In the Aftermath of the "Myriad Case" - Myriad Is Denied Preliminary Injunction Against Ambry Genetics

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On March 10, 2014, the U.S. District Court of Utah, Central Division, decided in University of Utah Research Foundation, et al., v. Ambry Genetics Corporation, holding that "Plaintiffs are not entitled to a preliminary injunction", as they "are unable to establish that they are likely to succeed on the merits of the claims" nor "that the equitable factors support issuance of the requested injunction".

This case note gives an overview of the U.S. District Court's of Utah memorandum decision and order denying plaintiffs' motion for preliminary injunction and discusses its implications for the implementation of the criterion of isolation to "synthetic" DNA sequences, such as primers and probes.

I. University of Utah Research Foundation, et al., v. Ambry Genetics Corporation

On 10 March 2014, the U.S. District Court of Utah, Central Division, denied Myriad preliminary injunction against Ambry Genetics Corporation in *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation* (the "Ambry Case" or "*Ambry*")[1] and the memorandum decision may clarify what are the implications of the U.S. Supreme Court's judgment in *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*[2] ("*Myriad*"), issued on 13 June 2013.

In this decision the Supreme Court unanimously held 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".[3] When the Court's judgment was released, it was immediately regarded as deeply affecting 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, as well as biotech companies' custom to claim for patents on *isolated* DNA sequences.

However, it was not clear whether this decision would have actually allowed Myriad's competitors to enter into the screening market for the BRCA1 and BRCA2 genes.

Following the decision, Gene by Gene and Ambry Genetics immediately announced that they would offer genetic testing on BRCA1 and 2 genes at a much lower price than Myriad. After this announcement, Myriad Genetics et al. filed a complaint for patent infringement and a motion for preliminary injunctive relief against these competitors to prevent them from selling their screening tests and eroding Myriad's monopolistic market.

Myriad, on the 9 July 2013, filed a motion for preliminary injunctive relief against Ambry Genetics,[4] claiming that it could suffer immediate and irreparable harm if Ambry is not enjoined from infringing activity of Myriad's patents.

Myriad asserted that it has created and nurtured to maturity a new market for clinical diagnostic testing for hereditary cancer predisposition. Allowing

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1 See In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Memorandum Decision and Order Denying Plaintiffs' Motion for Preliminary Injunction, 10 March 2014, available on the Internet at <https://ecf.utd.uscourts.gov/cgi-bin/show_public_doc?214md2510-7> (last accessed on 25 June 2014).

2 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 25 June 2014).

3 Ibid., at p. 2.

4 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 <https://archive.org/details/726487-gov-uscourts-utd-89779-5-0 > (last accessed on 25 June 2014), at p. 4.

Ambry to offer its BRCAPlus test for $2,280, whilst Myriad's competing test is priced at $4,040 – which includes the price of BRCAnalysis, that is $3,340, plus the price of "BART" (BRCAnalysis Rearrangement Test) that amounts to $700 – 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.

By filing lawsuits against these companies, shortly after the Supreme Court's decision, Myriad gave a clear signal to potential competitors: that, although the Court's ruling has potentially weakened its market advantage of being the lone provider of tests on BRCA1 and 2 genes, the company is willing to fight back any attempt to threaten its monopolistic market share over clinical diagnostic testing for hereditary breast and ovarian cancer predisposition.

However, after these two cases were consolidated to be handled together by Judge Shelby and while the ruling on Myriad's motion for a preliminary injunction was still pending, on 6 February 2014, Gene by Gene case was settled. Gene by Gene agreed to cease "selling or marketing clinical diagnostic tests within North America that include analysis of the BRCA1 and/or BRCA2 genes".[5]

Conversely, Ambry continued to oppose Myriad's patent infringement allegations and motion for preliminary injunction and succeeded, pending trial on the merits.

II. The "Ambry Case" Before the U.S. District Court of Utah

Judge Robert J. Shelby of the U.S. District Court of Utah, who issued the memorandum decision and order in the Ambry case, addressed whether Myriad was entitled to obtain a preliminary injunction enjoining its competitor's sales or offers to sell genetic tests including a BRCA1 or BRCA2 panel.

Under Title 35 U.S.C. § 283, a court having jurisdiction on patent cases "may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent, on such terms as the court deems reasonable".[6] Nevertheless, a plaintiff can obtain an injunction only if he is able to establish that "[it] is likely to succeed on the merits, that [it] is likely to suffer irreparable harm in the absence of preliminary relief, that the balance of equities tips in [its] favor, and that an injunction is in the public interest".[7] The proof of the first two factors is pivotal in determining whether an injunction should be granted or not.

First, the Judge assessed if Myriad was likely to suffer irreparable harm.

Plaintiffs alleged that they would be harmed in several ways: 1. through price erosion for Myriad's testing products, as the company would lose the advantages of its established pricing strategy; 2. by the loss of market share for its testing products; 3. by reputational injury due to the fact that the public would confuse Ambry's testing products with Myriad's allegedly superior ones; 4. through the loss of the benefit of the remaining limited term of patent exclusivity.[8]

The Court found most of the arguments in support of the likeliness of irreparable harm, raised by Myriad, convincing. Myriad has been the lone provider of tests on BRCA1 and 2 in the U.S. for seventeen years and the Supreme Court's decision in *Myriad* drastically changed this monopolistic market situation. In its aftermath, Ambry and many other competitors began to offer BRCA1 and 2 screening products, so that Myriad is already facing the immediate threat of losing its third-party payer customers, unless it lowers its prices. In fact, at least one of them, Centers for Medicare and Medicaid Services (CMS) has exercised its pressure on Myriad to reduce the reimbursement rate for BRCA1 and 2 testing from $2,700 to $1,438.[9]

Nevertheless, Myriad was considered to fall short in demonstrating that it would incur reputational harm and brand dilution. Plaintiffs showed no clear evidence that Ambry's testing products are less accu-

5 See "BRCA Patent Owners and Gene by Gene, Ltd. Resolve Patent Suit", available on the Internet at <http://investor.myriad.com/releasedetail.cfm?ReleaseID=824154> (last accessed on 25 June 2014).

6 Title 35 U.S.C. § 283 Injunction, available on the Internet at <http://uscode.house.gov/view.xhtml?path=/prelim@title35/part3&edition=prelim> (last accessed on 25 June 2014).

7 In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Memorandum Decision and Order Denying Plaintiffs' Motion for Preliminary Injunction, *supra* note 1, at p. 55.

8 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, *supra* note 4, at p. 30.

9 In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Memorandum Decision and Order Denying Plaintiffs' Motion for Preliminary Injunction, *supra* note 1, at p. 60.

rate and reliable than Myriad's tests and of actual consumers' confusion between the testing products of the two companies.

Judge Shelby, then, addressed whether the company was likely to succeed on the merits. As Ambry raised substantial questions on the validity of Myriad's patents, his decision has, therefore, focused on the subject matter eligibility of Myriad's patent claims, according to Title 35 U.S.C. § 101.

Ten patent claims are at the core of Myriad's lawsuit against Ambry and could be divided into two general categories: 1. four claims which refer to pairs of synthetic DNA strands, called "primers" (Primer Claims)[10] and 2. six method claims for analyzing BRCA1 and 2 sequences (Method Claims).[11] Primers are short, synthetic, single stranded DNA molecules, which bind specifically to an intended target nucleotide sequence,[12] generally created using oligonucleotide synthesizing machines and used for the Polymerase Chain Reaction ("PCR"), which is a fundamental step to get to sequence DNA.

Method claims are drawn "to the mental process of comparing a genomic DNA sample to a DNA sequence that may be found in the BRCA1 and 2 genes"[13] and can require the use of primers and probes, which are short segments of DNA that "are used to detect the presence or absence of a particular DNA sequence in a DNA sample".[14]

Under 35 U.S.C. § 282 (a) patents are generally presumed valid and the burden of proof of their invalidity rests on the party asserting it. At the preliminary stage, however, the court addresses only the persuasiveness of the challenger's evidence.

The Court examined the Primer claims in light of *Myriad*. Two opposing interpretations of the Supreme Court's decision conflicted in this case. According to Myriad, the isolated DNA found patent ineligible by the Supreme Court is only genomic DNA that is *extracted* from its natural environment, whereas cDNA was held patent eligible because it is *synthetic*. The term "isolation", therefore, is interpreted by Myriad as meaning only "extraction" of genomic DNA.[15] These Primer claims, which are drawn to *synthetic* DNA that is "markedly different" from naturally occurring DNA, should be considered, therefore, patent eligible. As the Court noted, in drawing this conclusion "Plaintiffs rely on the facts that the primers: 1) are single stranded, matched pairs of DNA; 2) are shorter than an entire BRCA1 or BRCA2 gene; and 3) have unique utility – to prime PCR".[16]

Judge Shelby pointed out, however, that Myriad urged a distinction between extracted-isolated genomic DNA (which is patent ineligible) and artificially created, synthetic DNA (which is patentable), which is not supported by the Supreme Court's ruling.[17] In his view, a systematic reading of the whole case confirms that the Supreme Court held that isolated DNA segments were patent ineligible "as long as they reflected naturally occurring BRCA1 and BRCA2 sequences"[18] and, therefore, excluded "from patent eligibility synthetic DNA that reflects naturally occurring BRCA1 and BRCA2 sequences".[19]

Conversely, he endorsed a different interpretation of the Court's decision, centered on the *informational content* of DNA sequences, where it does not matter if DNA sequences are synthetically designed, but only whether they are "markedly different" from native DNA or not.

Judge Shelby re-affirmed that, although isolating DNA from the human genome severs chemical bonds, Myriad's claims were not expressed in terms of chemical composition nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Myriad's claims focused, instead, on the genetic information encoded in the BRCA1 and 2 genes.[20]

10 Claims 16 and 17 of the '282 Patent and claims 29 and 30 of the '492 Patent. See In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Memorandum Decision and Order Denying Plaintiffs' Motion for Preliminary Injunction, *supra* note 1, at p. 49.

11 Claims 7 and 8 of the '441 Patent; claim 4 of the '857 Patent; claim 5 of the '721 Patent; claims 2 and 4 of the '155 Patent. Ibid., at pp. 50-54.

12 Ibid., at p. 13.

13 Ibid., at p. 49.

14 Ibid., at p. 15.

15 In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Plaintiffs' Reply Memorandum in Support of Motion for Preliminary Injunctive Relief, available on the Internet at <https://archive.org/details/726487-gov-uscourts-utd-89779-5-0> (last accessed on 15 April 2014), at p. 40.

16 In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Memorandum Decision and Order Denying Plaintiffs' Motion for Preliminary Injunction, *supra* note 1, at p. 75.

17 Ibid., at p. 78.

18 Ibid., at p. 75.

19 Ibid., at p. 76.

20 See Supreme Court of the United States, *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.*, *supra* note 2, at pp. 14-15.

As the Supreme Court, however, did not mention explicitly primers and probes in its decision as patent ineligible isolated DNA, Judge Shelby undertook an independent reading of the *Myriad* case in light of *Chakrabarty*.[21]

The Judge highlighted that, in evaluating patentable subject matter, *Chakrabarty* made clear that courts should evaluate: "(1) the similarity in *structure* between what is claimed and what is found in nature; and (2) the similarity in *utility* between what is claimed and what is found in nature".[22] He, then, analyzed the Primer claims and noted that they are directed to compositions structurally similar to native DNA. The primers' claim description, for example, refers to the natural nucleotide sequence found in chromosomes 17q (BRCA1) and 13 (BRCA2). Moreover, the Court pointed out that, even when primers are only 15 to 18 nucleotides and 25 to 30 nucleotides in length and refer to BRCA1 and 2 genes' nucleotide sequences set forth in the exon only sequence, they have the same nucleotide sequences as naturally occurring DNA.

Primers were also considered similar in utility to naturally occurring DNA sequences. This similarity was drawn from the fact that they are derived or isolated from BRCA1 and 2 sequences, they "hybridize to complementary segments of the genes just as native DNA must, according to Watson-Crick pairing"[23] and, during the PCR, they undergo replication in a similar way to genomic DNA in the human body.

Myriad's arguments were found, therefore, not persuasive, as they were focused on primers' distinctness grounded only on structural chemical changes and nucleotides' length, whereas for the Judge *Myriad* clearly showed that it is the *informational content* of the nucleotide sequences that is fundamental in determining the structural and functional similarity between what is claimed and what is found in nature.

Likewise, Method claims underwent close scrutiny in light of *Mayo*[24] and the Federal Circuit's second *Myriad* ruling. In the second *Myriad* ruling, all but one method claims at issue were held patent ineligible, as they were directed to abstract, mental steps of "comparing and analyzing two gene [BRCA] sequences" and did not involve actual transformative steps.

In the *Mayo* case, the U.S. Supreme Court held invalid several patent claims, which concerned the use of thiopurine drugs to treat certain autoimmune diseases. The patented processes were held patent ineligible, as they claimed laws of nature, namely the correlations between thiopurine metabolite levels and the toxicity or efficacy of thiopurine drug dosages. The rationale behind the holding was that a process focusing on laws of nature, natural phenomena or abstract ideas may be patentable subject matter only if it entails an "inventive concept"[25] and it does not "risk disproportionately tying up the use of the underlying natural laws, inhibiting their use in the making of further discoveries".[26]

According to Myriad, these claims should be considered valid, since they involve the use of "inventive DNA synthesized in a laboratory based upon knowledge of the BRCA1 and 2 genes",[27] they are confined to "specific application of the new biomarkers Myriad discovered"[28] and these techniques could not be previously well-understood, as the BRCA1 and 2 sequences were unknown.

Conversely, the Court contended that the method claims did not withstand the inventive step set forth in *Mayo*. Moreover, it drew an analogy with the recent decision *Ariosa Diagnostic, Inc. v. Sequenom, Inc.*[29] and pointed out that the only inventive concept related to Plaintiffs' claims in *Ambry* was the discovery of the naturally occurring BRCA1 and BRCA2 sequences and that allowing the Method Claims

21 U.S. Supreme Court, *Diamond v. Chakrabarty*, 447 U.S. 303, 16 June 1980, available on the Internet at <http://caselaw.lp.findlaw.com/scripts/getcase.pl?court=us&vol=447&invol=303> (last accessed on 25 June 2014).

22 In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Memorandum Decision and Order Denying Plaintiffs' Motion for Preliminary Injunction, *supra* note 1, at p. 83.

23 Ibid., at p. 85.

24 U.S. Supreme Court, *Mayo Collaborative Services, Mayo Medical Laboratories, et al. v. Prometheus Laboratories, Inc.*, 566 U.S. (2012), 20 March 2012, available on the Internet at <http://www.supremecourt.gov/opinions/11pdf/10-1150.pdf> (last accessed on 25 June 2012), at p. 1334.

25 Ibid., at p. 1294.

26 Ibid.

27 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 4, at p. 16.

28 In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Plaintiffs' Reply Memorandum in Support of Motion for Preliminary Injunctive Relief, *supra* note 15, at pp. 56-57.

29 U.S. District Court for the Northern District of California, *Ariosa Diagnostic, Inc. v. Sequenom, Inc.*, 30 October 2013, available on the Internet at <http://docs.justia.com/cases/federal/district-courts/california/candce/3:2011cv06391/249148/254> (last accessed on 25 June 2014).

would effectively "preempt PCR involving BRCA1 and 2 genes – the most widespread means of amplifying DNA to facilitate research and testing".[30]

Finally, the Court balanced the hardships and the public interests involved in its decision. Although Judge Shelby recognized that Myriad was likely to suffer irreparable harm due to price erosion, loss of market share and of the remainder of exclusive patent terms, he found that Ambry acted cautiously in launching its BRCA testing products after the definition of *Myriad* litigation and was risking to lose its entire business. Therefore, he concluded that the balance tipped slightly in favor of Ambry and further supported his decision to deny a preliminary injunction.

However, as far as the public interest was concerned, he admitted that both parties raised compelling arguments, but neither showed that "the public interest mandates either the imposition or denial of Plaintiffs' requested injunction".[31]

III. Comment

The Ambry case is directly related to the Supreme Court's ruling in *Myriad*. Both cases show that, at present, U.S. courts are less willing to back the long-standing practice of granting patents on DNA sequences only based on *isolation*. As *Myriad* pinpointed, the mere recitation of the word "isolated" is not sufficient to confer patent eligibility to a claim, unless it embeds and/or entails a *marked difference* from what is naturally occurring. In these cases, the courts have clearly struck a different balance of the competing interests involved in DNA patenting – access to genetic information by scientific researchers, patients' health care rights, IPRs granted to biotech companies and the development and marketing of less expensive genetic tests by patentees' competitors –, where general public health and clinical research issues gained more relevance and weighted against the Myriad's exclusive IP rights.

Ambry and *Myriad*, furthermore, pointed out the ambiguities related to the use and implementation of the criterion of isolation within the U.S. patent system. Isolation and purification are scientific concepts which gained legal relevance in the patent system to distinguish non-patentable DNA sequences from patentable ones. In the United States the introduction into the USPTO's revised Utility Examination Guidelines[32] of the criteria of isolation and purification has established the rationale to legally demarcate between naturally occurring DNA sequences and "artificial" isolated/purified ones. 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.

However, *Myriad* has overturned the United States Patent and Trademark Office's long-standing practice of granting patents on *isolated* DNA sequences, by changing the way wherein the concept of isolation has been interpreted and implemented since 2001. On the same day of the Supreme Court's decision, the USPTO published a short preliminary guidance for patent examiners, making clear that "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".[33]

On March 4, 2014 the USPTO issued a new guidance memorandum titled "Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws Of Nature, Natural Phenomena & Natural Products",[34] superseding the June 13, 2013, memorandum and implementing a new procedure "to address changes in the law relating to subject matter eligibility under 35 U.S.C. § 101 in view of recent court decisions".[35] The aim of the guidance is to assist examiners "in determining whether a claim reflects a significant difference from what exists in na-

30 In the United States District Court of Utah, Central Division, *University of Utah Research Foundation, et al., v. Ambry Genetics Corporation*, Memorandum Decision and Order Denying Plaintiffs' Motion for Preliminary Injunction, *supra* note 1, at p. 98.

31 Ibid., at p. 106.

32 USPTO, Utility Examination Guidelines, 5 January 2001, available on the Internet at <http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf> (last accessed on 25 June 2014).

33 USPTO, Memorandum on the Supreme Court Decision in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 13 June 2013, available on the Internet at <http://www.uspto.gov/patents/law/exam/myriad_20130613.pdf > (last accessed on 31 March 2014).

34 USPTO, Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws Of Nature, Natural Phenomena & Natural Products, 4 March 2014, available on the Internet at <http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf> (last accessed on 25 June 2014).

35 USPTO, Memorandum on the Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws Of Nature, Natural Phenomena & Natural Products, 4 March 2014, available on the Internet at <http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf> (last accessed on 25 June 2014).

ture and thus is eligible, or whether a claim is effectively drawn to something that is naturally occurring, like the claims found ineligible by the Supreme Court in *Myriad*".[36]

In the guidance, the overall process to assess subject matter eligibility under 35 U.S.C. § 101 is set out and the examiners should consider whether a patent claim is "significantly different" from a judicial exception, such as a natural product or phenomenon, or not. Some factors weigh for and against patent eligibility. As far as nucleic acids are concerned, the memorandum clarifies that their patent eligibility assessment would be based only on whether "a product claim reciting something that initially appears to be a natural product" is *markedly different* in structure from naturally occurring products or not.[37] As *Myriad* and *Ambry* suggest, this evaluation relies considerably on how the structure of nucleic acids, such as DNA, is interpreted and defined: whether they are considered chemical molecules or carriers of information. As Judge Shelby illustrated in *Ambry*, one of the main issues related to DNA patent eligibility is whether the informational content of the nucleotide sequences is the critical aspect of these nucleotides or not and what kind of information is embedded in them: namely, if the information encoded in DNA is only about its own molecular structure incidental to its biological function or is unique, as it reflects DNA's primary biological function: directing the synthesis of other molecules in the body, and can, therefore, be considered the physical embodiment of laws of nature .

If the decision on the merits in *Ambry* will uphold the arguments that Judge Shelby endorsed on Plaintiffs' patent claims, the implementation of the criterion of isolation to primers and probes could be affected and maybe, in the future, claims drawn to synthetic sequences are less likely to be considered *significantly different* from natural products and, therefore, patent eligible.

36 Ibid.

37 Ibid., at p. 4.