No. 2010-1406

United States Court of Appeals

FOR THE FEDERAL CIRCUIT

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, THE AMERICAN COLLEGE OF MEDICAL GENETICS, THE AMERICAN SOCIETY FOR CLINICAL PATHOLOGY, THE COLLEGE OF AMERICAN PATHOLOGISTS, HAIG KAZAZIAN, MD, ARUPA GANGULY, PHD, WENDY CHUNG, MD, PHD, HARRY OSTRER, MD, DAVID LEDBETTER, PHD, STEPHEN WARREN, PHD, ELLEN MATLOFF, M.S., ELSA REICH, M.S., BREAST CANCER ACTION, BOSTON WOMEN'S HEALTH BOOK COLLECTIVE, LISBETH CERIANI, RUNI LIMARY, GENAE GIRARD, PATRICE FORTUNE, VICKY THOMASON, and KATHLEEN RAKER,

Plaintiffs-Appellees,

—v.—

UNITED STATES PATENT AND TRADEMARK OFFICE,

Defendant,

—and—

MYRIAD GENETICS, INC.,

Defendant-Appellant,

—and—

LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG, in their official capacity as Directors of The University of Utah Research Foundation,

Defendants-Appellants.

ON APPEAL FROM THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK, IN CASE NO. 09-CV-4515, SENIOR JUDGE ROBERT W. SWEET

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CERTIFICATE OF INTEREST

Counsel for the Plaintiffs-Appellees, Association for Molecular Pathology; American College of Medical Genetics; American Society for Clinical Pathology; College of American Pathologists; Haig Kazazian, MD; Arupa Ganguly, PhD; Wendy Chung, MD, PhD; Harry Ostrer, MD; David Ledbetter, PhD; Stephen Warren, PhD; Ellen Matloff, M.S.; Elsa Reich M.S.; Breast Cancer Action; Boston Women's Health Book Collective; Lisbeth Ceriani; Runi Limary; Genae Girard; Patrice Fortune; Vicky Thomason; and Kathleen Raker certifies the following:

1. The full name of every party or amicus represented by me is:

Association for Molecular Pathology; American College of Medical Genetics; American Society for Clinical Pathology; College of American Pathologists; Haig Kazazian, MD; Arupa Ganguly, PhD; Wendy Chung, MD, PhD; Harry Ostrer, MD; David Ledbetter, PhD; Stephen Warren, PhD; Ellen Matloff, M.S.; Elsa Reich M.S.; Breast Cancer Action; Boston Women's Health Book Collective; Lisbeth Ceriani; Runi Limary; Genae Girard; Patrice Fortune; Vicky Thomason; and Kathleen Raker.

2. The name of the real party in interest represented by me is:

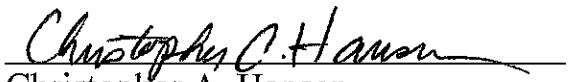
Same as above.

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

None.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

American Civil Liberties Union Foundation (Christopher A. Hansen; Sandra S. Park; Lenora M. Lapidus; Aden Fine); Public Patent Foundation (PUBPAT), Benjamin N. Cardozo School of Law (Daniel B. Ravicher; Sabrina Y. Hassan).



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STATEMENT OF RELATED CASES

Pursuant to Federal Circuit Rule 47.5, counsel for Appellees provide as follows:

(a) There have been no previous appeals in this case.

(b) They are aware of no other case that will be directly affected by the Court's decision in this case.

JURISDICTIONAL STATEMENT

The district court had jurisdiction of this case pursuant to 28 U.S.C. § 1338(a). This is an appeal from its final judgment.

STATEMENT OF THE ISSUES

1. Do Plaintiffs-Appellees – who include organizations representing over 150,000 physicians, researchers, clinicians, and other medical professionals who routinely sequence and analyze human genes, but cannot work with the patented genes, as well as those who seek to utilize those professionals – have standing to challenge the patent claims?

2. Is isolated human DNA patentable subject matter under 35 U.S.C. § 101, which prohibits patenting of laws of nature, natural phenomena, and products of nature?

3. Are unspecified methods of "comparing" human DNA sequences patentable subject matter under 35 U.S.C. § 101, which prohibits patenting of laws of nature, natural phenomena, products of nature, and abstract ideas?

4. Do the patent claims violate the First Amendment?

STATEMENT OF THE CASE

Certain mutations in the two human genes at issue in this case, BRCA1 and BRCA2, are associated with an increased risk of breast and ovarian cancer. (A146.) Many patients want to find out if they have those

mutations before making potentially life-altering medical decisions. (A147; A2727-30.) Defendant-Appellant Myriad Genetics controls patents on these genes. Myriad obtains samples of blood from patients, primarily women. Then, using methods long established in the scientific community, Myriad extracts (or "isolates") the two human genes from that blood. It sequences the genes to see if they are normal or not. Myriad sends a report back to the patient who provided the sample that in effect says: "Because the genes we isolated from your blood sample and looked at in our lab are identical to those in your body, we can say that you do [or do not] have normal BRCA1/2 genes in your body." (A1598; A1602; A2443-46; A2606; A3080; A3085; A6972-73.) Myriad's entire business is premised on the knowledge that the "isolated" genes are the same as the genes in the body. (A224-25; A7037; A7039-40.) Yet, Myriad asserts that "isolated" genes are so different that they constitute a human invention.

This case is brought by organizations composed of over 150,000 medical professionals and six nationally recognized clinicians and researchers. (A7-17, A98-103.) Plaintiffs take patient samples daily, isolate the patient's genes, and then determine if they are normal or not. (A9-17, A67; A151; *e.g.*, A1283-84; A1305-06; A1343; A1358; A1436.) The sole reason Plaintiffs do not do so for the BRCA1/2 genes is that Myriad's

aggressive and widely known assertion of its patents against those who perform such testing (including non-profit organizations and academic researchers) has caused them to fear being subject to a patent infringement threat or suit. (A31-36; A67-68; *e.g.,* A1305; A1343; A1358; A1464; A1509-11; A2674; A2708-09; A2730.)

Plaintiffs also include six patients who want the plaintiff medical professionals to look at their BRCA1/2 genes, two genetic counselors who routinely order and interpret genetic testing results, and two breast cancer and women's health organizations who routinely assist such patients. (A17-25; A68-69; A103-08.)

In some cases, the plaintiff patients have been tested but want a second opinion or access to different testing before deciding on such treatment options as surgery. (A22-23; A106; *e.g.*, A3065; A3069; A3072; A3077; A3081.) For example, Plaintiff Genae Girard was diagnosed with breast cancer in 2006 when she was 36 years old. (A22-23; A1601-3.) Ms. Girard obtained BRCA genetic testing through Myriad and was informed that she was positive for a cancer-correlated mutation on her BRCA2 gene. *Id.* Her doctors told her the positive result should be a major factor in deciding whether to get prophylactic breast and ovarian surgery. *Id.* Before making those decisions, she wanted another laboratory to perform full

sequencing on her genes to confirm that result, but learned that Myriad was the only laboratory due to its patents. *Id.* Ms. Girard would immediately seek such testing from another lab, if it were available. *Id.* Co-Plaintiff Dr. Harry Ostrer of NYU Medical Center has all the tools and expertise necessary to look at Ms. Girard's genes. (A14-15; A2932-36.) He wants to conduct this test for Ms. Girard. *Id.* There is only one thing stopping him: He is afraid that he will be sued by Myriad for patent infringement. *Id.*

In other cases, patients have sought testing from Myriad but cannot afford Myriad's price. (A20-21, 24-25; A106-08; *e.g.*, A3064; A3068; A3076; A3081; A3085.) Other labs would be willing to offer testing at significantly lower cost. (*E.g.*, A2936.) Myriad has sued or threatened every lab to ever offer clinical BRCA1/2 sequencing and forbids any lab from giving patients a second opinion. (*E.g.*, A2650; A2850-52; A2888-93; A3022-23.) This well-known, intimidating campaign of patent assertion has created a substantial chilling effect, and caused leading researchers, clinicians, and patients to abandon BRCA1/2 genetic testing despite having the complete capability and desire to do so.

The district court found that Plaintiffs[1] had standing to challenge the patent claims in this case. 669 F. Supp. 2d 365 (S.D.N.Y 2009). (A1-88.)

[1] Unless otherwise noted, "Plaintiffs" refer to all Plaintiffs-Appellees.

The court then granted Plaintiffs' motion for summary judgment (A1634-1724; A6886-6957) and denied Myriad's cross-motion (A3429-3611),[2] making extensive factual findings based on a careful analysis of the undisputed facts, citing expert declarations submitted by both parties, and holding these patent claims invalid under 35 U.S.C. § 101. 702 F. Supp. 2d 181 (S.D.N.Y. 2010). (A89-248.) Plaintiffs' declarants included two Nobel Laureates – a geneticist and an economist – and prominent oncologists, geneticists, pathologists, and social scientists. Although Myriad hints that the district court resolved disputed issues, *e.g.*, Myriad Br. 52, Myriad does not identify a single factual finding that it believes was clearly erroneous or even that was improperly resolved against it.[3]

Until this case, the question of whether isolated DNA is patentable subject matter had never been decided. *Cf. Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1293 (Fed. Cir. 2010) (Dyk, J., concurring in part). Virtually the entire medical community has joined Plaintiffs because these patent claims stifle vital clinical and research practices to the detriment of women's health

[2] Unless otherwise noted, "Myriad" refers to all Defendants-Appellants.

[3] Myriad does assert, for example, that it provided evidence that isolated DNA has "markedly different characteristics" from native DNA. Myriad Br. 52. However, the district court relied on the undisputed characteristics of isolated DNA and native DNA. (A119-39; A214-28.) Myriad's objection is not to the court's factual findings but to its legal conclusions drawn on the basis of undisputed facts.

and scientific progress. (A109-12.) The patenting of basic elements of nature and abstract ideas is contrary to the purposes of the patent system.

STATEMENT OF FACTS

A. Human Genes

Every human body contains genes that determine, in part, the structure and functions of the body. (A26; A117-19; A121-22; A2441; A2602.) Genes are created by nature. (A123; A2441; A2558; A2608; A2778; A2983.) Through naturally-occurring processes in the body, genes create proteins (or polypeptides), and those proteins do the work of the body. (A121; A131-32; A2442-43; A2602-04.) Genes vary from one individual to another. Genetic alterations can be inherited or can occur after birth, but in both instances they come about naturally. (A27; A124; A136; A2443, 2445-46; A2604-05; A2773-74; A2983.) Alterations can appear to be unimportant, correlate with an increased risk of disease or disorder ("mutations"), or have unknown significance ("variant of unknown significance"). (A30; A125; A227; A2605.) The significance of the alteration is created entirely by nature. (A136; A1304; A2445-46; A2605; A2773-74; A2983.)

It is useful for pathologists, clinical laboratory scientists, other medical professionals, and researchers to conduct genetic testing for

clinically significant alterations. (A27-28; A30-31; A127; A2443; A2606; A2648-49; A2773-74.) There are a variety of methods by which medical professionals can examine genes, including sequencing. (A123; A136-39; A282; A2443-45; A2606-08; A2648-49; A2773-74; A2982.) Thousands of medical professionals around the world sequence genes daily, and the processes by which sequencing is done are not at issue here. (A28; A136-39; A2444; A2606; A2608; A2753; A2773-74; A2813; A2934; A2936; A2977-78; A2982.)

At the end of the sequencing process, the medical professional has a long string of four letters (A, C, T, and G) that correspond to the four nucleotides (adenine, cytosine, thymine, and guanine) that make up DNA and genes. (A27; A120; A2442; A2604, 2606; A2773-74.) The structure, function, and sequence of the nucleotides are created entirely by nature. (A123; A227; A2607-08; A6965-66; A6971-72; A7024-25; A7036-37.) After sequencing, the medical professional looks to see if there are variants; *e.g.*, whether natural processes have caused there to be a C where a T would normally be. (A2445-46; A2606; A2773-74; A2983; *see also* A664 (cl.7(a) of '282 referring to A626).)

B. Hereditary Breast and Ovarian Cancer

Some mutations in the BRCA1/2 genes correlate with an increased risk of breast and/or ovarian cancer. (A146-47; A186; A588.) "Women with BRCA1 and BRCA2 mutations face up to an 85% cumulative risk of breast cancer as well as an up to 50% cumulative risk of ovarian cancer. . . . The existence of BRCA1/2 mutations is therefore an important consideration in the provision of clinical care for breast and/or ovarian cancer." (A146-47; A2645.)

C. The Patent Claims

This case is not about genetic engineering, new drugs, or new methods of sequencing. It is about the validity of certain patent claims on human genes. (A4.) Plaintiffs challenged only seven of Myriad's many BRCA-related patents. (A36; A172-73; A259-967.) These seven patents contain a total of 179 claims. (A358-59; A463-64; A566-67; A664-65; A771-72; A868-69; A965-66.) Plaintiffs challenged only fifteen claims. (A33; A172-73.) The case is thus a narrowly targeted challenge and not, as Myriad and its *amici* argue, an attack on all patents related to genetics or biotechnology.

By contrast, the claims themselves are not narrowly drawn. Myriad claims patents on (and the sole right to look at) the "isolated" BRCA1/2

genes of the more than 300 million people within the jurisdiction of U.S. patent law (*see* A175.) It claims genes whose structure and sequence it has never seen. It claims not *a* molecule, but literally hundreds of millions of molecules, most of whose sequence or composition Myriad cannot now describe. The thousands of Americans who have the technology and expertise to isolate and look at their own BRCA1/2 genes may not do so because of the patents.

1. The Composition Claims

Claims 1, 2, 5, 6, and 7 of Patent '282, claims 1, 6, and 7 of Patent '492, and claim 1 of Patent '473 are claims to the portion of human DNA known as the BRCA1/2 genes. (A173; A664-65; A868; A358.) Each begins with "An isolated DNA..." For example, claim 1 of patent '282 is:

> An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

(A173; A664.) Each of the claims defines isolated DNA according to how DNA functions in the body. *Id.*

Some of these claims are to DNA that is unaltered or wild-type.[4] (A664-65; A868.) Others are claims to DNA with certain specific

[4] This includes Claims 1, 2, 5, and 6 of Patent '282 and claim 1 of Patent '492.

alterations that occur in nature.[5] (A664; A358.) The remaining claims are to any BRCA1/2 DNA with any alterations that occur in nature, including those that neither Myriad nor any other person has ever seen.[6] (A868.)

Myriad has asserted that its claims reach DNA regardless of whether it has been separated from other genetic material. (A3451 ("extracted from a cell or chromosome"); A597 ("substantially separated from . . . many other [but not necessarily all other] human genome sequences").) (*But see* A185.) They reach DNA with introns (non-coding regions) and DNA without introns. (A220-21.) Each claim may also reach cDNA (A221-22), and "recombinant or cloned DNA isolates as well as chemically synthesized analogs or analogs synthesized using biochemical systems." Myriad Br. 7. All of the claims reach BRCA1/2 genes that are as little as 55% or 60% similar to the genes listed in the patents. (*See, e.g.*, A599.) Because polypeptides can be made by DNA with different sequences, those claims defined as DNA that codes for a polypeptide each reach multiple DNA sequences. (A173-75.)

In addition, each of the claims covers small segments of DNA. Claims 5 and 6 of Patent '282 explicitly claim any DNA having as few as 15

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[5] Claim 7 of Patent '282 and claim 1 of Patent '473.

[6] Claims 6 and 7 of Patent '492.

nucleotides that make up BRCA1. (A174; A664.) Undisputed evidence in the record establishes that this would reach much of the human genome. (A7017-21; A7228-30.) The other claims also appear to cover small segments of BRCA1/2 DNA. Myriad's principal expert noted that claims such as claim 1 of Patent '282 reach "isolated DNA coding for a BRCA..." and that "coding for" means it can be used to create mRNA and/or a polypeptide "or a fragment thereof." (A4291-92.) A fragment is defined in the patents as "at least about nine to 13 contiguous amino acids..." (A600, 25:36-37; *see, e.g.*, A696, 6:38-40 (invention includes a "portion" of the gene).)

2. The Method Claims

Claim 1 of Patent '999, claim 1 of Patent '001, claim 1 of Patent '441, claims 1 and 2 of Patent '857, and claim 20 of Patent '282 are set forth as method claims. (A175-78; A230-42; A463; A566; A771; A965; A665.) The claimed "method" involves "comparing" or "analyzing" two sequences of BRCA1/2 DNA (or RNA or cDNA) to see if they are the same or different. For example, claim 1 of Patent '441 is:

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

(A771.) In some instances, the claims additionally require the person engaged in the comparison to think that the differences have clinical significance. (*E.g.*, A965.) The language of the claims covers the comparing of sequences, not genes or molecules. (*E.g.*, A771.) They cover comparing short sequences as well as full gene sequences. (*E.g.*, A703, 19:45-47; A703, 20:10-11, 37-38; A705, 24:15-22.)

None of the claims identifies any of the comparisons as requiring "isolated" DNA, RNA or cDNA. If a medical professional compared or analyzed DNA, RNA, or cDNA sequences even without isolating them, she would infringe the claims. Thus, Myriad's argument that the process of isolating the genes somehow transforms them is irrelevant. Myriad Br. 56-57.

None of these claims identifies any of the technical steps necessary to compare or analyze. The claims do not define a single method by which one

compares sequences and encompass methods that are unpatented and even unknown by Myriad. (A230; *e.g.*, A700, 13:18 through A701, 16:10.)

Myriad's method claims cover the abstract idea of looking at DNA sequences and thinking about their significance. (A234-35.) As such, they do not constitute patentable subject matter.

3. Waiver of Other Constructions of the Claims

The construction of the claims above is identical to that asserted by Plaintiffs in the district court. Some of Myriad's *amici*, and the United States, suggest that some of the claims should be construed more narrowly and cover only cDNA. Myriad, however, never argued that any of its claims were limited to cDNA. (A6907-08.) Thus, this claim construction, and any other newly proffered constructions, have been waived. *Eli Lilly & Co. v. Aradigm Corp.*, 376 F.3d 1352, 1360 (Fed. Cir. 2004) (holding that claim construction was waived); *see also Conoco, Inc. v. Energy & Envtl. Int'l, L.C.*, 460 F.3d 1349, 1358-1359 (Fed. Cir. 2006); *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1346-47 (Fed. Cir. 2001). But under any of the proffered constructions, these claims are invalid for the reasons discussed below.

D. Isolated DNA

Myriad did not create the structure, functions, or sequence of the nucleotides that constitute the BRCA1/2 genes, the structure or function of the BRCA1/2 genes, or the significance of the sequence for breast and/or ovarian cancer risk. Nature did. (*E.g.*, A1304; A1308; A1469; A1513; A2441-46; A2558; A2606; A2608; A2939; A2983; A6965-68; A6971-72; A7024-25; A7036.)

Under Myriad's view, any naturally-occurring thing that is "isolated" from its natural environment becomes patentable because once separated, it is definitionally different in structure and function. Myriad Br. 33-50. Thus, "isolated" gold, *i.e.* gold removed from the streambed, would become patentable because it is structurally different – no longer integrated into the gravel or sand – and functionally different – potentially useful for jewelry-making. But even if those distinctions are true, the "isolated" gold is still gold and a natural phenomenon. Myriad also argues that "isolated DNA" cannot perform some of the functions of DNA. But "isolated" gold can no longer comprise the sediment that influences the stream's channel, flow, and ecology once it leaves the stream. It is still gold, and if redeposited into the water, it will settle into the streambed and perform its original functions. Similarly, "isolated" DNA remains DNA even after it has undergone

standard processes of isolation – it has simply been removed from its natural environment. It embodies the same genetic information. If reinserted into the cell, "isolated" DNA could function again. (A6969-72.) While a new and improved goldpan used to extract the gold from the streambed, like a new type of DNA analyzing machine, could be patented, the extracted gold or isolated DNA cannot.

Myriad repeatedly argues in a conclusory fashion that "isolated" DNA is "structurally and functionally distinct from any substance found in the human body – indeed all of nature." Myriad Br. 8-9. The only characteristic Myriad points to for this proposition is that isolated DNA can be used "as molecular tools (*e.g.*, primers and probes)," but Myriad does not cite to supporting facts.[7] Myriad Br. 9.

Myriad argues that its claims reach, among other things, full length BRCA genes. However, entire genes cannot be used as primers. *Compare* A4341 (primer is 15-30 nucleotides) *with* A4340 (BRCA1 cDNA is 5914 nucleotides). (*See also* A129, n. 14; A223-24; A6973-74; A7022.) None of

[7] For example, a string-cite on page 35 includes two citations to Myriad's brief or Statement of Material Facts and twelve citations to district court *amicus* briefs. None of these is, of course, evidence on which Myriad can rely for its factual assertions. Even when Myriad cites to declarations, they are often conclusory and without factual support (*e.g.*, A4540), and others consist of pure legal analysis (*e.g.*, A4413) ("plaintiffs misinterpret the case law . . .").

the claims at issue in this case is limited to the use of BRCA1/2 as a primer. Myriad has obtained such patents. Claim 16 of Patent '282 is one such claim and is not challenged here. (A665.) Similarly, isolated DNA cannot be used as a probe without further alteration by adding a "detectable, *e.g.*, fluorescent or radioactive, marker."[8] (A4323; A6973-6974; A7021.) The challenged claims do not require that additional alteration, though Myriad has obtained patents on DNA as probes. Claim 6 of '473 is one example and not challenged here. (A359.) The Court is thus not being asked to rule on the patentability of DNA as either primers or probes.

Although Myriad discusses no other facts that distinguish isolated DNA from DNA, it conclusorily asserts that the structure of the isolated DNA is different from DNA in the body. *See, e.g.*, Myriad Br. 35. Myriad appears to argue simply that DNA outside the body is structurally different because it is not surrounded by the body. The district court found that this argument confuses parts of the body in which DNA is often packaged (*e.g.*, chromatin) with DNA itself; any differences between DNA *in* a cell and DNA *isolated from* a cell are differences between chromatin and DNA. (A220; A6963-68.) Asserting that removing DNA renders it structurally

[8] Probes are also generally smaller than the entire BRCA1/2 genes. (A129, n.13; A223-24.)

different is the equivalent of asserting that "isolating" gold or a leaf from a tree makes it different.

DNA is a chemical, as is "isolated" DNA; however, to suggest that they are chemicals like any other is simply incorrect. (*See generally* A215-28.) DNA is foremost an informational molecule. (A7029.) No other known molecule has the ability to store vast quantities of information and to transmit that information through self-replication. (A2441; A6968; A7019-21; A7029-7032.) The information is stored through the sequence of nucleotide bases within the DNA strand. (A2442-43; A2602; A2604; A6971-73; A7024; A7029.) The order of the nucleotides is of prime importance, because this order contains the genetic code, the information that directs human cells to grow, to differentiate into specialized structures, to divide, and to respond to environmental changes. (A7031-32.) It is this instructional capacity of DNA that renders it both a product of nature and a law of nature. (A215-28.)

E. Myriad's Predictions of Doom

Myriad and its *amici* seek to cast this case as signaling the demise of advances in health and even the entire patent system.[9] The district court

[9] *See, e.g., Amicus* Br. Boston Patent Law Association 19 ("The BPLA views this case … as an attack on the patent system itself."); *Amici* Br.

properly rejected these apocalyptic and hotly disputed predictions. (A216, n. 51.) Plaintiffs challenge only a small number of patent claims on the basis of long-standing doctrine. Plaintiffs do not challenge the patentability of new drugs, devices, or sequencing methods.

The district court also noted the significant evidence, albeit partially disputed, that these patent claims were not necessary for the identification of the BRCA1 and BRCA2 genes (A2560-61; A2674-75; A2702-4; A7059-66), and that the patent claims were not necessary to induce clinicians to sequence and analyze the BRCA1 and BRCA2 genes for patients. (A2753; A2774-76; A2813-14; A2828; A2935-36; A2980; A3035-36.)

The evidence also demonstrated that these patent claims have had a negative impact on both breast and ovarian cancer research and clinical practice. (A153; A2448-49; A2646-49; A2652-53; A2674-75; A2775-78; A2937-39; A2980-83; A3022-23; A3037-39; A3068; A3080; A3085.) The patent claims permit Myriad to preclude all research into genes correlated with an increased risk of breast and/or ovarian cancer and thus deterred at least some research into this area critical for women's health. *Id.* (A2672-74; A7271-73.) The patent claims have also prevented other labs from looking at these genes. (*See, e.g.,* A2650; A2753; A2775; A2813; A2828;

Genomic Health, *et al.* 4 (new advances likely to "change the face of medicine" will cease).

A2850-51; A2888-91; A2934-36; A2978-81; A3022; A3035-36.) In some instances, the effect has been devastating, as Myriad utilized a test for years that failed to identify all variants of clinical significance and advised women that no deleterious mutations were found, when other methods existed that would have found additional mutations. (*See* A39; A2649-50; A3068; A3080; A3085.) Myriad does not share the data gathered as a result of its patents with other researchers, which means that advances in understanding the significance of variants that could save lives have been slowed. (A2448-49; A2646-48; A2776-77; A2938-39; A2981-82; A3068-69; A3023.)

Clinical care has also been harmed. First, many women cannot get tested because they cannot afford Myriad's prices. (A2851; A2936; A3022; A3024-25; A3036-40; A3064; A3076; A3081; A3085-86.) The patents preclude others from providing testing even where they could do so for a lower price or for free to the indigent. (A149; A151.) Myriad has contracts with only half of the state Medicaid insurance programs. (A150; A4703-04.) Only 130 million of America's 308 million people can receive insurance coverage for their testing. *Id.* Second, patients cannot get a second opinion to confirm the accuracy or the meaning of the results. (A160; A2652; A2937-38; A3065; A3072-73; A3077.) Other diagnosticians cannot evaluate or ensure the quality of the testing done by Myriad by attempting to

replicate it. (A2777; A2937-38; A2982-83; A3037-38.) Third, Myriad refuses to do some critical tests. (A2777-78.) Finally, labs have been deterred from developing new tests. (A2773-74; A2979-80.)

None of this is surprising. Nobel Prize-winning economist Joseph Stiglitz explained why patenting of basic elements of nature has the negative effects described above. (A7055-66.) The Secretary's Advisory Committee of the U.S. Department of Health and Human Services, consisting of nationally recognized, independent, genetic experts, largely agreed with all of Plaintiffs' contentions, including that gene patenting is not necessary to provide adequate incentives and can cause harmful results. Sec'y's Advisory Comm. on Genetics, Health, and Soc'y, *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* (2010), *available at* http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf.

> The Committee found that the prospect of patent protection of a genetic research discovery does not play a significant role in motivating scientists to conduct genetic research. . . . Thus, patents are not needed for much of U.S. basic genetic research to occur. . . . Importantly, the Committee found that patents can also harm genetic research. . . . Where patents and licensing practices have created a sole provider of a genetic test, patient access to those tests has suffered in a number of ways.

Id. at 1-3.

The Court need not and should not resolve this case on the basis of Myriad's hysterical assertions that this case will end biotechnological development. But to the extent Myriad relies on those assertions to influence the Court's legal holdings, the Court should also consider Plaintiffs' extensive evidence that the patents were unnecessary and have been harmful to women's health and scientific progress.

SUMMARY OF ARGUMENT

I. Plaintiffs have standing to bring this case. Myriad does not dispute that Plaintiffs are more than meaningfully prepared to undertake activities that could infringe the patent claims-in-suit but nonetheless argues that there is no "controversy." Myriad Br. 18-19. To the contrary, this case is about real women faced with risk of hereditary cancer who wish to receive screening of their own genes and about real doctors who have all the capability, machinery, training, and desire to read these patients' genes and give them knowledge about their own predispositions for cancer. All legitimately fear, based on Myriad's conduct, that they will be sued for patent infringement if they do so. It is that fear alone that has forced them to abandon activity they fully believe they have the right to undertake.

II. The nine challenged composition claims on "isolated DNA" are invalid under section 101 because they cover laws of nature, natural

phenomena, and products of nature. "Isolated DNA" is DNA that has simply been isolated from other cellular components, and the information it embodies – the nucleotide sequence that contains the instructions for the functioning of the body's cells – remains the same. Thus, isolated DNA has neither a "distinctive name, character, and use," or "markedly different characteristics from any found in nature"; it is "nature's handiwork." *Diamond v. Chakrabarty*, 447 U.S. 303, 309-10 (1980); *see Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948). Because these claims cover the isolated BRCA1/2 DNA of all people, these patents preempt scientific work on these genes and access to any person's genetic information.

III. The six challenged method claims are invalid under section 101 because they cover laws of nature and abstract ideas. The claims do not delineate specific methods for testing genes but instead cover the mental process of comparing genetic *sequences* – for example, a sequence from a human sample with the reference sequence – which can be accomplished without any "machine or transformation."

IV. The claims all violate the First Amendment, constituting patents on thought and knowledge.

STANDARD OF REVIEW

This appeal is from a denial of a motion to dismiss on the ground of standing. While Myriad is correct that this Court reviews a district court's denial of a motion to dismiss for lack of subject matter jurisdiction *de novo*, this Court reviews the underlying related factual findings for clear error. *Hewlett-Packard Co. v. Acceleron LLC*, 587 F.3d 1358, 1361 (Fed. Cir. 2009). Thus, the factual findings of the district court in its opinion on standing must be taken as true, and Myriad has not argued that any were made in clear error.

This case is also an appeal from the granting and denial of summary judgment which is reviewed *de novo*.

ARGUMENT

I. PLAINTIFFS HAVE STANDING.

A. Plaintiffs Have Standing Under *MedImmune*'s "All The Circumstances" Analysis, Which Has No Bright Line Rules And Is To Be Guided By The Purpose Of The Declaratory Judgment Act.

All parties agree that the Supreme Court abrogated what had been the prevailing standard set by this Court for standing in patent Declaratory Judgment ("DJ") cases. *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007). In *MedImmune*, the Supreme Court declared that the correct analysis, as in all other Article III cases, "'is whether the facts alleged, under

all the circumstances, show that there is a substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.'" *Id.* at 127 (citation omitted); *see also Holder v. Humanitarian Law Project*, 130 S. Ct. 2705, 2717 (2010) (citing *MedImmune* in a non-patent case for the proposition that plaintiffs need not await actual enforcement before bringing a lawsuit or to have a credible fear of enforcement). *MedImmune* states that bright line rules and steadfast requirements have no place in a DJ standing analysis. *Prasco, LLC v. Medicis Pharm. Corp.*, 537 F.3d 1329, 1336 (Fed. Cir. 2008).

This Court has recognized that the *MedImmune* analysis is "more lenient" than the reasonable apprehension of suit test and has resulted in a greater "ease of achieving declaratory judgment jurisdiction." *Micron Tech., Inc. v. Mosaid Techs., Inc.*, 518 F.3d 897, 902 (Fed. Cir. 2008). Myriad correctly points out that "a lowered bar does not mean no bar at all." Myriad Br. 19. *MedImmune* explained that a DJ plaintiff must seek more than "'an opinion advising what the law would be upon a hypothetical state of facts.'" *Hewlett-Packard Co. v. Acceleron LLC*, 587 F.3d 1358, 1362 (Fed. Cir. 2009) (quoting *MedImmune*, 549 U.S. at 127). This Court has also said that mere awareness of a patent is insufficient. *SanDisk Corp. v.*

STMicroelectronics, Inc., 480 F.3d 1372, 1380-81 (Fed. Cir. 2007). DJ standing, therefore, requires something more than mere awareness of a patent, but less than a reasonable apprehension of suit.

Where Plaintiffs (and the lower court) disagree with Myriad is how to apply *MedImmune*. While it pays lip service to the fact that the reasonable apprehension of suit test has been abrogated, Myriad now asks this Court to again adopt certain standing requirements. That request should be denied.

Viewing all the circumstances in this case – including all the facts regarding the ability of Plaintiffs to immediately undertake potentially infringing activity and Myriad's affirmative acts of asserting the patents-in-suit – while keeping in mind the purpose of the DJ Act, leads to the unmistakable conclusion that DJ jurisdiction exists. This Court has said repeatedly that the purpose of the DJ Act is to avoid forcing parties to make "an *in terrorem* choice between the incurrence of a growing potential liability for patent infringement and abandonment of their enterprises." *Micron Tech.*, 518 F.3d at 902 (citations omitted). "When these objectives are served, dismissal is rarely proper." *Id.*; *see also Cat Tech LLC v. Tubemaster, Inc.*, 528 F.3d 871, 883-84 (Fed. Cir. 2008). Myriad's motion to dismiss was, as a consequence, properly denied.

1. Plaintiffs Are Meaningfully Prepared To Immediately Undertake Potentially Infringing Activity.

"[A] party need not have engaged in the actual manufacture or sale of a potentially infringing product to obtain a declaratory judgment . . . ." *Cat Tech*, 528 F.3d at 881. Rather, "a showing of 'meaningful preparation'" to undertake potentially infringing activity is sufficient. *Id.* (*quoting Arrowhead Indus. Water, Inc. v. Ecolochem, Inc.*, 846 F.2d 731, 736 (Fed. Cir. 1988)). As the district court found, each of the Plaintiffs has taken more than sufficient steps to satisfy the "meaningful preparation" standard. (A64-71.) If the Myriad patents were invalidated today, Plaintiffs could – and would – begin *BRCA*-related activity immediately because they all have the capability and desire to do so. (*See, e.g.*, A1283 ("Our lab could begin sequencing BRCA1 and BRCA2 genes, and analyzing them to determine if there are variants and if those variants have clinical significance virtually immediately.")) The only reason Plaintiffs are not undertaking these activities is their fear of patent infringement allegations by Myriad. (*E.g.*, A1284.)

It is telling that Myriad does not now dispute the meaningful preparation of each Plaintiff. Nor could it, as that legal conclusion was fully supported by facts in the record that were adopted by the district court without clear error. For example, the medical professional Plaintiffs have

the immediate ability and desire to provide BRCA screening, as they already perform screening for countless other genetic sequences and have all the necessary tools, machinery, training and personnel to do so. (A7-17; A2775-77; A2852; A2893; A2936-37; A2939; A2980-81.)[10] The genetic counselor Plaintiffs similarly have the immediate ability and desire to begin assisting patients in seeking, receiving, and interpreting BRCA diagnostic testing, all of which could constitute inducement of infringement. (A3024-25; A3036-40.)

The patient Plaintiffs, in turn, have the immediate ability and desire to receive that screening, whether it be to confirm test results received from Myriad, to obtain further analysis of a mutation reported by Myriad to have "uncertain significance," or to get a test that they cannot obtain through Myriad. (A20-25; A1594-95; A1598-99; A1602-3; A1606-7; A1610-11; A1614-17.) If the patient Plaintiffs were to utilize the services of the medical professional Plaintiffs, knowing that such could constitute direct infringement of Myriad's patents, these women could be liable for inducing infringement of those patents. *See Symantec Corp. v. Computer Assocs.*

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[10] The organizational Plaintiffs representing the medical professionals likewise have standing under the "doctrine of associational standing." *United Food & Commer. Workers Union Local 751 v. Brown Group*, 517 U.S. 544, 552-53 (1996) (citation omitted). (A65; A2751; A2753-54; A2770; A2775-77; A2810; A2813-14; A2825; A2828.)

Int'l, Inc., 522 F.3d 1279, 1292 (Fed. Cir. 2008). Given that potential inducement of infringement could occur by asking a medical professional to do the analysis for them and providing a genetic sample, the patient Plaintiffs are more than "meaningfully prepared" to induce infringing activity.

The breast cancer and women's health advocacy organization Plaintiffs have the immediate ability and desire to begin assisting patients in seeking, receiving, and interpreting BRCA diagnostic testing, all of which could constitute inducement of infringement. They have the capability and desire to immediately (i) encourage researchers and clinicians to perform BRCA-related activities, including BRCA genetic testing and research, and/or (ii) refer patients to laboratories other than or in addition to Myriad, including those run by other Plaintiffs, to perform clinical BRCA genetic testing. (A17-20; A1585-87; A1589-92); 35 U.S.C. § 271(b) ("Whoever actively induces infringement of a patent shall be liable as an infringer."); *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365 (Fed. Cir. 2004) (holding that disseminating medical information and a directory of medical service providers was sufficient to trigger liability for inducing infringement).

In the few cases where this Court has not found an actual controversy

post-*MedImmune* based on circumstances related to the DJ plaintiff, (i) the DJ plaintiff only sued for a DJ of non-infringement, not invalidity, *Prasco*, 537 F.3d at 1342, n.12; (ii) the DJ plaintiff could not undertake the potentially infringing activity for at least six to eight years from when the complaint was filed, *Benitec Austl., Ltd. v. Nucleonics, Inc.*, 495 F.3d 1340, 1346 (Fed. Cir. 2007); and (iii) the DJ plaintiff conceded that another patent not in the suit prevented it from undertaking potentially infringing activities for at least another eight months, *Janssen Pharmaceutica, N.V. v. Apotex, Inc.*, 540 F.3d 1353, 1357, 1360 (Fed. Cir. 2008). None of these circumstances exists here. Plaintiffs have sued for a DJ of invalidity of Myriad's patent claims, and the district court found as a matter of fact that Plaintiffs could undertake potentially infringing activity immediately upon a favorable ruling.

2. Myriad's Affirmative Acts Support A Finding Of DJ Standing.

The district court found, without any clear error, numerous facts relating to affirmative acts taken by Myriad with respect to the patents-in-suit to support Plaintiffs' standing. First, the record establishes that Myriad has sued or threatened every known lab to ever offer clinical BRCA testing, including the University of Pennsylvania lab directed and operated by two of the Plaintiffs, Drs. Kazazian and Ganguly. (A35-36, A61-62; A2850-52;

A2888-93; A2907-17.) "Prior litigious conduct [against third parties] is one circumstance to be considered in assessing whether the totality of circumstances creates an actual controversy." *Prasco*, 537 F.3d at 1341; *see also Green Edge Enters., LLC v. Rubber Mulch Etc., LLC*, 620 F.3d 1287, 1301 (Fed. Cir. 2010) ("Under *MedImmune*, a threat of suit in the form of a cease and desist letter, in addition to other litigious conduct, is sufficient to confer declaratory judgment jurisdiction."); *Innovative Therapies, Inc. v. Kinetic Concepts, Inc.*, 599 F.3d 1377, 1382 (Fed. Cir. 2010) (pre-complaint history of litigation should be considered). Thus, Myriad's previous lawsuits enforcing these patents against others weigh in favor of finding DJ jurisdiction for Plaintiffs, not just with respect to Drs. Kazazian and Ganguly.

The district court also found that Myriad has systematically and continuously sent threatening patent license letters and demanded license agreements from any academic or other institution wishing to perform BRCA diagnostic testing, including the NYU lab directed by plaintiff Dr. Harry Ostrer. (A33-34 (finding that Myriad had asserted its patents through licensing demand letters to the National Cancer Institute, Georgetown University and Yale DNA Diagnostics Lab); A2964-74.) Myriad made a face-to-face threat of patent assertion against Dr. Kazazian. (A31-32;

A2850-51.) Myriad also asserted its patent rights with plaintiff Ellen Matloff when she asked whether the Yale lab could offer a BRCA test not offered by Myriad at the time. (A34-35; A1552-53.)

Myriad's aggressive patent assertion against any clinical *BRCA*-related activity has been well-documented in publications. (A36 (citing comprehensive study that found that nine laboratories had stopped performing BRCA testing as a result of Myriad's patent assertion); A2672-75; *see also* A2705-10; *cf.* A7128 (estimating chilling effect of BRCA1/2 patents on research).) As a result of Myriad's well-known aggressive patent assertion, no other laboratory in the nation is currently offering clinical full sequencing of the BRCA genes.[11] The absence of recent patent infringement lawsuits or threatening letters underscores Myriad's success at chilling others' activities, rather than demonstrating a lack of controversy.

Plaintiffs' awareness of Myriad's systematic assertion against others supports a finding of DJ jurisdiction. *See Green Edge Enters.*, 620 F.3d at 1301; *Micron Tech.*, 518 F.3d at 899, 901; *cf. Innovative Therapies*, 599 F.3d at 1382. It is the effect of a patentee's acts that matters, "even though

[11] In the district court, Myriad pointed to licenses it has contracted with two labs that are allowed to perform testing for specific BRCA mutations. (A3666.) These labs cannot provide patients with full sequencing of the genes in the first instance or confirm a negative result received through Myriad. (A7273.)

the patentee had not threatened the declaratory judgment plaintiff with an infringement suit." *Sony Elecs., Inc. v. Guardian Media Techs., Ltd.*, 497 F.3d 1271, 1284 (Fed. Cir. 2007). The key is what is objectively reasonable to infer from Myriad's conduct. *Hewlett-Packard*, 587 F.3d at 1363. Plaintiffs here must either proceed with the BRCA-related activity that they have the ability and desire to undertake and risk patent infringement liability, or continue to refrain from such activity despite believing these patents are invalid. This is precisely the "dilemma" that the Declaratory Judgment Act was meant to address, and DJ jurisdiction exists in this case. *MedImmune*, 549 U.S. at 129; *see Humanitarian Law Project*, 130 S. Ct. at 2717; *SanDisk,* 480 F.3d at 1379-80. (A63-64.)

Myriad cites *SanDisk* for the proposition that some affirmative act by Myriad against Plaintiffs themselves is required. Myriad Br. 20. Yet, *SanDisk* explicitly stated it was *not* setting forth the limits of DJ standing. 480 F.3d at 1381 ("We need not define the outer boundaries of declaratory judgment jurisdiction, which will depend on the application of the principles of declaratory judgment jurisdiction to the facts and circumstances of each case."). *SanDisk* comports with a flexible approach to application of DJ standing law, holding that DJ jurisdiction "generally will not arise" based "merely" on learning of the existence of a patent "without some affirmative

act by the patentee." *Id.* at 1380-81. Where, as here, there are facts and circumstances beyond "merely learning of a patent" that support a finding of an actual controversy, *SanDisk* does not mandate an affirmative act by the patentee against each plaintiff.

Myriad argues that a lapse in time following its acts directed specifically at Plaintiffs negates the relevance of those acts. However, this Court held in *Micron Tech* that a lapse in time does not defeat DJ standing if the patentee continued to assert its patent against others during that period, 518 F.3d at 901, which is precisely the case here. Myriad has not ceased asserting its patents in a broad and widely-known fashion since the day they were issued. Thus, the lawsuit Myriad filed to stop the work of Drs. Kazazian and Ganguly continues to have a chilling effect today. Strikingly, Myriad has refused to enter into any covenant-not-to-sue despite Plaintiffs' two requests.[12] Indeed, Myriad reserves the right in its brief to sue Plaintiffs

[12] Plaintiffs have written twice to Myriad during the district court and these appellate proceedings, seeking a straight-forward answer as to whether Myriad would sue Plaintiffs for patent infringement if they undertook the specific activities they have repeatedly expressed a capacity and desire to undertake. (A1256-58; A3364; Pls.-Appellees' Opp. to Defs.-Appellants' Mot. for a 60-Day Extension 2.) Plaintiffs concede that if Myriad entered a covenant-not-to-sue, standing in this case would immediately cease to exist. Rather than clarify its position, Myriad has chosen instead to wholly retain its right to sue Plaintiffs, while also contesting their standing. It would be inequitable to encourage Myriad's gamesmanship. These letters – and Myriad's failure to provide Plaintiffs with clarity – are circumstances that

for patent infringement in the future. Myriad Br. 29 ("Myriad . . . *may* never sue plaintiffs at all" (emphasis added)). Absent the entry of a blanket covenant-not-to-sue, this Court has never reversed a district court's finding that a DJ plaintiff had standing.[13] This case does not justify a departure from the Court's established practice.

3. Myriad's Attempt To Impose Rigid Standing Requirements Must Be Rejected.

In its attempt to avoid the impact of *MedImmune*'s all the circumstances test, Myriad asserts that several circumstances must be met for standing to exist, none of which have any merit. Myriad argues that a DJ defendant must have taken some affirmative action relevant to the plaintiff and shown an intention to litigate against the plaintiffs. To the contrary, any act by the patentee relating to either the patents in suit *or* the plaintiffs can support DJ standing. *See SanDisk*, 480 F.3d at 1381; *Prasco*, 537 F.3d at 1341. For example, that a patentee "pursues a systematic licensing and litigation strategy" supports a finding of an actual controversy, even if no

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weigh in favor of standing. *Prasco*, 537 F.3d at 1341 ("'[A] patentee's refusal to give assurances that it will not enforce its patent is relevant to the determination. . . .'").

[13] *Compare Dow Jones & Co. v. Ablaise Ltd.*, 606 F.3d 1338 (Fed. Cir. 2010) (reversing denial of motion to dismiss for lack of standing because a complete covenant-not-to-sue had been entered) *with Teva Pharms. USA, Inc. v. Eisai Co.*, 620 F.3d 1341 (Fed. Cir. 2010) (reversing dismissal even where a blanket covenant-not-to-sue was entered).

litigation has yet been threatened against a plaintiff. *Micron Tech.*, 518 F.3d at 899, 901. Similarly, *Hewlett-Packard v. Acceleron*, relied on by Myriad, is limited to situations involving "a communication from a patent owner to another party, merely identifying its patent and the other party's product line, *without more*." Myriad Br. 21-22 (citing 587 F.3d at 1362) (emphasis added). As discussed above, the district court found many other circumstances beyond communications between Myriad and Plaintiffs that support standing here.

Myriad then cites *Prasco* for the proposition that because "plaintiffs have no 'current products' or methods," the parties cannot have any adverse legal interest. Myriad Br. 20. That assertion is contrary to the clear findings of fact made by the district court that Plaintiffs already have all the machinery, expertise, staff, and other capacity necessary to begin immediately undertaking potentially infringing activity. It also fails to recognize that *Prasco* spoke only to DJ for non-infringement, not DJ for invalidity. 537 F.3d at 1342, n.12. Thus, *Prasco* is inapposite, because Plaintiffs here seek a DJ of invalidity, *not* a DJ of non-infringement.

Myriad's "requirements" directly conflict with the Supreme Court's endorsement of flexible case-by-case standards. *Bilski v. Kappos*, 130 S. Ct. 3218, 3259 (2010) (rejecting "machine-or-transformation" as the sole test

for patent eligibility); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 415 (2007) (rejecting the "rigid" *TSM* requirement for obviousness); *eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. 388, 393 (2006) (reversing this Court's "general rule" regarding permanent injunctions).

In several cases that Myriad conveniently ignores, this Court has recognized that a flexible case-by-case analysis of DJ standing is the correct approach. *See, e.g., Revolution Eyewear, Inc. v. Aspex Eyewear, Inc.*, 556 F.3d 1294, 1297 (Fed. Cir. 2009) ("The [Supreme] Court [in *MedImmune*] held that all of the circumstances must be considered for each particular case."); *Cat Tech,* 528 F.3d at 879 ("There is, however, no facile, all-purpose standard to police the line between [DJ] actions which satisfy the case or controversy requirement and those that do not. . . . [T]he analysis must be calibrated to the particular facts of each case. . . ."); *Caraco Pharm. Labs., Ltd. v. Forest Labs., Inc.*, 527 F.3d 1278, 1290-91 (Fed. Cir. 2008); *Sony Elecs.*, 497 F.3d at 1284 ("[O]ur post-*MedImmune* decisions, while not attempting to define the outer boundaries of declaratory judgment jurisdiction, have made clear that a declaratory judgment plaintiff does not need to establish a reasonable apprehension of a lawsuit in order to establish that there is an actual controversy between the parties."); *Teva Pharms. USA, Inc. v. Novartis Pharms. Corp.*, 482 F.3d 1330, 1339 (Fed. Cir. 2007)

("[W]e follow *MedImmune*'s teaching to look at 'all the circumstances. . . .'").

The district court here followed these principles. Considering all of the circumstances, it correctly held that "Plaintiffs' allegations establish the existence of sufficient 'affirmative acts' by the Defendants for purposes of declaratory judgment jurisdiction." (A63.)

B. If One Plaintiff Has Standing, The Court Need Not Decide If All Plaintiffs Have Standing.

Although each Plaintiff has standing to bring this case, this declaratory judgment action can move forward based on the standing of just one Plaintiff. *Horne v. Flores*, 129 S. Ct. 2579, 2592-93 (2009). Thus, it is sufficient to affirm the district court's denial of Myriad's motion with respect to all of the Plaintiffs if this Court finds that one Plaintiff has standing.

II. THE BRCA1/2 ISOLATED DNA CLAIMS ARE INVALID UNDER SECTION 101 BECAUSE THEY COVER LAWS OF NATURE, NATURAL PHENOMENA, PHYSICAL PHENOMENA, AND PRODUCTS OF NATURE.

The patenting of human genes violates long-established Supreme Court precedent that prohibits the patenting of laws of nature, natural phenomena, products of nature, and abstract ideas. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). "[T]hese exceptions have defined

the reach of the statute as a matter of statutory *stare decisis* going back 150 years." *Bilski*, 130 S. Ct. at 3225 (citing *Le Roy v. Tatham*, 55 U.S. 156, 174-75 (1853)). The Court has explained repeatedly that "[s]uch discoveries are 'manifestations of . . . nature, free to all men and reserved exclusively to none.'" *Chakrabarty*, 447 U.S. at 309 (quoting *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948)).

Crossing the section 101 threshold of subject matter eligibility does not depend on utility, novelty, or the need to recoup investment. "The obligation to determine what type of discovery is sought to be patented must precede the determination of whether that discovery is, in fact, new or obvious." *Parker v. Flook*, 437 U.S. 584, 593 (1978); *see also Diamond v. Diehr*, 450 U.S. 175, 189-90 (1981); U.S. Br. 34-36. *Bilski* did not intertwine questions of novelty and patent-eligible subject matter as Myriad asserts. Myriad Br. 40. Nothing in *Bilski* overturns *Flook* and *Diehr*; instead, the opinion resoundingly re-affirms their reasoning and holdings. *Bilski*, 130 S. Ct. at 3229-31.

Moreover, the Court has explained that section 101 is not satisfied just because something can be called a "composition of matter" or "process." "The rule that the discovery of a law of nature cannot be patented rests, not on the notion that natural phenomena are not processes, but rather on the

more fundamental understanding that they are not the kind of 'discoveries' the statute was enacted to protect." *Flook*, 437 U.S. at 593. *See also Bilski,* 130 S. Ct. at 3226 ("Concerns about attempts to call any form of human activity a 'process' can be met by making sure the claim meets the requirements of § 101."). *See also* U.S. Br. 27-29. Section 101 scrutiny is not a semantics exercise, as Myriad suggests. Myriad Br. 31, 61.

A. Isolated DNA Is Not Patentable Subject Matter Under Supreme Court Precedent.

Once Supreme Court precedent is applied to the nine challenged patent claims over "isolated DNA," they do not survive section 101 because they cover natural phenomena and products of nature. Contrary to Myriad's assertion, the Court has described "products of nature" as an exception, along with laws of nature, physical phenomena, natural phenomena, and abstract ideas. *Diehr*, 450 U.S. at 185; *Chakrabarty*, 447 U.S. at 309. "'[T]he relevant distinction' for purposes of § 101 is not 'between living and inanimate things, but between products of nature, whether living or not, and human-made inventions.'" *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*, 534 U.S. 124, 130, 134 (2001) (quoting *Chakrabarty*, 447 U.S. at 313). *See also Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928) ("Manifestly he did not create pure tungsten, nor did he create its characteristics. These were created by nature and on that fact finding the

reasoning as to the validity of the product claims will be based."); *In re Marden* (Marden II), 47 F.2d 958, 959 (C.C.P.A. 1931) ("[P]ure vanadium is not new in the inventive sense, and, it being a product of nature, no one is entitled to a monopoly of the same."); *In re Marden* (Marden I), 47 F.2d 957, 957 (C.C.P.A. 1931) ("Uranium is a product of nature, and the appellant is not entitled to a patent on the same, or upon any of the inherent natural qualities of that metal.").

Three Supreme Court cases are fundamental to the section 101 analysis. Most recently, the Court recognized the patentability of a genetically-engineered bacterium capable of breaking down crude oil in *Chakrabarty*. The Court considered whether the claimed product had "a distinctive name, character [and] use" and "markedly different characteristics from any found in nature." 447 U.S. at 309-10. Comparing the genetically-engineered *Chakrabarty* bacterium with the unpatentable combination of bacteria in *Funk Brothers*, the Court concluded that the former has "markedly different characteristics from any found in nature" and that its "discovery is not nature's handiwork." *Id.* at 310.[14]

[14] Myriad dismisses the district court's use of "markedly different characteristics" in its analysis, even though this phrase comes directly from the most recent Supreme Court case interpreting whether a composition falls within a section 101 exception.

> "The combination of species produces no new bacteria, no change in the six species of bacteria, and no enlargement of the range of their utility. Each species has the same effect it always had. The bacteria perform in their natural way. Their use in combination does not improve in any way their natural functioning. They serve the ends nature originally provided and act quite independently of any effort of the patentee."
>
> Here, by contrast, the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly it is patentable subject matter under section 101.

Id. (quoting *Funk Bros.*, 333 U.S. at 131). The "isolated" *Funk Brothers* bacteria, on the other hand, could not be patented even though they did not exist together naturally, and even though their aggregate nitrogen-fixing capability had been newly identified and had commercial utility. 333 U.S. at 130-31. The patent holder did "not create a state of inhibition or of non-inhibition in the bacteria. Their qualities are the work of nature. Those qualities are of course not patentable." *Id.* at 130.[15]

The Court's analysis in these cases logically extended from *American Fruit Growers, Inc. v. Brogdex Co.*, rejecting the patenting of a fruit that had been treated with mold-resistant borax. 283 U.S. 1 (1931). Although the "complete article is not found in nature," and despite the "treatment, labor

[15] Myriad erroneously tries to reclassify *Funk Brothers* as a section 103 case, Myriad Br. 43, when *Bilski*, 130 S. Ct. at 3225, and *Chakrabarty*, 447 U.S. at 309-10, cite to it as defining the 101 exceptions.

and manipulation" that produced the fruit, the Court held that it did not become an "article of manufacture" unless it "possesses a new or distinctive form, quality, or property" distinct from nature. *Id.* at 11-12.

These seminal cases prohibit the patenting of a product of nature even if it has undergone some degree of change, does not appear naturally in that form in nature, and is novel or highly useful. They also lay out the key clues to applying section 101: whether the product has a distinctive name, character and use, *Chakrabarty*, 447 U.S. at 309-10; whether it has markedly different characteristics from any found in nature, *id.* at 310; and whether the patent is on "nature's handiwork" or covers qualities that are the work of nature. *Id.*; *Funk Bros.*, 333 U.S. at 130.

Just as the fruit and the aggregation of bacteria strains were natural phenomena in those cases, so too are the genes in this case. Myriad apparently concedes that "native" DNA is a product of nature and not patentable but argues "isolated" DNA is different. The patent claims themselves define isolated DNA according to naturally-occurring biological qualities – namely, that it codes for a naturally-occurring polypeptide or has a naturally-occurring nucleotide sequence. The claims acknowledge that, unlike other chemicals, DNA stores and conveys specific information – as dictated by the order of nucleotides – that serves as the blueprint for all of

the proteins, cells, and organs that make up the human body. (*E.g.*, A2441; A7029.) While chemical molecules like water can be described as H_2O, HOH, or OH_2 because they consist of any two hydrogen atoms and an oxygen atom, DNA is not described according to the sugars and phosphates of its backbone, but by its nucleotide sequence. (*E.g.*, A7024; *see* A7031-32.) Because this blueprint is the defining characteristic of DNA and remains the same before and after isolation, isolated DNA has neither a distinctive name, character, and use from naturally-occurring DNA nor markedly different characteristics. (A214-28.) Both are DNA, their chemical structures are not markedly different, the protein coded for by each is the same, and their use in storing and transmitting information about a person's heredity is identical. (A6964-74.) Isolated DNA contains all the genetic information necessary to transmit a trait. (A6969-72.) It is useful because the sequence – the result of "nature's handiwork" – informs the medical professional about how the gene operates in one's body. (A7029-38.) *See also* U.S. Br. 17-27. If isolated DNA had markedly different characteristics, or if it were different in name, character, and use, it would be of no diagnostic value to medical professionals.

These "isolated DNA" claims also have a preemptive effect. In interpreting section 101, the Supreme Court has expressed deep concern

about preempting any use of the underlying abstract idea and law or product of nature, because such preemption would impede science, knowledge, and progress. *Bilski*, 130 S. Ct. at 3230-31 ("Allowing petitioners to patent risk hedging would pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea."); *Gottschalk v. Benson*, 409 U.S. 63, 71-72 (1972) (observing that "[t]he mathematical formula involved here has no substantial practical application except in connection with a digital computer . . . the patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself"); *Funk Bros.*, 333 U.S. at 130 ("The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. . . . He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes."). *See also Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 126-27 (2006) (Breyer, J., dissenting) ("[S]ometimes *too much* patent protection can impede rather than 'promote the Progress of Science and useful Arts.'").

Myriad has not denied that its patents allow it to exclude anyone from working with the BRCA1/2 molecules – a product of nature – and identifying the law of nature represented by a person's BRCA1/2 genetic

sequence, regardless of the person from whom the sample is taken and regardless of whether that person's purpose is research or clinical. (A7016; A7060-63.) U.S. Br. 8. Any scientist who wants to analyze the BRCA1/2 genes for any reason, including reasons unrelated to breast and/or ovarian cancer predisposition, may not do so. This problem is particularly acute as we learn the importance of analyzing the interaction of these genes with other critical genes. (*E.g.*, A2777-78; A2983.)

B. The United States Has Concluded That Isolated Genomic DNA Is Not Patentable.

Myriad urges this Court to defer to the government's Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001) ("Utility Guidelines"). Myriad Br. 37-39. Such deference is unwarranted. (A196-98.) In addition, the Utility Guidelines no longer represent the position of the United States. After consultation with numerous federal agencies, including the PTO, U.S. Br. 1, the U.S. concluded that "isolated but otherwise unaltered genomic DNA is not patent-eligible subject matter under 35 U.S.C. § 101." U.S. Br. 18. If deference to the decisions of the United States is due, that deference now supports invalidation of the claims.

J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc., contrary to Myriad's assertion, does not support deference to the PTO in this case. The issue in *J.E.M. Ag Supply* was not whether the patented plant products fell

within a section 101 exception, but instead whether two other statutes limited issuance of utility plant patents. 534 U.S. at 131-32. The case here presents the separate question of whether isolated DNA is a product of nature, and thus an exception to 101. *Id.* at 130.

C. Other Precedent Either Supports The Conclusion That "Isolated DNA" Is Not Patentable Or Does Not Squarely Address Section 101 Subject Matter Eligibility.

Other authorities also have concluded that naturally-occurring products cannot be patented even when they have been extracted, distilled, or purified. In *Ex parte Latimer*, the Patent Commissioner refused to allow a patent on pine needle fibers that were suited for textile production. 1889 Dec. Comm'r Pat. 123 (1889). That decision's discussion of products of nature is useful for analyzing this case, as well as the patentability of a leaf "isolated" from a plant. *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282, 1294-95 (Fed. Cir. 2010) (Dyk, J., concurring in part). While the fibers were stronger and more durable once removed from the needle, *Latimer* concluded that they could not be patented. 1889 Dec. Comm'r Pat. at 125 ("Nature made them so and not the process by which they are taken from the leaf or the needle"). Even if this had been the first discovery of the fiber, patents could not be issued on a "natural product"; otherwise, the "impossible" result would be patenting fiber from *Pinus australis*, *Pinus sylvestris*, and all tree

species. *Id.* at 125-27. Yet under Myriad's logic, the pine needle fiber, like a leaf isolated from the plant, could be patented because it had been removed from its natural environment and put to new uses – the fiber could be used for making textiles, and the leaf could be placed in a centerpiece. Even assuming arguendo Myriad first identified the BRCA1/2 genes, patents cannot issue on a natural product like a gene without tying up the genome.

The Third Circuit likewise ruled against a patent on "substantially pure tungsten having ductility and high tensile strength," despite the superiority of purified tungsten over its naturally-occurring, brittle form. *Gen. Elec. Co. v. De Forest Radio Co.*, 28 F.2d 641, 643 (3d Cir. 1928). *General Electric* confirms that a naturally-occurring substance does not automatically become a patentable product upon isolation and purification, as the characteristics of a purified substance can be inherent to nature rather than created by the researcher. *See also In re King*, 107 F.2d 618, 620 (C.C.P.A. 1939) (rejecting patent on vitamin C purified from lemon juice); *In re Merz*, 97 F.2d 599, 601 (C.C.P.A. 1938) (rejecting patent on purified ultramarine); *In re Marden* (Marden II), 47 F.2d 958, 959-60 (C.C.P.A. 1931) (rejecting patent on purified vanadium); *In re Marden* (Marden I), 47 F.2d 957, 958 (C.C.P.A. 1931) (rejecting patent on purified uranium). *See also* U.S. Br. 29-34.

Myriad's defense of its isolated DNA patents hinges on lower court cases that did not squarely address subject matter eligibility under section 101 or are otherwise inapposite.[16] For example, *In re Kratz*, 592 F.2d 1169 (C.C.P.A. 1979), and *In re Bergstrom*, 427 F.2d 1394 (C.C.P.A. 1970), are now understood as anticipation cases that did not analyze section 101. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir. 2003); *In re Bergy*, 596 F.2d 952, 961 (C.C.P.A. 1979) (noting that *Bergstrom* "in effect treated the [section 101] rejection as if it had been made under § 102"). *Parke-Davis & Co. v. H.K. Mulford Co.* upheld a patent claim on purified adrenaline based on its commercial utility and novelty. 189 F. 95 (S.D.N.Y. 1911). Unlike the DNA at issue here, which serves as an informational molecule, the purified adrenaline was used as a therapeutic, and patents thereon did not impede determination of patient adrenaline levels. (A6972-73; A7030-31.) In addition, that court's dictum

[16] Myriad's reliance on section 103(b)(1) to support the patentability of isolated DNA is similarly misplaced. Myriad Br. 32-33. The fact that Congress mentioned "nucleotide sequence" in section 103(b)(1) – a statutory provision which deals with the obviousness of processes – does not support the notion that Congress intended isolated DNA to be patentable compositions. An organism can be engineered to express a "nucleotide sequence" that is not naturally-occurring. And unlike section 273(a)(3), which defined "method" as a method of doing or conducting business for the purpose of a prior use defense, *Bilski*, 130 S. Ct. at 3228-29, there is no language in the Patent Act defining compositions of matter to include "isolated DNA."

that an "extracted product without change" was patentable contradicts the later holdings of the Supreme Court discussed above. 189 F. at 103. Likewise, in *Merck & Co. v. Olin Mathieson Chemical Corp.*, patents were upheld on purified B-12 on the grounds of its novelty and utility. 253 F.2d 156, 164 (4th Cir. 1958). Notably, the patent claim did not reach crystalline forms of purified vitamin B-12 or those derived from other sources. *Id.* at 160. Myriad's patents, by contrast, preclude examination of any and all BRCA1/2 genes. The *Bergy* product claim over a "biologically pure culture of the microorganism . . . being capable of producing the antibiotic lincomycin" was limited to a specific function – creating a named antibiotic that could not otherwise be produced by the microorganism. *In re Bergy*, 596 F.2d at 967, 972, *appeal dismissed as moot*, 444 U.S. 1028 (1980). The DNA at issue here encodes for BRCA1/2 proteins, and it is not limited to uses other than encoding information.

D. None Of The Challenged Claims Is Limited To cDNA, But In Any Case, cDNA That Is An Exact Copy Of Naturally-Occurring RNA Is Not Patentable.

Amicus United States argues that claims limited to cDNAs would not violate section 101. U.S. Br. 14-17. That issue is not material to this case. None of the parties – including the PTO, a defendant below – has ever

argued that any of the challenged claims is limited to cDNAs.[17] (*See, e.g.,*A4290-91). Thus, that claim construction has been waived. *See supra* p. 13. Because the umbrella of "isolated DNA" as used in the claims covers DNA that is simply extracted from the genome, this Court need not address the cDNA question. For all of these claims, the Court need only find that some of what is covered is a natural phenomenon. *Cf. Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) ("It is also an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art.").

However, should this Court choose to reach the cDNA question, it should also invalidate claims on cDNA that is an exact copy of naturally-occurring mRNA. (A2608; A6974-75; A7023.) cDNA ("complementary DNA"), as covered in these claims, is a complementary sequence that represents an exact genetic copy of the mRNA, which is naturally created in the cell through splicing out of intron sequences and the addition of a poly A tail, among other changes. (A2607.) The value of cDNA lies in its sequence

[17] Defendants' expert described all of the claims as DNA. (A4290.) He later suggested that at least some claims are cDNA, pointing to one "example" in the patent. (A4299.) But the patent recites that examples "are offered by way of illustration and are not intended to limit the invention in any manner." (A605, 35:31-2.)

and the fact that it results from the biological machinery of the cell – both natural phenomena that were not invented by Myriad. cDNA "is an exact copy of one of the protein coding sequences encoded by the original genomic DNA . . . In this respect, cDNA contains the identical protein coding informational content as the DNA in the body…" (A133; *see also* A222 ("not only are the coding sequences contained in the claimed DNA identical to those found in native DNA, the particular arrangement of those coding sequences is the result of the natural phenomena of RNA splicing.")).

As the U.S. acknowledges, cDNA does exist naturally in the body through a naturally-occurring process in which RNA is reverse-transcribed into cDNA. (A7023-24.); U.S. Br. 15 (discussing retroviruses); *see also* Bruce Alberts et al., *Molecular Biology of the Cell* 289 (4th ed. 2002) ("Alberts").[18] Some of these cDNAs are then reinserted into the genome in the form of pseudogenes. (A6974-75; A7013-14; A7023-24.) cDNAs made in the laboratory that are structurally, functionally, and chemically identical to these naturally-occurring cDNAs are accordingly not patentable. (A2608; A6974-75; A7023.) *See Cochrane v. Badische Anilin & Soda Fabrik*, 111 U.S. 293, 311 (1884) (holding that an artificial version of naturally-

[18] The U.S. refers to retroviruses as a rare exception; however, retroviruses are the cause of many human infections and cancers.

occurring alizarine could not be patented because it was not a "new composition of matter").

These cDNAs are distinct from other biotechnological products referred to by the U.S., which could be patentable because human engineering gives them markedly different characteristics; *e.g.*, the *Chakrabarty* bacterium. Recombinant plasmids and cloning vectors involve the use of manipulated cDNA sequences that are linked to another non-native sequence. *See* Alberts 500-1 (describing plasmid vectors as "recombinant molecules containing foreign DNA inserts"). cDNA copied from naturally-occurring mRNA and routinely used to inform doctors about a patient's genetic code or gene expression is thus qualitatively different from recombinant plasmids and cloning vectors which are engineered such that a sequence of interest is either deleted or added for use as a tool or other specific purpose. The former cannot be patented without blocking access to basic genetic information; the latter are the type of inventions that meet the section 101 threshold.

III. THE CHALLENGED PROCESS CLAIMS ARE INVALID UNDER SECTION 101 BECAUSE THEY COVER LAWS OF NATURE AND ABSTRACT IDEAS.

The same fundamental section 101 principles apply to the patentability of the six challenged method claims. *See supra*, pp. 37-39. In

Bilski, the Court relied on the reasoning of *Benson*, *Flook*, and *Diehr* to invalidate a method claim. *Bilski v. Kappos,* 130 S. Ct. 3218, 3229-31 (2010). As in *Benson* and *Flook*, the method claims here patent an abstract idea. Claim 1 of '857 provides one example:

> A method for identifying a mutant BRCA2 nucleotide sequence in a suspected mutant BRCA2 allele which comprises comparing the nucleotide sequence of the suspected mutant BRCA2 allele with the wild-type BRCA2 nucleotide sequence, wherein a difference between the suspected mutant and the wild-type sequence identifies a mutant BRCA2 nucleotide sequence.

(A965.) The idea here – the comparing of one sequence to a reference wild-type sequence to identify differences or mutations – is applied to BRCA2 sequences. But as in *Flook*, limiting the application of an idea to a specific situation is insufficient. "*Flook* rejected '[t]he notion that post-solution activity, no matter how conventional or obvious in itself, can transform an unpatentable principle into a patentable process.'. . . *Flook* stands for the proposition that the prohibition against patenting abstract ideas 'cannot be circumvented by attempting to limit the use of the formula to a particular technological environment' or adding 'insignificant postsolution activity.'" *Bilski*, 130 S. Ct. at 3230 (citation omitted).

Considered as a whole, the method claims at issue here clearly cover a phenomenon of nature – whether two BRCA sequences are different or the same. *Bilski* observed that the claims there "add even less to the underlying

abstract principle than the invention in *Flook* did, for the *Flook* invention was at least directed to the narrower domain of signaling dangers in operating a catalytic converter." *Id.* at 3231. Here, the same concern arises: most of the method claims cover any comparison of two BRCA1/2 sequences, including comparisons to determine predisposition to other diseases like prostate and pancreatic cancers. *See Gottschalk v. Benson*, 409 U.S. 63, 67, 72 (1972) (observing that "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts" are not patentable because they "wholly preempt" the public's access to the "basic tools of scientific and technological work").

Claim 2 of '857 covers comparing a BRCA2 sequence from a sample with the wildtype sequence, wherein any alteration indicates a predisposition to breast cancer, and further illustrates the preemptive effect. The claim does not specify which alterations are covered and makes the scientifically incorrect assumption that any alteration indicates cancer predisposition. (A2443; A2605.) Thus, the claim exemplifies how a patent on a general correlation between a gene and disease monopolizes a law of nature. A scientist who wants to identify which alterations in fact indicate a breast cancer predisposition will run afoul of the patent claim as soon as he or she compares two gene sequences and considers the significance of an alteration.

See also Brief for the United States as Amicus Curiae on Petition for a Writ of Certiorari 6, *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006) (No. 04-607) (claim at issue "appears to involve such a natural phenomenon, because it asserts and relies on the existence of a naturally occurring correlation between elevated levels of total homocysteine and deficiencies in cobalamin or folate"). These claims surely are not amongst the "advanced diagnostic medical technologies" that might concern the *Bilski* plurality,[19] given how they "transgress[] the public domain." 130 S.Ct. at 3227.

Application of the "machine or transformation" test, which remains "a useful and important clue," also establishes the invalidity of these claims. *Bilski*, 130 S. Ct. at 3227. "Transformation and reduction of an article 'to a different state or thing' is the clue to the patentability of a process claim that does not include particular machines." *Benson*, 409 U.S. at 70. No transformation occurs in these claims, as they involve comparing or analyzing two given genetic sequences. (A2479-81; A2574-75.) Claim 1 of the '441 patent and of the '001 patent do not involve the comparing of genes, but the comparing of sequences. Similarly, claims 1 and 2 of the

[19] Justice Scalia did not join this portion of the opinion.

'857 patent are on the "comparing" of genetic sequences, and claim 1 of '999 involves "analyzing" sequences.

In order to argue "transformation," Myriad imports entirely new terms and processes into the claims' plain language. Myriad argues that "sequence" should be understood as the isolated DNA molecule and that the method claims necessarily involve isolating, sequencing, and hybridization of DNA or genes using a primer or probe. Myriad Br. 56-58. Yet, none of these processes is required by the challenged claims themselves and for that reason, they cannot be magically inserted. *See ASM Am., Inc. v. Genus, Inc.*, 401 F.3d 1340, 1344-45 (Fed. Cir. 2005) (holding that discussion of separate steps of a method in specification does not support interpreting plain claim language covering only one step to inherently include other step); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (*en banc*) (same). In fact, possession of the sequences is assumed by the claim language, and it is the mere mental process of comparing them that is covered. (A2479-81; A2574-75.)

Clear evidence that the challenged claims do not incorporate these steps can be found in the dependent claims (not challenged by Plaintiffs) that do require hybridizing, amplifying, electrophoresing, and/or cloning. *E.g.*, cl. 4 of '857; cls. 4, 6-12 of '441. (A965; A771.) "[T]he presence of a

dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim." *Phillips*, 415 F.3d at 1315. Thus, Myriad's reading must be rejected, for claim differentiation "prevents the narrowing of broad claims by reading into them the limitations of narrower claims." *Clearstream Wastewater Sys., Inc. v. Hydro-Action, Inc.*, 206 F.3d 1440, 1446 (Fed. Cir. 2000); *see also Karlin Tech. Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 972 (Fed. Cir. 1999).

The phrases "from a human subject" or "from a nontumor sample," the specifications, and the prosecution history do not change this analysis. These simply acknowledge that the sequence information must come from a human sample. (A235-36.) The claims themselves are not limited to particular samples or samples obtained through particular steps. The Court should also reject any argument that a transformation occurs simply when isolating DNA, for the same reasons discussed *supra* Part II.

The absence of transformation is apparent in light of *Prometheus Labs, Inc.. v. Mayo Collaborative Servs.*, 581 F.3d 1336 (Fed. Cir. 2009), *cert. granted, judgment vacated, and remanded*, 130 S. Ct. 3543 (2010). The *Prometheus* claim necessarily required the processing of a human blood sample after the administration of the drug in order for metabolite levels to

be determined; it was not a claim on "comparing" determined metabolite levels. *See id.* at 1340, 1346-47. "Comparing" sequences in the challenged claims does not include antecedent steps and can be accomplished by "mere inspection." *See id.* at 1347. One can do a side-by-side comparison by visual scan or use a simple program (*see* Basic Local Alignment Search, http://blast.ncbi.nlm.nih.gov/Blast.cgi), or another algorithm. Nothing in the claims precludes the use of one or more of these methods. Moreover, the claims would cover the "comparing" of the BRCA section of a patient's entire genomic sequence with the reference sequence, even though the geneticist doing the comparing had not performed the underlying sequencing or ever "isolated" the DNA, and even though Myriad does not currently offer whole genome sequencing. These claims, analyzed in their entirety, are directed at noting differences between two sequences, a mental process analogous to what occurs in the "wherein" clauses of the *Prometheus* claim. *See id.* at 1348.

Myriad argues that the patented "methods are new and useful processes" and "very real ways of diagnosing and treating cancers," and thus survive section 101. Myriad Br. 61. Both assertions are simply false. Comparing sequences can sometimes be "useful" but the only "new" part of the claims is the BRCA1/2 sequences that are compared. Determining if a

variant exists neither diagnoses cancer nor provides a method of treatment. Notably, Myriad's argument seeks to revive elements of the "useful, concrete, and tangible result" test of *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*, 149 F.3d 1368, 1373 (Fed. Cir. 1998), despite judicial disapproval. *Bilski*, 130 S. Ct. at 3231; *id.* at 3232 n.1 (Stevens, J., concurring); *id.* at 3259 (Breyer, J., concurring); *In re Ferguson*, 558 F.3d 1359, 1364 (Fed. Cir. 2009).

Claim 20 of '282 patents the abstract idea of comparing growth rates of two cells, which are dictated by nature, and preempts a basic scientific principle extended to the BRCA1 gene context: that a slower rate of cell growth in the presence of a compound may indicate that the compound is a cancer therapeutic. *See Parker v. Flook*, 437 U.S. 584, 595 (1978) (finding the "respondent's claim is, in effect, comparable to a claim that the formula 2 r can be usefully applied in determining the circumference of a wheel"). The claim does not seek to patent a particular cancer therapeutic, only an elementary, otherwise non-patentable method for screening one. The step of "growing a transformed … cell" in the presence of a compound is merely a preparatory, data-gathering step. *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989) (noting that "[t]he presence of a physical step in the claim to derive data for the algorithm will not render the claim statutory"). Moreover, it is

possible that the test compound would have no effect on the cells and thus provide no basis for finding a transformation. (A241-42.)

IV. THE PATENT CLAIMS ARE UNCONSTITUTIONAL UNDER THE FIRST AMENDMENT.

It is clear that the First Amendment limits the reach of intellectual property laws. In copyright, where the potential conflict is more obvious, the Supreme Court has suggested that doctrines, like the idea/expression distinction, that are incorporated into statute are required by the First Amendment. *Harper & Row Publishers, Inc. v. Nation Enters.*, 471 U.S. 539, 556 (1985); *Eldred v. Ashcroft*, 537 U.S. 186, 219 (2003). *See also Salinger v. Colting*, 641 F. Supp. 2d 250, 255 (S.D.N.Y. 2009), *rev'd on other grounds*, 607 F.3d 68 (2d Cir. 2010); *Maxtone-Graham v. Burtchaell*, 631 F. Supp. 1432, 1435 (S.D.N.Y. 1986). Although the section 101 doctrine prohibiting patenting of abstract ideas has not been described previously as compelled by the First Amendment, there can be little doubt that patenting of abstract ideas or an entire body of knowledge would violate the First Amendment.

The First Amendment prevents the government from limiting thought. In *Palko v. Connecticut*, 302 U.S. 319, 326-27 (1937), the Supreme Court referred to "... freedom of thought and speech. Of that freedom one may say that it is the matrix, the indispensible condition, of nearly every other

form of freedom." *See also Stanley v. Georgia*, 394 U.S. 557, 566 (1969) ("Whatever the power of the state to control public dissemination of ideas inimical to the public morality, it cannot constitutionally premise legislation on the desirability of controlling a person's private thoughts."); *Griswold v. Connecticut*, 381 U.S. 479, 482 (1965) ("The right of freedom of speech . . . includes not only the right to utter or to print, but the right to . . . freedom of inquiry, freedom of thought. . . ."); *United States v. Reidel*, 402 U.S. 351, 355-56 (1971) ("Our whole constitutional heritage rebels at the thought [sic] of giving government the power to control men's minds."). More recently, in *Ashcroft v. Free Speech Coalition*, 535 U.S. 234, 253 (2002), the Court explained, "First Amendment freedoms are most in danger when the government seeks to control thought or to justify its laws for that impermissible end. The right to think is the beginning of freedom . . . ."

None of the method claims purports to cover any specified process of comparing or analyzing gene sequences or testing therapeutics. The only instructive part of these claims is that at the end, the medical professional thinks, "They are the same" or "They are different" or "They are different in a way that is significant." In other words, it is the thought that is patented, not a particular process. *See supra* Part III. Enforcement of such a patent by

a governmental actor, such as the Defendant University of Utah Research Foundation, would violate the First Amendment.

The inability to compare gene sequences in order to think about them also interferes with the right to scientific inquiry. The framers of the Constitution were concerned about the sacred nature of scientific inquiry. Gary L. Francione, *Experimentation and the Marketplace Theory of the First Amendment*, 136 U. Pa. L. Rev. 417, 428-29 (1987). For one entity to be able to prevent scientific inquiry into a field of knowledge is not permissible under the First Amendment. *Griswold*, 381 U.S. at 482 ("The State may not, consistently with the spirit of the First Amendment, contract the spectrum of available knowledge."); *see also Epperson v. Arkansas*, 393 U.S. 97, 100-101 (1968).

The isolated DNA claims also violate the First Amendment. The doctrine that prevents the patenting of natural phenomena, abstract ideas, and products and laws of nature is partially premised on the obvious conclusion that it is impossible to invent around those things; patenting them would not advance the useful arts. For a typical invention, such as a carburetor, once the patent is published, others can try to build a better carburetor using different materials or methods. In contrast, if oxygen were patented, no one could invent a new oxygen. Similarly, once a human gene

is patented, nobody can invent a new human gene.[20] (*See* A2449; A2774.) Because patents on the isolated BRCA1/2 DNA prevent access to each person's genetic information, it is inaccurate to treat genes as if they were carburetors or discrete chemicals. (A2617-18, A2629.) Indeed, rather than leading to a greater understanding or a better product, the patent claims challenged in this case exclude others from further work with these genes. (*E.g.*, A2449; A2675; A3061.) The patents give entire control over a body of knowledge and over pure information to Defendants. That, under the First Amendment, is impermissible.

The district court found it unnecessary to reach the First Amendment claims, applying the constitutional avoidance doctrine. (A244.) If this Court upholds the patents under section 101, it must reach the constitutional claims. The Court should clarify that patent law is limited by the First Amendment and invalidate these patent claims.

[20] DNA molecules with new sequences can be invented, of course, that have never existed in nature. Those are not at issue here.

CONCLUSION

The judgment of the district court should be affirmed.

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CERTIFICATE OF SERVICE

I hereby certify that on this 30th day of November, 2010, I caused twelve true and correct copies of the foregoing Brief for Appellees to be mailed to the Court via FedEx and for two true and correct copies of the Brief to be served upon the following counsel of record listed below via FedEx.

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CERTIFICATE OF COMPLIANCE

1. This brief complies with the type-volume limitation of Federal Rule of Appellate Procedure 32(a)(7)(B), because it contains 13,930 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii) and Federal Circuit Rule 32(b).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of the Federal Rule of Appellate Procedure 32(a)(6), because it has been prepared in a proportionally spaced typeface using Microsoft Word 2003 in Times New Roman 14 point font.

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