The Product of Nature Doctrine in the Myriad Saga II

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In June 2013, the U.S. Supreme Court decided Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al., holding that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring".

This case note gives an overview of the U.S. Supreme Court's decision, which is focused on the product of nature doctrine, and discusses its implications for the implementation of the criterion of isolation to DNA sequences and the United States Patent and Trademark Office's long-standing practice of granting patents on isolated DNA sequences (author's headnote).

I. The "Myriad Case" before the U.S. Supreme Court

On June 13, 2013, the Supreme Court of the United States decided *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*[1] (the "Myriad case"), and its holding may affect the United States Patent and Trademark Office's (USPTO) long-standing practice of granting patents on *isolated* DNA sequences and the implementation of the concept of *isolation* in order to establish patent eligibility.

The Myriad case involves some very controversial patents in both Europe[2] and the United States on BRCA1 and 2 genes, whose mutations are linked to genetic breast and ovarian cancer. The BRCA1 gene, discovered in 1990, is a tumor-suppressor gene linked to genetic breast and ovarian cancer. Women who have a mutation of this gene tend to have a high incidence of breast cancer, as well as ovarian cancer. In 1995 the BRCA2 gene was mapped and sequenced. While BRCA1 affects only women and also carries an increased risk of ovarian cancer, BRCA2 raises the risk of breast cancer alone, and can affect both women and men.[3]

Litigation started on May 12, 2009 when an assortment of medical organizations[4] and a group of patients, researchers and genetic counselors working on the prevention and cure of breast cancer sued Myriad Genetics, the directors of the University of Utah Research Foundation, and the U.S. Patent and Trademark Office (USPTO). The plaintiffs challenged fifteen claims of seven patents owned or exclusively licensed to Myriad Genetics, a company involved in diagnostic testing, and asked for summa-

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1 See Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 13 June 2013, 569 U.S. 12-398 (2013), available on the Internet at <http://www.supremecourt.gov/opinions/12pdf/12-398_1b7d.pdf> (last accessed on 14 August 2013).

2 See Mariachiara Tallacchini, *Gene Patenting in Europe* (forthcoming): "In Europe, after two patents on BRCA1 (Patents EP0699754 and EP0705902) were granted by the EPO in January and November 2001, Switzerland's Social Democratic Party, Greenpeace Germany, the French Institute Curie, Assistance Publique-Hôpitaux de Paris, the Belgian Society of Human Genetics, the Netherlands, the Austrian Federal Ministry of Social Security et al. filed an opposition with the support of the European Parliament. Opponents argued that both inventions lacked novelty, inventive step and industrial application and posed ethical and policy concerns. One of the patents was revoked and the other was amended. After Myriad's appeal and opposition they were restored, but in an amended form".

3 G. De Wert, R. Ter Meulen, R. Mordacci and M. Tallacchini, *Ethics and Genetics. A Workbook for Practitioners and Students* (Oxford-New York: Berghahn Books, 2003). On the discovery of BRCA1 and 2 genes see also S. Parthasarathy, *Building Genetic Medicine. Breast Cancer, Technology, and the Comparative Politics of Health Care* (Cambridge MA: The MIT Press, 2007), at pp. 3-7.

4 (1) The Association of Molecular Pathology (AMP); (2) The American College of Medical Genetics (ACMG); (3) The American Society for Clinical Pathology (ASCP); (4) The College of American Pathologists (CAP).

ry judgment on their invalidity. These claims fall into two main categories: product claims[5] and method claims.[6]

The public debate raised by these patents focuses on whether the claims are patentable subject matter according to Title 35 § 101 U.S.C.,[7] since they include the so-called "wild type" sequences,[8] namely DNA sequences not altered and mutated.[9] These sequences are the basis for performing any kind of clinical genetic predisposition test for breast and ovarian cancer, in order to establish the actual existence of mutations in the BRCA1 and 2 genes of individuals.

The claims have been challenged on legal and constitutional grounds. According to the plaintiffs the claims fall within the judicial patentability exclusion affirmed in *Diamond v. Chakrabarty*[10] on the laws of nature, natural phenomena and abstract ideas. Furthermore, they infringe the First Amendment,[11] which deals with liberty of expression and association, and Article I, section 8, clause 8 of the U.S. Constitution.[12]

Myriad was accused of having pursued, since the '90s, a commercial strategy aimed at gaining a monopoly on BRCA1 and 2 mutations testing:

1. Myriad patented several BRCA1 and 2 sequences, as well as the methods to compare them.
2. Then it enforced its patents and exclusive licenses against other researchers, clinicians and laboratories offering similar services, by sending cease and desist letters and proposing collaboration licenses.

This monopolistic strategy was considered to have hindered clinical research on cancer, limited the performance of alternative/complementary clinical diagnostic tests for hereditary cancer predisposition, raised considerably the health insurance costs related to BRCA1 and 2 mutations testing and restrained access to health care for patients.

The District Court granted summary judgment to the petitioners on the composition claims and concluded that Myriad's claims, including the ones related to cDNA,[13] were invalid since they covered products of nature.

On July 29, 2011, the Court of Appeals for the Federal Circuit held valid most of Myriad's patents on BRCA1 and 2 genes, reaffirming the USPTO's long-standing practice of granting patents on isolated DNA sequences. On the merits, the Court reversed the District Court's decision that Myriad's composition claims to "isolated" DNA molecules cover patent-ineligible products of nature under Title 35 § 101 U.S.C. since the molecules, as claimed, do not exist in nature. It reversed the decision that Myriad's method claim to screening potential cancer therapeutics via changes in cell growth rates is directed to a patent-ineligible scientific principle. It, however, affirmed the decision that methods claims directed to

5 The "product category" includes: (a) Claims that cover the isolated BRCA genes (claim 1 of the '282 patent, claim 1 of the '473 patent, and claims 1 and 6 of the '492 patent); (b) Claims that cover only the BRCA cDNA (claims 2 and 7 of the '282 patent and claim 7 of the '492 patent); (c) Claims that cover portions of the BRCA genes and cDNA as small as 15 nucleotides long (claims 5 and 6 of the '282 patent).

6 The "method category" encompasses method claims directed at comparing or analyzing a patient's altered BRCA sequence with the normal one or wild-type one to identify the presence of cancer-predisposing mutations (e.g. claim 1 of the '999 and '001 patents).

7 See 35 U.S.C. § 101 *Inventions patentable*, available on the Internet at <http://www.wipo.int/clea/docs_new/pdf/en/us/us007en.pdf> (last accessed on 14 August 2013).

8 Plaintiffs point out claims 1, 2, 5 and 6 of "patent '282"; claim 1 of "patent '492". See*Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, Complaint, 12 May 2009, available on the Internet at <http://docs.justia.com/cases/federal/district-courts/new-york/nysdce/1:2009cv04515/345544/1/0.pdf?ts=1243609964> (last accessed on 14 August 2013), at pp. 20–21.

9 Scientists often use the term "wild-type" to refer to the normal gene sequence, i.e. the sequence of a gene without any variation, against which individuals' gene sequences are compared. *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, Case 1:09-cv-04515-RWS, 29 March 2010, available on the Internet <http://graphics8.nytimes.com/packages/pdf/national/20100329_patent_opinion.pdf?scp=3&sq=Myriad%20Genetics&st=cse> (last accessed on 14 August 2013), at p. 31. However, Senior Judge Sweet points out that "there is an increasing recognition that the notion of a single 'normal' gene sequence may not be entirely accurate in light of the high frequency of variations in a gene sequence between individuals". See note 8, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 29 March 2010, at p. 31.

10 U.S. Supreme Court, *Diamond v. Chakrabarty* (447 U.S. 303), 16 June 1980, the "Chakrabarty case".

11 On the First Amendment of the U.S. Constitution see A. Roddey Holder and J.T. Roddey Holder, *The Meaning of the Constitution* (NY Hauppauge: Barron's, 1997), at p. 57.

12 Art. I, section 8, clause 8 states: "The Congress shall have the Power … To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries". See A. Roddey Holder and J.T. Roddey Holder, *The Meaning of the Constitution*, *supra* note 11, at p. 28.

13 cDNA or complementary DNA is "a man-made copy of the coding sequences of a gene; cDNA is produced in a test tube – it is not a natural product. In a living cell, the protein-coding sequences of DNA are transcribed as mRNA. Molecular biologists use reverse transcriptase, an enzyme that makes DNA copies from RNA, to make copies of the mRNA. The resulting cDNA – a copy of a copy, so to speak – may then be analyzed by various methods". See Daniel J. Kevles and Leroy Hood (eds.), *The Code of Codes: Scientific and Social Issues in the Human Genome Project* (Cambridge MA: Harvard University Press, 2000), at p. 376.

comparing or analyzing DNA sequences are not patent-eligible because such claims cover only abstract mental steps.[14]

On March 26, 2012, the U.S. Supreme Court granted the petition for a writ of certiorari on the case.[15] This decision vacated the judgment of appeal and remanded the case to the United States Court of Appeals for the Federal Circuit for further consideration in light of *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* (the "Mayo case").[16] In the Mayo case the U.S. Supreme Court, in a unanimous opinion written by Justice Stephen Breyer, held invalid several patent claims, which concerned the use of thiopurine drugs to treat certain autoimmune diseases. The patented processes were not considered patent eligible as they claimed laws of nature, namely the correlations between thiopurine metabolite levels and the toxicity or efficacy of thiopurine drug dosages.

On remand, on August 16, 2012, the Court of Appeals affirmed the District Court in part and reversed in part, with each member of the panel writing separately. The Court agreed that only one petitioner, Dr. Ostrer, had standing.[17] On the merits, it held that both isolated DNA and cDNA sequences were patent eligible under § 101.[18] The Court reversed the District Court's holding that Myriad's method claim to screening potential cancer therapeutics via changes in cell growth rates of transformed cells is directed to a patent-ineligible scientific principle and affirmed that Myriad's method claims directed to comparing or analyzing DNA sequences are patent-ineligible.[19]

The central issue discussed by the panel members was whether the act of isolating a DNA sequence, separating a sequence of nucleotides from the rest of the chromosome, is an inventive act that entitles the person who first did it to a patent or not. Each member of the panel had a different point of view on the question. While Judges Lourie and Moore agreed that Myriad's DNA sequences were patent-eligible, but disagreed on the rationale, Judge Bryson dissented in part and argued that isolated DNA is not patent-eligible.

II. The product of nature doctrine applied to isolated DNA sequences

On November 30, 2012, the Supreme Court granted again petition for a writ of certiorari on the Myriad case, but limited it to one question presented by petitioners – "Are human genes patentable?" – [20] and dismissed the other two, which concerned Myriad's method claims and petitioners' standing.[21] The Court's judgment of June 13, 2013 has, therefore, dealt only with patent eligibility of DNA sequences and focused on whether they are patentable subject matter, according to Title 35 § 101 U.S.C., or fall within one of the implicit exceptions to this provision established for laws of nature, natural phenomena and abstract ideas. The rationale of these exceptions to patentability is that they represent "the basic tools of scientific and technological work"[22] that lie beyond the domain of patent protection. The first two excep-

14 U.S. Court of Appeals for the Federal Circuit, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 29 July 2011, available on the Internet at <http://www.aclu.org/files/assets/10-1406.pdf> (last accessed on 14 August 2013), at p. 8.

15 See U.S. Supreme Court Order 11-725, 26 March 2012, available on the Internet at <http://www.supremecourt.gov/orders/courtorders/032612zor.pdf> (last accessed on 14 August 2013).

16 U.S. Supreme Court, *Mayo Collaborative Services, Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, 20 March 2012, 566 U.S. (2012), available on the Internet at <http://www.supremecourt.gov/opinions/11pdf/10-1150.pdf> (last accessed on 15 July 2013).

17 U.S. Court of Appeals for the Federal Circuit, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 16 August 2012, available on the Internet at <http://www.cafc.uscourts.gov/images/stories/opinions-orders/10-1406.pdf> (last accessed on 14 August 2013), at p. 7.

18 U.S. Court of Appeals for the Federal Circuit, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 16 August 2012, *supra* note 17, at pp. 7-8.

19 U.S. Court of Appeals for the Federal Circuit, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 16 August 2012, *supra* note 17, at p. 8.

20 See In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, on Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit, Petition for a Writ of Certiorari, 25 September 2012, available on the Internet at <http://sblog.s3.amazonaws.com/wp-content/uploads/2012/11/12-398-Petition.pdf> (last accessed on 14 August 2013), at p. i.

21 See In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, on Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit, Petition for a Writ of Certiorari, *supra* note 20, at p. i: "2. Did the Court of Appeals err in upholding a method claim by Myriad that is irreconcilable with this Court's ruling in *Mayo Collaborative Servs. v.Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012) 3. Did the Court of Appeals err in adopting a new and inflexible rule, contrary to normal standing rules and this Court's decision in *MedImmune, Inc. v. Genentech, Inc.*, 549 U.S. 118 (2007), that petitioners who have been indisputably deterred by Myriad's "active enforcement" of its patent rights nonetheless lack standing to challenge those patents absent evidence that they have been personally threatened with an infringement action?"

22 *Mayo Collaborative Services, Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, 20 March 2012, *supra* note 16, at p. 3, citing *Benson,* 409 U. S.

tions/exclusions to patentable subject matter, which regard the laws of nature and natural phenomena, result from the so-called product of nature doctrine, which can be traced back to the XIX century and was re-affirmed in *Diamond v. Chakrabarty*.[23] According to it, the laws of nature and natural phenomena are excluded from patent protection, whereas a non-natural occurring manufacture or composition of matter – a product of human ingenuity – is patent-eligible. In order to assess whether this doctrine could be applied to Myriad's composition claims on DNA's sequences, the Court examined what Myriad's invention consisted of and concluded that "Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13".[24] Confronting Myriad's gene claims with Chakrabarty's invention, it observed that Chakrabarty's bacterium was new, "with *markedly different* characteristics from any found in nature", whereas "Myriad did not create anything ... it found an important and useful gene, but separating that gene from its surrounding genetic materials is not an act of invention".[25] Justice Thomas, who delivered the opinion of the Court, argued that although isolating DNA from the human genome severs chemical bonds, Myriad's claims were not expressed in terms of chemical composition nor did they rely in any way on the chemical changes that result from isolation of a particular section of DNA.

The Judge pointed out that the claims, instead, focused on the genetic information encoded in the BRCA1 and 2 genes[26] because it is the genetic information that is valuable for Myriad. As a matter of fact, "if the patents depended upon the creation of a unique molecule, then a would be infringer could arguably avoid at least Myriad's patent claims on entire genes ... by isolating a DNA sequence that included both the BRCA1 or BRCA2 gene and one additional nucleotide pair". Since such a molecule would not be chemically identical to the molecule invented by Myriad, there would not be any patent infringement. However, as the Court argued, Myriad would resist that outcome, since its claims are concerned primarily with the information in the genetic sequence, not with the specific chemical composition of a particular molecule.

The Court, therefore, concluded unanimously that "genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material".[27] This holding may have significant consequences on the USPTO long-standing practice of granting patents on *isolated* DNA sequences because, for the first time, the Supreme Court made clear that extensive research effort and the mere isolation of DNA sequences are insufficient to satisfy the demands of § 101.

The Court, however, deemed cDNA patent eligible under § 101 since it is not naturally occurring. As the U.S. Court of Appeals for the Federal Circuit explained,[28] DNA molecules can be also synthesized in the laboratory and one type of synthetic DNA molecule is complementary DNA or cDNA. 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 (the coding regions for proteins) and none of the intron sequences (the non-coding regions) from a chromosomal gene sequence. The creation of a cDNA sequence from mRNA results in an exons-only molecule that does not exist in nature. Therefore, cDNA sequences were considered patent-eligible.

III. Comment

As regards DNA sequences, isolation and purification are scientific concepts that have acquired legal relevance in patent systems to distinguish non-patentable sequences from patentable ones.[29] In the

23 U.S. Supreme Court, *Diamond v. Chakrabarty*, 16 June1980, *supra* note 10.

24 See Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 13 June 2013, *supra* note 1, at p. 12.

25 See Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 13 June 2013, *supra* note 1, at p. 12.

26 See Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 13 June 2013, *supra* note 1, at pp. 14-15.

27 Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 13 June 2013, *supra* note 1, at p. 18.

28 U.S. Court of Appeals for the Federal Circuit, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 16 August 2012, *supra* note 17, at pp. 16-17.

29 In the European Union the criteria of isolation and purification were introduced (art. 5.2) with the approval of the European Parliament and Council Directive 98/44/EC on the Legal Protection of Biotechnological Inventions, available on the Internet at <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1998:213:0013:0021:EN:PDF> (last accessed on 30 July 2013).

United States the introduction[30] into the USPTO's revised Utility Examination Guidelines[31] of 2001[32] of the criteria of isolation and purification has established the rationale to legally demarcate between naturally occurring DNA sequences and artificially isolated/purified ones. According to the Guidelines, "an isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound". The inclusion of these criteria in the USPTO's Utility Examination Guidelines has supported DNA sequences patentability, reducing the risks for DNA patent holders to incur the "product of nature" doctrine's objections.[33]

Although the meanings of "isolation" and "purification" seem to be clear, the Myriad case has instead shown all the ambiguities related to their practical implementation. Genes, as Judge Sweet pointed out, are of a double-nature: on one hand, they are chemical substances or molecules and, on the other, they are carriers of information. In the Myriad case the former viewpoint had to face the latter,[34] according to which "DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature".[35] If the latter is considered more scientifically and legally sound in describing the very nature of DNA sequences, it can be concluded that isolated DNA molecules fall within the "product of nature"[36] exception under 35 U.S.C. § 101 because such isolated DNAs are not "markedly different" from native DNAs.[37]

The judges who decided the Myriad case expressed opposing views about what is DNA (a chemical molecule or information), whether it is better described by its structure or its function and what the criterion of isolation means within each of these different frames. For instance, Judge Lourie of the Court of Appeals for the Federal Circuit stated that the process of excising a selected portion of DNA from its cellular environment results in a molecule that is *structurally* different from native DNA, since each end of the isolated DNA segment is no longer bonded to the rest of the gene. According to him, the fact that "isolated DNA has been cleaved (i.e., had covalent bonds in its backbone chemically severed) or synthesized to consist of just a fraction of a naturally occurring DNA

30 As the U.S. Department of Justice explained in its brief for the United States as *amicus curiae* in support of neither party, in 2001 the USPTO issued its first written explanation of its practice of granting patents for isolated DNA molecules. In response to comments concerning proposed revisions to its Utility Examination Guidelines (66 Fed. Reg. 1092, January 5, 2001), the PTO held that an isolated DNA molecule is not a product of nature "because that DNA molecule does not occur in that isolated form in nature". See In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, Brief of the United States as *amicus curiae* in support of neither party, 31 January 2013, available on the Internet at <http://www.americanbar.org/content/dam/aba/publications/supreme_court_preview/briefs-v2/12-398_neither_amcu_us.authcheckdam.pdf> (last accessed on 14 August 2013), at pp. 27-28.

31 In 2001 the USPTO published a revised version of the Utility Examination Guidelines to be used by office personnel in their review of patent applications for compliance with the 'utility' requirement of 35 U.S.C. § 101, that became effective on January 5, 2001. See USPTO, <http://www.uspto.gov/web/offices/com/sol/og/2001/week05/patutil.htm> (last accessed on 14 August 2013).

32 After the controversial granting in the '90s of some patents on the so-called ESTs (expressed sequence tags), in 2001 the USPTO had to enact new Utility Examination Guidelines to stem the "far-west patent rush" to DNA sequences (see M.A. Heller and R.S. Eisenberg, "Can Patents Deter Innovation? The Anticommons in Biomedical Research", *Science,* 1 May 1998, Vol. 280, at p. 699). In the Guidelines were set forth the concepts of *isolation* and *purification* to discriminate non-patentable DNA sequences from patentable ones: "An isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound" (USPTO, January 5, 2001, Utility Examination Guidelines, 66 Fed. Reg., at p. 1092).

33 The origin of the "product of nature" doctrine can be traced back to the XIX century, at least in 1889 when *Ex parte Latimer* [Commn. Dec. 123(1889)] was decided by the Commissioner of patents. See J. Wilson, "Patenting Organisms. Intellectual Property Law Meets Biology", in D. Magnus, A. Caplan, G. McGee (eds.) *Who Owns Life*? (Amherst NY: Prometheus Books, 2002) at pp. 47-48. For a critical historical reconstruction of the "product of nature" doctrine, see L.J. Demaine and A.X. Fellmeth, "Reinventing the Double Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent", in 55 *Stanford Law Review* (2002), at pp. 303-462.

34 See L.E. Kay, *Who Wrote the Book of Life? A History of the Genetic Code* (Stanford CA: Stanford University Press, 2000).

35 U.S. District Court for the Southern District of New York, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 29 March 2010, available on the Internet at <http://graphics8.nytimes.com/packages/pdf/national/20100329_patent_opinion.pdf?scp=3&sq=Myriad%20Genetics&st=cse> (last accessed on 14 August 2013), at pp. 7-8.

36 The main substantive argument advanced by the plaintiffs and agreed on by Judge Sweet is based on the "product of nature doctrine". See U.S. District Court for the Southern District of New York, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, Complaint, *supra* note 8, at p. 18.

37 See U.S. District Court for the Southern District of New York, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 29 March 2010, *supra* note 35, at p. 8.

molecule"[38] makes it "markedly different" from native DNA. Furthermore, he embraced a structural description of DNA sequences, pointing out that although "biologists may think of molecules in terms of their uses, genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions".[39]

Conversely, the U.S. Supreme Court endorsed the view that genes carry information and it is their information that makes them valuable for patent purposes. Like the U.S. Department of Justice, which wrote a brief for the United States as *amicus curiae* in support of neither party, the Court considered the structural difference between isolated DNA and native DNA (namely the isolated segment's "snipped" ends) with no functional consequences, as the truncation does not alter the operative properties of the isolated DNA segment.[40] This perspective is focused on the function that DNA performs in the human body and in a laboratory. If the function performed is the same and the "additional utility" that isolation adds is simply the ability of researchers to study and exploit in a laboratory the inherent natural properties that isolated DNA shares with native DNA, isolated DNA sequences will not be patent eligible, according to the brief.[41]

The word "isolation" generally refers to "separating a specific gene or sequence of nucleotides from the rest of the chromosome".[42] However, in order to establish patent eligibility of a specific isolated DNA sequence, the patent examiner must ascertain whether isolation makes the sequence "markedly different" from the one found in nature or not. The USPTO issued patents on isolated DNA sequences for more than twenty years. This practice, as the United States District Court for the Southern District of New York pointed out, was based on the analogy between DNA sequences and chemical compounds.[43] Nonetheless, if this view, grounded on the chemical analogy, is questioned, the boundaries between naturally occurring products and man-made inventions may change.

Although, according to Myriad, the USPTO's past practice of awarding gene patents should be entitled to deference by the courts, the Supreme Court disagreed, recalling the Department of Justice's brief. The brief made clear that the USPTO's revised Utility Examination Guidelines do not have the force of the law and do not specifically address patents on DNA, but were revised to fix a standard for determining utility generally.[44] Moreover, Congress has never specifically considered the USPTO's practice of granting patents on isolated DNA in its bills related to patents on genetic materials.[45] The correctness of the USPTO's practice was never challenged in litigation prior to the Myriad case, but the Supreme Court designed an opposite frame to describe the "nature" of genes, centred on their biological information and function. Within this frame, in order to assess gene patent eligibility, the concept of isolation entails more than extensive research and economical investments to achieve the separation of a DNA sequence from the rest of the chromosome.[46]This choice in favor of defining genes by their informational character and function may, therefore, affect the application of the criteria of isolation in the future and bring about a substantial change in the USPTO's practice of granting patents on native DNA sequences.

In deciding the case, the Supreme Court was guided by the consideration that "patent protection

38 U.S. Court of Appeals for the Federal Circuit, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 16 August 2012, *supra* note 17, at p. 45.

39 U.S. Court of Appeals for the Federal Circuit, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 16 August 2012, *supra* note 17, at p. 48.

40 In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, Brief of the United States as *amicus curiae* in support of neither party, 31 January 2013, *supra* note 30, at p. 22.

41 In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, Brief of the United States as *amicus curiae* in support of neither party, 31 January 2013, *supra* note 30, at p. 23.

42 Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 13 June 2013, *supra* note 1, at p. 8.

43 U.S. District Court for the Southern District of New York, *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.*, 29 March 2010, *supra* note 35, at p. 7. Eisenberg explained why the chemical analogy was applied to genes in such a successful way. R.S. Eisenberg, "Why Gene Patenting Controversy Persists", 77 *Academic Medicine* (2002), at p. 1381; R.S. Eisenberg, "Patenting Genome Research Tools and the Law", 326 *Comptes Rendus Biologies* (2003), at p. 1116.

44 In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, Brief of the United States as *amicus curiae* in support of neither party, *supra* note 30, at p. 28.

45 See, for example, *Genomic Science and Technology Innovation Act* of 2002 (H.R. 3966, 107th Cong., 2d Sess., 2002); *Genomic Research and Diagnostic Accessibility Act* of 2002 (H.R. 3967, 107th Cong., 2d Sess., 2002); *Life Patenting Moratorium Act* of 1993 (S. 387, 103d Cong., 1st Sess., 1993); *Consolidated Appropriations Act* of 2004 (Pub. L. No. 108-199, § 634, 118 Stat. 101).

46 In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, Brief of the United States as *amicus curiae* in support of neither party, 31 January 2013, *supra* note 30, at p. 28.

strikes a 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'".[47] As the Department of Justice noted, "an overbroad conception of patent eligibility under §101 can impose significant social costs by requiring the public to pay to study and exploit that which ought to be 'free to all men and reserved to none'".[48] The product of nature doctrine exceptions to §101 reflect the public interest in avoiding undue restrictions imposed by patents that could preempt natural laws and substances. Unlike the USPTO's long-standing practice, the Supreme Court struck a different balance of the opposite interests involved in patenting DNA sequences: access to genetic information by scientific researchers and clinicians, patients' health care rights and intellectual property rights held by biotech companies.

IV. In the aftermath of the U.S. Supreme Court's decision

On June 14, 2013, the day after the Supreme Court's decision was issued, Myriad's stock fell by 5.6%, and it became clear to analysts that, even though the company was partially successful before the Court, its market share in the genetic testing on BRCA1 and 2 genes was expected to decrease.[49]

Shortly afterwards, Myriad Genetics, Inc., together with the University of Utah Research Foundation, the Trustees of the University of Pennsylvania, HSC Research and Development Limited Partnership and Endorecherche Inc. filed a complaint for patent infringement and a Motion for Preliminary Injunctive Relief against two competitors, Gene by Gene Ltd[50] and Ambry Genetics Corporation,[51] which announced that they would offer genetic testing on BRCA1 and 2 genes at a much lower price than Myriad had offered before the decision. As Myriad made clear in the Motion for Preliminary Injunctive Relief and Memorandum in Support against Defendant Ambry Genetics,[52] before the Supreme Court's ruling on June 13, 2013, Myriad held 24 patents containing 520 claims concerning BRCA1 and 2 genes. After the Court held that five patent claims covering isolated naturally occurring DNA were not patent-eligible, Myriad's patent estate was reduced to 24 patents and 515 patent claims. Nonetheless, these two cases do not involve any of those five rejected claims,[53] but only methods-of-use and synthetic DNA patent claims concerning BRCA1 and 2 genes, which are valid and, therefore, enforceable.

As regards the first civil action, Myriad complained that Gene by Gene infringed and induced the infringement of, literally and/or under the doctrine of equivalents, several claims related to nine patents,[54] owned or exclusively licensed to Myriad and asked for damages. Gene by Gene began, in fact, offering its BRCA 1 and 2 analysis and clinical diagnostic and genomic services as part of its testing menu as soon as the Court's opinion was issued, on June 13, 2013.[55]

47 Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, 13 June 2013, *supra* note 1, at p. 11.

48 In the Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, Brief of the United States as *amicus curiae* in support of neither party, 31 January 2013, *supra* note 30, at p. 33.

49 See Johanna Bennett, "About Face on Myriad Genetics, Stock Falls 5.6%", available on the Internet at <http://blogs.barrons.com/stockstowatchtoday/2013/06/13/about-face-on-myriad-genetics-stock-falls-5-6/> (last accessed on 30 July 2013).

50 In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Gene by Gene LTD*, Complaint Demand for Jury Trial, 10 July 2013, available on the Internet at <http://files.priorsmart.com.s3.amazonaws.com/utdce/89792/Complaint.pdf?Signature=7Cgxhnu5Qlu%2FgM7jCmSRghLXeZI%3D&Expires=1375782713&AWSAccessKeyId=AKIAJWOP3U6XRH5BBMOA> (last accessed on 31 July 2013).

51 In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Motion for Preliminary Injunctive Relief and Memorandum in Support, 9 July 2013, available on the Internet at <http://www.patentlyo.com/myriad-motionforpreliminaryrelief.pdf> (last accessed on 31 July 2013), at p. 4.

52 See In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Motion for Preliminary Injunctive Relief and Memorandum in Support, 9 July 2013, *supra* note 51, at p. 4.

53 See In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Motion for Preliminary Injunctive Relief and Memorandum in Support, 9 July 2013, *supra* note 51, at p. 4.

54 Myriad alleged that Gene by Gene was infringing the following patents, owned or exclusively licensed to Myriad: U.S. patent No. 5,709,999 (the "'999 Patent"); U.S. patent No. 5,747,282 (the "'282 Patent"); U.S. patent No. 5,753,441 (the "'441 Patent"); U.S. patent No. 5,837,492 (the "'492 Patent"); U.S. patent No. 6,033,857 (the "'857 Patent"); U.S. patent No. 5,654,155 (the "'155 Patent"); U.S. patent No. 5,750,400 (the "'400 Patent"); U.S. patent No. 6,951,721 (the "'721 Patent"); U.S. patent No. 7,250,497 (the "'497 Patent).

55 In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Gene by Gene LTD*, Complaint Demand for Jury Trial, 10 July 2013, *supra* note 50, at p. 4.

Furthermore, on July 9, 2013, Myriad filed a Motion for Preliminary Injunctive Relief against Ambry Genetics, claiming that it could suffer immediate and irreparable harm if Ambry was not enjoined from infringing the activity of Myriad's patents.[56] Such harm consists of "price erosion and the loss of the benefit of Myriad's established pricing strategy; the loss of market share; reputational injury; and loss of the benefit of the remaining limited term of patent exclusivity and Myriad's patent business plans for that period".[57] Myriad asserted that it had created and nurtured to maturity a new market for clinical diagnostic testing for hereditary cancer predisposition.[58] Allowing Ambry to offer its BRCAPlus test for $2,280, whilst Myriad's competing test is priced at $4,040, would cause a decline in market prices for Myriad, since third party payers, such as insurers and/or Health Maintenance Organizations, would exert pressure on the company to lower its prices in response to Ambry. In addition, other competitors could potentially enter the market and, therefore, Myriad's market share would drop. As a consequence, Myriad argued, the overall quality of tests on BRCA1 and 2 would decrease, as the company contends that its tests are more reliable and accurate than Ambry's products.

By filing lawsuits against Gene by Gene and Ambry Genetics shortly after the Supreme Court's decision, Myriad sent a clear signal to potential competitors that, although the Court's ruling has potentially weakened its market advantage of being the only provider of tests on BRCA1 and 2 genes, the company is willing to fight any attempt to threaten its monopolistic market share over clinical diagnostic testing for hereditary breast and ovarian cancer predisposition. However, the reason why Myriad's patents became so controversial in the United States is that they are at the core of a monopolistic strategy that was considered to hinder clinical research on breast and ovarian cancer, raising health insurance costs related to BRCA1 and 2 mutations testing and restraining access to health care for patients. All these issues, which were raised by the plaintiffs in the Myriad case, involve public interests that had to confront Myriad's patent claims and its substantial investment towards developing genetic diagnostic testing. Not only is Myriad the owner of many patents related to BRCA1 and 2 genes, but it is also the exclusive licensee of others,[59] which are owned or co-owned by universities and are partially based on federally-funded research. Some of these exclusive licenses, together with several patents granted to Myriad, were challenged in the Myriad case and are at present enforced against Gene by Gene and Ambry.

Since the 1980s the U.S. Congress has backed a policy to promote the utilization of federally-sponsored inventions with the passage of the Bayh-Dole Act[60] and the Stevenson-Wydler Technology Innovation Act.[61] The goal of this legislation was to transform universities into major, active patent claimants for federally funded research, so that they could attract private investors that could transform their discoveries into commercial products and would become the exclusive licensees of their patents. In more than 20 years U.S. universities have taken the opportunities opened by this legislation and filed patent applications on basic research discoveries, such as DNA sequences and protein structures. Although this policy has largely fostered investments in biomedical research and favored impressive scientific results, in the long run it has entailed some problems, namely hindering subsequent research and limiting patients' access to health care, as the Myriad case and its aftermath show.

Addressing one of these issues, on July 12, 2013, U.S. Senator Patrick Leahy of Vermont sent a letter to the Director of the National Institutes of Health (NIH), Francis Collins, urging him to consider exer-

56 Myriad alleged that Ambry Genetics is infringing: claims 16 and 17 of patent '282, claims 29 and 30 of patent '492, claims 8 and 7 of patent '441, claim 4 of patent '857, claim 5 of patent '721, claims 2 and 4 of patent '155. See In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Motion for Preliminary Injunctive Relief and Memorandum in Support, 9 July 2013, *supra* note 51, at p. 15.

57 In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, *supra* note 51, at p. 30.

58 In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, *supra* note 51, at p. 3.

59 For example, U.S. patent No. 5,747,282 (the "'282 Patent"), which is owned by the University of Utah, along with the Public Health Service, through the National Institutes of Health and is exclusively licensed to Myriad; U.S. patent No. 5,753,441 (the "'441 Patent"), which is owned by the University of Utah and Public Health Service and exclusively licensed to Myriad. See In the United States District Court for the District of Utah, Central Division, *University of Utah Research Foundation, et al., v. Gene by Gene LTD*, Complaint Demand for Jury Trial, 10 July 2013, *supra* note 50, at pp. 6-7.

60 The Bayh-Dole Act was passed in December 1980 (Act of December 12, 1980, Pub. L. No. 96-516, § 6(a), 94 Stat. 3015, 3019-3028, 1980, codified as amended at 35 U.S.C. §§ 200-212, 1994). Its main purpose is "to use the patent system to promote the utilization of inventions arising from federally funded research or development …". See 35 U.S.C. § 200.

61 The Stevenson-Wydler Technology Innovation Act was passed in 1980 (Pub. L. No. 96-480, § 2, 94 Stat. 2311-2320, 1980, codified as amended at 15 U.S.C. §§ 3701-3714, 2000).

cising "march-in" rights under the Bayh-Dole Act to ensure greater access to genetic testing for breast and ovarian cancer.[62] As several patents held by Myriad are based in part on federally funded research, they are subject to the Bayh-Dole Act's provisions. Under the Bayh-Dole Act, federal agencies, such as the NIH, can exercise march-in rights *ex post* to compel licensing of patents on inventions made through federally funded research. The federal agency can take this initiative only in some circumstances, such as when the "action is necessary to alleviate health or safety needs which are not reasonably satisfied by the contractor, assignee, or their licensees".[63]

Senator Leahy highlighted the importance of Myriad's genetic test for public health and the fact that the company is its only provider, because it is covered by patent protection, and charges between $3,000 and $4,000. Since, by exercising march-in rights, the NIH can require the patent holder to grant a license on reasonable terms (that can be non-exclusive, partially exclusive or exclusive), Senator Leahy claims that this initiative would meet the health needs of the public who cannot afford the testing provided by Myriad.

As early as 2003 Arti Rai and Rebecca Eisenberg,[64] discussing the Bayh-Dole's reform and the progress of biomedicine, pointed out that biomedical tradition of open science has been eroded considerably over the past decades, since "proprietary claims have reached farther upstream from end products to cover fundamental discoveries that provide the knowledge base for future product development",[65] and that this change is partially due to the narrowing of the conceptual gap between fundamental research and commercial application. According to them, the changes in the economic structure of research and in the case law, that adopted an expansive approach to patent eligibility while relaxing the standards for patent protection, such as utility and non-obviousness, may sometimes, in the long run, hinder rather than accelerate biomedical research.[66]

As a response to the problems arising from the frenzy of patent claims on upstream research tools, they envisaged a set of solutions, which included the reinvigoration of the product of nature limitation on patent eligibility, so that discoveries of DNA sequences and proteins could be excluded from patent protection, and to fortify the utility standard to limit the patenting of broadly enabling research tools. In addition, they argued that march-in rights could be used by agencies to better assure the public interest in federally funded patented inventions, but the administrative hurdles are so cumbersome that the NIH has never exercised these rights.[67]

In the Myriad case, the Supreme Court has already intervened decisively, reinvigorating the product of nature doctrine and reshaping the criterion of isolation. However, since citizens' health interests at stake are so relevant, maybe for the first time the NIH would actually exercise march-in rights in order to serve and fulfill the public interest involved in federally funded inventions.

62 See Senator Patrick Leahy's Letter addressed to Doctor Francis S. Collins, Director of the National Institutes of Health, available on the Internet at <http://www.leahy.senate.gov/download/07-12-13-pjl-to-nih-re_-myriad-march-in> (last accessed on 14 August 2013), at p. 1.

63 See 35 U.S.C. § 203 March-in rights, available on the Internet at <http://www.gpo.gov/fdsys/pkg/USCODE-2011-title35/pdf/USCODE-2011-title35-partII-chap18-sec203.pdf> (last accessed on 14 August 2013).

64 Arti K. Rai and Rebecca S. Eisenberg, "Bayh-Dole Reform and the Progress of Biomedicine", in James Boyle (ed.), *Law and Contemporary Problems*, Vol. 66: 2003, Nos. 1 & 2, at pp. 289-314.

65 Arti K. Rai and Rebecca S. Eisenberg, "Bayh-Dole Reform and the Progress of Biomedicine", *supra* note 64, at pp. 289.

66 See Arti K. Rai and Rebecca S. Eisenberg, "Bayh-Dole Reform and the Progress of Biomedicine", *supra* note 64, at pp. 290-291.

67 See Arti K. Rai and Rebecca S. Eisenberg, "Bayh-Dole Reform and the Progress of Biomedicine", *supra* note 64, at p. 294.