will assume the worst and undertake unnecessary prophylactic measures, including potentially surgery, even though the underlying variant may be benign. *Id*., ¶ 20. Allowing Ambry to proceed with its intent to enter the marketplace would be injurious to the public interest, and Ambry should be enjoined from doing so.

CONCLUSION

For the foregoing reasons, and because every element of the four-part test for preliminary injunctive relief is met, Myriad requests the issuance of an Order enjoining Ambry from any further sales or offers to sell genetic tests including a BRCA1 or BRCA2 panel pending judgment on the merits.

DATED this 9th day of July, 2013.

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CERTIFICATE OF SERVICE

On this 9th day of July 2013, I hereby certify that I electronically filed the foregoing **PLAINTIFFS' MOTION FOR PRELIMINARY INJUNCTIVE RELIEF AND MEMORANDUM IN SUPPORT** with the Clerk of Court using the CM/ECF system.

I also caused the foregoing to be served by hand, along with Plaintiffs Complaint and Motion for Preliminary Injunctive Relief and Memorandum in Support, on the following party:

Ambry Genetics Corporation
15 Argonaut
Aliso Viejo, CA 92656

/s/ David G. Mangum