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Unanimous U.S. Supreme Court and Angelina Jolie: BRCA1 & BRCA2 Patentability

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Introduction

On June 13, 2013, the Supreme Court of the United States issued its unanimous, landmark decision in the long-awaited and much anticipated case of *Association For Molecular Pathology et al. v. Myriad Genetics, Inc., et al.* [1] That same day,the decision was prominently featured on several world news media outlets and firmly grasped the attention of more than just the intellectual property community.

Background

Formed in 1991, Myriad Genetics, Inc. ("Myriad") is a molecular diagnostic company based in Salt Lake City, Utah. Myriad positions itself in the market as a discoverer that commercializes transformative tests to assess a person's risk of developing disease, guide treatment decisions and assess risk of disease progression and recurrence. In 1996, Myriad allegedly introduced the first molecular diagnostic test for hereditary breast and ovarian cancer.

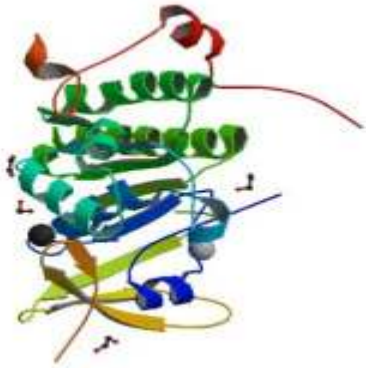
Founded in 1995, The Association for Molecular Pathology ("AMP") is a not-for profit scientific society dedicated to the advancement, practice, and science of clinical molecular laboratory medicine and translational research based on the applications of genomics and proteomics. AMP members participate in basic and translational research aimed at broadening the understanding of gene/protein structure and function, disease processes, and molecular diagnostics, and provide clinical medical services for patients, including diagnosis of breast cancer. [2]

BRCA1 and BRCA2[3] are human genes that belong to a class of genes known as tumor suppressors. Mutation of these genes bears strong correlation to hereditary breast and ovarian cancer. In the early 1990s, Myriad discovered the precise location and genomic sequence of the BRCA1 and BRCA2 genes. Subsequently, Myriad filed for, and received, patent protection of its discovery of these isolated DNA sequences. These patents then gave Myriad exclusive rights to offer genetic testing services for the sequences it had located.

Breast Cancer 1, early onset

Protein Data Bank in Europe rendering based on 1jm7.

Breast Cancer 2, early onset



Protein Data Bank in Europe rendering based on 1n0w.

On May 12, 2009, AMP—along with several other petitioners (hereafter collectively referred to as AMP)—filed its Complaint in the

Southern District of New York seeking a declaratory judgment that the composition claims at issue[4] are invalid and/or unenforceable. Ultimately, the District Court granted summary judgment to AMP predicated on its conclusion that Myriad's claims, including claims related to cDNA[5], were invalid because they covered products of nature.[6]

Thereafter, the Defendants appealed the decision to the United States Court of Appeals for the Federal Circuit, wherein the Federal Circuit reversed the District Court's ruling. The Supreme Court granted certiorari, vacated the Federal Circuit's judgment, and remanded the case to the Federal Circuit. On remand, the Federal Circuit affirmed the District Court in part and reversed in part, holding that "both isolated DNA and cDNA were patent eligible under §101" [7] although each Circuit judge held a different view on the patentability of isolated DNA.[8] However, and contrastingly, all three Circuit judges agreed that patent claims relating to cDNA met the patent eligibility requirements of §101.[9]

Long before the most recent Supreme Court grant of certiorari to the Federal Circuit in this matter, the disharmonious Federal Circuit opinion on the patent eligibility of isolated DNA dramatically set the stage for argument in front of the High Court.

Discussion & Analysis

At issue before the Supreme Court, are nine of Myriad's composition claims from three of its patents. The central issue presented to the Court is whether "a naturally occurring segment of deoxyribonucleic acid (DNA) is patent eligible under 35 U. S. C. §101 by virtue of its isolation from the rest of the human genome." [10]

The preceding, seminal Supreme Court case of *Diamond v. Chakrabarty*[11] provided a fertile field for the growth of patent protection in the biotechnology arena. In *Diamond*, the Court held that a genetically engineered microorganism was patentable. Important to this discussion is the further teaching of *Diamond* where the Court stated that products of na-ture are not created, and "'manifestations . . . of nature [are] free to all men and reserved exclusively to none'."[12] With this in mind, the Supreme Court states that the well-established principle that it must apply to the issue presented is striking the delicate balance between creating "incentives that lead to creation, invention, and discovery" and "imped[ing] the flow of information that might permit, indeed spur, invention."[13]

The Court made exceedingly clear that while Myriad did indeed discover the precise location and genetic sequence of BRCA1 and BRCA2 within chromosomes 17 and 13, it did not create anything. A tenet of patent law is that invention is necessarily comprised of conception plus reduction-to-practice. The Court opined that it is axiomatic that Myriad's discovery is important, yet the act of "separating that gene from its surrounding genetic material is not an act of invention."[14] Vis-à-vis the isolated DNA itself, because Myriad did not create anything (conception), there can be no patentable invention.

By examining one of the claims at issue, the analysis is well-illustrated. For example, claim 1 of the '492 patent is as follows:

> "An isolated DNA molecule coding for a BRCA2 polypeptide, said DNA molecule comprising a nucleic acid sequence encoding the amino acid sequence set forth in SEQ ID NO:2. "

In this claim, Myriad is asserting rights to the DNA code that instructs a cell to produce the BRCA2 amino acids listed in SEQ ID NO:2. In this claim, and the other claims at issue, Myriad fails to satisfy the novelty requirement for compositions of matter found of 35 U.S.C. § 101. The reason being is that the Court has "long held that this provision contains an im-portant implicit exception[:] Laws of nature, natural phe-nomena, and abstract ideas are not patentable."[15] Myriad did not alter or create the genetic coding of BRCA1 or BRCA2, but merely discovered their location and sequence. Such discovery, albeit innovative or arguably brilliant, falls outside of the ambit of patent protection because of the law of nature exception.

Ostensibly, according to the Court, Myriad's fate was further sealed by its own 35 U.S.C. § 112 written description requirement. For example:

> "a section of the '282 patent's Detailed Description of the Invention indicates that Myriad found the location of a gene associated with increased risk of breast cancer and identified mutations of that gene that increase the risk...In subsequent language Myriad explains that the location of the gene was unknown until Myriad found it among the approximately eight million nucleotide pairs contained in a subpart of chromosome 17." [16]

The Supreme Court utilizes this supporting evidence to further make clear that extensive discovery efforts will not result in otherwise ineligible law of nature claims transforming into a patent.

Neither was the Court moved by Myriad's patent guile. Myriad argued that the act of isolating DNA severs chemical bonds and thereby creates a non-naturally occurring molecule.[17] The key distinction is that Myriad's claims are directed to the genetic coding of BRCA1 and BRCA2—which occurs naturally—and not the act of isolating these genes.

Myriad also argued that that the USPTO's past practice of awarding gene patents is entitled to deference. The Court concisely disposed of this argument by stating that: 1) in this case, in light of *J. E. M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.*[18] , Congress has not endorsed the views of the USPTO in subsequent legislation; and, 2) the United States argued in the Federal Circuit and Supreme Court that isolated DNA was *not* patent eligible under §101, and that the USPTO's practice was not "a sufficient reason to hold that isolated DNA is patent-eligible." [19]

Next, the Court addressed the patentability of cDNA. Contrastingly, the Court held that the patentability impasse of isolated DNA is not present with respect to cDNA. As discussed *supra*, cDNA is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription. Because it is synthesized from mRNA, cDNA contains only the exon sequences, and thus none of the intron sequences, from a native gene sequence. Simply put, subject to exception, cDNA synthesis is non-naturally occurring thereby eliminating the law of nature exception to patent eligibility.

Celebrity Personalized Medicine

On May 14, 2013, Hollywood actress and director Angelina Jolie, in *The New York Times*, The Opinion Pages article entitled "My Medical Choice[20] ," announced that she finished three months of medical procedures at the Pink Lotus Breast Center in California on April 27, 2013 that included preventive double mastectomy and reconstruction.

A woman's risk of developing breast and/or ovarian cancer is greatly increased if she inherits a deleterious BRCA1 or BRCA2 mutation. Men with these mutations also have an increased risk of breast cancer. Jolie inherited the BRCA1 gene mutation from her mother. Her doctors estimated that she had an 87 percent risk of breast cancer and a 50 percent risk of ovarian cancer. Her preventive double mastectomy decision decreased her probability of developing breast cancer from 87 percent to under 5 percent.[21]

Jolie decided to 'go public' with her medical treatment to inspire and empower other similarly situated women to make the best medical decisions. While

clearly laudatory, there may be another persuasive argument to be made for her well-timed op-ed article. Reasonably, given Jolie's renowned humanitarian efforts, it is plausible that Jolie made a conscious effort to publicly disclose her genetic diagnosis and treatment ahead of the Supreme Court's long-expected June 2013 decision. A world famous example of the benefits of medical diagnostic testing of genetic sequences and the life-saving medical decisions as a result of that information.

> "Breast cancer alone kills some 458,000 people each year, according to the World Health Organization, mainly in low-and middle-income countries. It has got to be a priority to ensure that more women can access gene testing and lifesaving preventive treatment, whatever their means and background, wherever they live. The cost of testing for BRCA1 and BRCA2, at more than $3,000 in the United States, remains an obstacle for many women." [22]

The inextricable nexus is clear. Jolie's worldwide call for greater access to genetic testing and lifesaving preventive treatment would have been stymied but for the Supreme Court's subsequent decision that isolated, naturally-occurring DNA is not patentable. It is undeniable that Jolie's revelations increased awareness of BRCA1 medical diagnostic testing and the options available to manage cancer risk, such as surveillance, prophylactic surgery, risk avoidance, and chemoprevention.

Sampling of Industry Reaction

AMP

"AMP applauds the U.S. Supreme Court on their ground breaking, unanimous decision. There is no question that this is a critical and right decision for the future of medicine and science. Biomedical researchers, clinicians, and most importantly patients will see great benefit from this development."[23]

-- Jennifer L. Hunt, MD, MEd, AMP President

Myriad

" Myriad Genetics, Inc. (Nasdaq:MYGN) today said the Supreme Court of the United States upheld its patent claims on complementary DNA, or cDNA. However, the Court ruled that five of Myriad's claims covering isolated DNA were not patent eligible."[24]

-- Myriad Genetics, Inc., Globe Newswire

The American Medical Association

"The U.S. Supreme Court's unanimous rejection of patenting human genes is a clear victory for patients that will expand medical discovery and preserve access to innovative diagnosis and treatment options. The American Medical Association (AMA) has long advocated for a clear prohibition against human gene patents."[25]

-- Jeremy Lazarus, MD, President (June 13, 2013)

The aftermath of the Supreme Court's decision expectedly prompted numerous industry statements that resembled the position of a particular side of the litigants. But, one of the loudest statements concerning the Court's decision was made by investors. Before the Court's decision was issued on Wednesday, June 12, 2013, Myriad's stock price was trading at about $34 a share. At the close of the market on Monday, June 17, 2013, Myriad's stock price plummeted to $26.62 a share, approximately representing a 22 percent decrease in value (*see supra*, Yahoo! Finance NASDAQ report).

Apparently, interested investors listen to the Supreme Court and speak with their wallets.

Future Implications

A 2005 study found that 4,382 of the 23,688 human genes in the National Center for Biotechnology Information's gene database are explicitly claimed as intellectual property.[26] Undoubtedly, those patents that are directed to isolated, naturally-occurring DNA will no longer confer the same set of enforceable rights. This reasoning is further supported by the USPTO's June 13, 2013 recent memorandum to the examining corps.

> "As of today, naturally occurring nucleic acids are not patent eligible merely because they have been isolated. Examiners should now reject product claims drawn solely to naturally occurring nucleic acids or fragments thereof, whether isolated or not, as being ineligible subject matter under 35 U.S.C. § 101." [27]

under 35 U.S.C. § 101. [27]

As such, expect an increase in the market of medical diagnostic testing for isolated DNA Sequences. This increased competition should accomplish two things. First, there will be a greater market supply of said diagnostic services. Second, the increased supply is likely to result in greater pricing competition that should result in more affordable testing for consumers.

The future implications surrounding other issues of gene patentability are addressed, in part, by the Court. Besides finding cDNA patent eligible, the Supreme Court carefully crafted its decision to state that its ruling does not implicate method claims or new applications of knowledge about the BRCA1 and BRCA2 genes. [28] To this end, expect to see a marked increase in the number of patent applications claiming methods for genetic sequence isolation as well as new applications of knowledge. Additionally, Myriad—and those that enjoyed isolated DNA patent exclusivity—will likely have an advantage when applying for genetic sequencing method patents because a previous effect of the claims at issue was that said claims effectively precluded others from performing the method that yielded the isolated DNA.

The Court also stated that, in its ruling, it does not take into consideration the patentability of DNA with altered nucleotides.[29] However, the USPTO's Memorandum to the Examination Corps paints a clearer, patentability picture of genetically altered sequences:

> "Claims clearly limited to non-naturally-occurring nucleic acids, such as a cDNA or a nucleic acid in which the order of the naturally-occurring nucleotides has been altered (e.g., a man-made variant sequence), remain eligible."[30]

In the end, the Supreme Court strikes the delicate balance between facilitating research and development, and the promotion of the progress of science and useful arts. Suffice it to say, this is not the last biotechnology case that will make its way to the Supreme Court.

Endnotes

1 *Association For Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 569 U.S. ___ (2013).

2 *Association For Molecular Pathology v. USPTO*,669 F. Supp. 2d 365, 370 (S.D.NY. 2009).

3 BRCA1 and BRCA2 stand for breast cancer susceptibility genes 1 and 2, respectively.

4 Specifically, at issue, are claims 1, 2, 5, 6, and 7 of U. S. Patent 5,747,282 (the '282 patent), claim 1 of U. S. Patent 5,693,473 (the '473 patent), and claims 1, 6, and 7 of U. S. Patent 5,837,492 (the '492 patent). See *Association For Molecular Pathology et al.*, 569 U.S. ___ (2013) (slip op. at 5 n.2).

5 Complementary DNA ("cDNA") is a type of synthetic DNA molecule. cDNA is synthesized from mRNA using complementary base pairing in a manner analogous to RNA transcription. The process results in a double-stranded DNA molecule with a sequence corresponding to the sequence of an mRNA produced by the body. Because it is synthesized from mRNA, cDNA contains only the exon sequences, and thus none of the intron sequences, from a native gene sequence. *See Ass'n for Molecular Pathology v. US Patent and Trademark Office*, 653 F.3d 1329, 1339 (Fed. Cir. 2011).

6 *See Association For Molecular Pathology et al.*, 569 U.S. ___ (2013) (slip op., at 7).

7 *See id*., at ___ (slip op. at 8)

8 *See Ass'n for Molecular Pathology v. US Patent and Trademark Office*, 653 F.3d 1329, 1333 (Fed. Cir. 2011) (stating that the "[o]pinion for the court filed by Circuit Judge LOURIE. Opinion concurring in part filed by Circuit Judge MOORE. Opinion concurring in part and dissenting in part filed by Circuit Judge BRYSON.")

9 *See Association For Molecular Pathology et al.*, 569 U.S. ___ (2013) (slip op. at 10).

10 *See id*., at ___ (slip op. at 1).

11 *See Diamond v. Chakrabarty*, 447 U.S. 303, 100 S.Ct. 2204, 65 L.Ed.2d 144 (1980).

12 *See Diamond*, 447 U.S. at 309.

13 *See Association For Molecular Pathology et al.*, 569 U.S. ___ (2013) (slip op. at 11).

14 *See id*. at ___ (slip op. at 12).

15 *Id*. at ___ (slip op. at 11).

16 *Id*. at ___ (slip op. at 13-14).

17 *Id*. at ___ (slip op. at 14).

18 *See* 534 U.S. 124 (2001).

19 *See Association For Molecular Pathology et al.*, 569 U.S. ___ (2013) (slip op. at 16).

20 Angelina Jolie, *My Medical Choice*, The N.Y. Times Opinion Pages, at *http://www.nytimes.com/2013/05/14/opinion/my-medical- choice.html?smid=tw-share&_r=2&* (May 14, 2013).

21 *See id*.

22 *Id*.

23 *See* Jennifer L. Hunt, *AMP Celebrates SCOTUS Decision on AMP v. Myriad Case*, *at* http://www.amp.org/documents/20131306_SCOTUSAMPvMYRIAD.pdf (June 13, 2013).

24 *See* Myriad Genetics, Inc., *Supreme Court Upholds Myriad's cDNA Patent Claims*
, *at* http://investor.myriad.com/releasedetail.cfm?ReleaseID=771232 (June 13, 2013).

25 *See* Jeremy Lazarus, *AMA Welcomes an End to Human Gene Patents*, *at* http://www.ama- assn.org/ama/pub/news/news/2013/2013-06-13-end-to-human-gene-patents.page (June 13, 2013).

26 *See* Kyle Jensen & Fiona Murray, "Intellectual Property Landscape of the Human Genome," *Science* 310(5746):239-240 (October 14, 2005).

27 *See* Andrew H. Hirshfeld, *Supreme Court Decision in Association for Molecular Pathology v. Myriad Genetics, Inc.*, *at* http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf (June 13, 2013).

28 *See Association For Molecular Pathology et al.*, 569 U.S. ___ (2013) (slip op. at 17).

29 *See id*. at ___ (slip op. at 18).

30 *See* Andrew H. Hirshfeld, *Supreme Court Decision in Association for Molecular Pathology v. Myriad Genetics, Inc.*, *at* http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf (June 13, 2013).