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Nature-Based Claims And the Patent-Eligibility Landscape Post-'Mayo' and 'Myriad'

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The Supreme Court recently decided two cases in which the central question was whether certain patent claims involving natural materials and biomolecules constituted patent eligible subject matter under 35 U.S.C. §101. In *Mayo Collaborative Services v. Prometheus Laboratories*,[1] the U.S. Supreme Court held that patent claims to "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage … will prove ineffective or cause harm" are not patent eligible because they generally recite a law of nature, and the addition of certain claim steps directed to "well understood, routine, conventional activity" does not change that conclusion. In *Association for Molecular Pathology v. Myriad Genetics*,[2] the court held that "genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material."

Shortly after the Supreme Court's decision in *Myriad*, the Patent Office published the 2014 Interim Guidance on Patent Subject Matter Eligibility (Guidance), which sets forth a three-step inquiry for evaluating the patent eligibility of claims involving natural and biologic material.[3] The Patent Office's Guidance also provides illustrative examples of patent eligible, and ineligible, claims involving natural principles and/or products, including claims directed to various nature-based bacterial mixtures, genetically modified bacteria, nucleic acids, purified proteins, antibodies and food.

While the PTO is still soliciting public feedback and continuing to grapple with the prospective effects of *Mayo* and *Myriad*, federal district courts and the Federal Circuit have been contributing to a growing body of case law that is likely to decide the fate of existing patent claims involving natural materials and biomolecules. In this article, we review recent cases applying *Mayo* and *Myriad* and examine how courts have analyzed the patent eligibility of compositions reflecting genetic information (e.g., certain primers, man-made mutations and clones)[4] and method claims involving natural materials and biomolecules (e.g., certain methods for correlating, amplifying and sequencing DNA).[5]

The Section 101 Threshold

Section 101 of the Patent Act is the sole tool for assessing whether a claim is directed to patent eligible subject matter.[6] Discoveries of "new and useful … composition[s] of matter, or any new and useful improvement thereof" are patent eligible.[7] Laws of nature, natural phenomena, and abstract ideas, however, are not.[8] The Supreme Court has long held that these three "judicial exceptions" cannot pass the §101 threshold.[9]

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In *Mayo*, the patents at issue claimed processes to help doctors treat patients with autoimmune diseases and, specifically, to determine whether a given dosage level of thiopurine drugs is too low or too high by identifying correlations between metabolite levels and the likelihood that the drug would be effective The Supreme Court found that the claims did not constitute eligible subject matter because they "set forth laws of nature—namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm." The court concluded that although the patents recited additional steps in addition to the law of nature, the additional steps were insufficient to transform the character of the claims into patent-eligible subject matter, because those steps "consist of well understood, routine, conventional activity already engaged in by the scientific community [which], when viewed as a whole, add nothing significant beyond the sum of their parts taken separately."

The Supreme Court in *Myriad* faced the question of whether Myriad's patents—which claimed the genetic sequence of two genes involved in breast cancer, BRCA1 and BRCA2—were directed at "new and useful" compositions of matter, or if they were instead directed at "naturally occurring phenomena." The court held that Myriad did not create or alter any genetic information encoded in the BRCA genes, and Myriad's success in isolating the genes by separating them from the genome by breaking chemical bonds was not enough to save the claims. Synthetically created cDNA was held to be patent eligible, however, because its exons-only chemical structure is not naturally occurring.

Compositions Encoding Gene Information

Primers. Primers are short sequences of synthetic DNA complementary to a specific DNA sequence, and are used to initiate the process known as polymerase chain reaction whereby nucleotides are added to a growing chain of DNA. In a follow-on case related to *Myriad*, the District Court for the District of Utah held that claims to synthetic primers having the same sequence as human DNA were not patent eligible.[10] The district court interpreted *Myriad* narrowly, finding that the claimed primers, although synthetically designed, were not "markedly different" from naturally occurring DNA, and that synthetic DNA is patent ineligible when it reflects the same nucleotide sequence as natural genomic DNA.[11] On appeal, the Federal Circuit agreed that "[t]he primers before us are not distinguishable from the isolated DNA found patent-ineligible in *Myriad* and are not similar to the cDNA found to be patent-eligible," because they are "structurally identical to the ends of DNA strands found in nature."[12] The Federal Circuit cited the Supreme Court's reasoning from *Myriad* to conclude that primers are not patent eligible merely because they have been separated from other genetic material. According to the court, the functions of primers are also not fundamentally different, because "the naturally occurring material is used to form the first step in a chain reaction—a function that is performed because the primer maintains the exact same nucleotide sequence as the relevant portion of the naturally occurring sequence."[13]

Man-Made Mutations. In a portion of *Myriad* that was not on appeal to the Supreme Court, the Federal Circuit held that a claim directed to a screening method for cancer treatment was patent eligible under §101. The claimed process at issue consisted of growing host cells transformed with a mutated BRCA gene in the presence of a compound suspected of being a cancer therapeutic while maintaining some of the transformed cells apart from the potentially therapeutic compound, and subsequently determining the growth rate of the host cells in both groups by comparing growth rates (wherein a slower growth rate of host cells in the presence of such a compound is indicative of a cancer therapeutic).[14] In holding that this claim covered patent-eligible subject matter, the Federal Circuit explained that it amounted to more than the simple application of a law of nature, since it involved the application of certain steps to transformed, man-made cells that were not the product of nature.[15] Thus, these man-made cells were patent-eligible subject matter, and "once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature."

Clones. A clone is an identical genetic copy of a cell, cell part, or organism. In *In re Roslin Institute (Edinburgh)*, the Federal Circuit addressed the patent eligibility of "Dolly the Sheep" and other mammals cloned using what the court described as "a breakthrough scientific method." Noting that the patent claims directed to the method of cloning were not at issue, the court invalidated claims directed to clones developed from donor mammals because they shared exact genetic identity with the donor.[16] The court held that naturally occurring organisms are not patent eligible subject matter under both pre- and post-*Myriad* case law, even where the cloned species is the work of human ingenuity and not "nature's handiwork."

Use of Natural Materials, Biomolecules

Correlations Based on Analysis of Drug Metabolites. In *Ameritox v. Millenium Health*, the method claims at issue involved, in part, "detecting," "normalizing," and "quantifying" the amount of drug metabolites in a urine sample.[17] In denying defendant's motion for summary judgment, the court explained that while each of the steps in the claimed method involved "conventional" scientific techniques, the "combination" of each of these steps produced "a new and useful result." In contrast to *Mayo*, in which the court found that "at least the combination of those steps, were in context obvious, already in use, or purely conventional," the district court in *Ameritox* noted that the defendant could not point to any "reference demonstrating the existence of or even suggesting the *combination* of the comparative step with the additional steps of the invention." Because nothing in the prior art suggested that such a combination was well-known, the method claim passed muster under §101 in light of *Myriad* and *Mayo*.

Correlations Based on Genetic Analysis. A number of decisions have addressed patent claims directed to analyzing the correlations between certain conditions, including disease conditions, and the presence (or absence) of a genetic marker. The Federal Circuit in *Myriad* found that certain method claims at issue were patent ineligible under §101. Most of those claims involved "comparing" or "analyzing" a patient's BRCA sequence with the normal, or "wild-type," sequence to identify the presence of cancer-predisposing mutations.[18] The court concluded that these claims were not directed to patent-eligible subject matter because they "recite[ ] nothing more than the abstract mental steps necessary to" compare or analyze different nucleotide sequences.[19]

In *PerkinElmer v. Intema*, the claims were directed to specific screening methods to estimate the risk of fetal Down syndrome, using markers from the first and second trimesters of pregnancy.[20] The claim at issue covered a multi-step method of: (1) measuring the levels of certain biological markers from both the first and second trimester of pregnancy; and (2) determining whether an increased risk of Down syndrome existed by comparing those markers.[21] The court in *PerkinElmer* held that the claims recited patent-ineligible subject matter under §101 because the steps only instructed the user "to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field."

In *Genetic Technologies v. Laboratory Corporation of America Holdings*, the court considered a method claim drawn to predicting "potential sprinting, strength, or power performance" in elite athletes by

"analyzing a sample" for the presence of a specific gene, "detecting" the presence of two specific alleles, and using those analytics to "predict" athletic performance was held invalid under §101.[22] The claim was found patent ineligible, because the "analyzing," "detecting," and "predicting" steps simply tell users to apply the natural law and do not add anything to allow the process to qualify as patent eligible.

Amplifying and Detecting DNA. Courts have also addressed claims that, in addition to correlation steps, also require certain steps involving amplifying, sequencing and/or hybridizing DNA. In *Ariosa Diagnostics v. Sequenom*, for example, the district court analyzed patent claims directed to certain methods of amplifying and detecting cell-free fetal DNA (cffDNA). The parties agreed that neither cffDNA nor the discovery of cffDNA in maternal plasma or serum was patentable, because the presence of cffDNA in maternal plasma or serum is a natural phenomenon. The issue before the court was whether method claims reciting the steps of "amplifying a paternally inherited nucleic acid from the serum or plasma sample" and "detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample" were patent eligible.[23] The court held they were not, finding that the claimed processes at issue—apart from the natural phenomenon of paternally inherited cffDNA—involve no more than well-understood, routine, conventional activity, previously engaged in by those in the field. In addition, the court considered whether the claims posed a risk "of preempting a law of nature, natural phenomenon, or abstract idea," and found that they did because alternative methods for detecting cffDNA were "not commercially viable" and "the effect of the patent in practice would be to preempt all uses of the natural phenomenon."

In other cases—*Genetic Technologies v. Agilent Technologies*[24] and *Genetic Technologies v. Bristol-Myers Squibb*[25]—two different courts considered a method claim involving "amplifying genomic DNA with a primer pair that spans a non-coding region sequence" and then "analyzing the amplified sequence to detect the [target]."[26] In *Agilent*, the court held that the claim was arguably limited to a patentable application of natural law, noting that "the application of primer pair amplification to intron sequences … may well have been 'novel and unconventional' [and] whether those in the field would consider applying genomic amplification to non-coding regions conventional or routine is a factual question better addressed at a later stage." In *Bristol-Myers*, however, the court concluded that "the 'amplifying' step is insufficient to meaningfully limit the claims" because "the 'said primer pair' limitation merely recites the natural phenomenon itself—the linkage correlation—just as the 'wherein' steps in *Mayo* recited the characteristics of the metabolite correlations." The court in *Bristol-Myers* concluded that the "primer-pair" limitation merely "sets forth a condition that is inherently required in order to implement the natural law and, therefore, does nothing to impart an 'inventive concept.'"

Sequencing and Hybridizing DNA. Similarly, in *University of Utah Research Foundation v. Ambry Genetics*, the court concluded that certain method claims involving the use of BRCA1 or BRCA2 sequences were not patent eligible, where the only "inventive concepts" in the claims at issue were the patent ineligible naturally occurring BRCA1 and BRCA2 sequences themselves.[27] The court found that the claimed steps relating to "DNA amplification, sequencing, comparisons, detecting alterations in sequences, [ ] hybridizing probes to alleles" and "designing or using probes, primers, or arrays" were merely "conventional activities that were well-understood and uniformly employed by those working with DNA." Because the claims covered the use of PCR, "the most widely used means to amplify DNA," the court held that the claims preempted the field as they would "effectively construct a wall around the naturally occurring BRCA1 and BRCA2 genetic sequences."

Conclusion

Following the Supreme Court's decisions in *Mayo* and *Myriad*, federal courts have analyzed the patent eligibility of certain nature-based claims, including claims directed to compositions reflecting genetic information (e.g., certain primers, man-made mutations and clones) and method claims involving natural materials and biomolecules (e.g., certain methods for correlating, amplifying and sequencing DNA). As the PTO's Guidance document demonstrates, however, there are numerous other types of nature-based claims—including claims directed to certain bacterial mixtures, genetically modified bacteria, purified proteins and antibodies—many of which are likely to be litigated at both the Patent Office and in the courts in the years to come.

1. *Mayo Collaborative Servs. v. Prometheus Labs.*, 132 S. Ct. 1289, 1296 (2012).
2. 133 S. Ct. 2107, 2120 (2013).
3. 79 Fed. Reg. 74618-33 (Dec. 16, 2014) (to be codified at 37 C.F.R. pt. 1). The Guidance directs patent examiners to determine whether the claim is directed to a process, or composition of matter. If it is, examiners must determine if the claim is directed to a law of nature or natural phenomenon. For nature based products to meet eligibility criteria, the claim must recite elements that amount to "significantly more" than the natural product or law of nature.
4. See *Univ. of Utah Research Found. v. Ambry Genetics (In re BRCA1- & BRCA2- Based Hereditary Cancer Test Patent Litig.)*, 3 F. Supp. 3d 1213 (D. Utah 2014); *In re Roslin Inst. (Edinburgh)*, 750 F.3d 1333 (Fed. Cir. 2014); *In re Bentwich*, 566 F. App'x 941 (Fed. Cir. 2014).
5. See *Ambry Genetics*, 3 F. Supp. 3d 1213; *Genetic Techs. v. Lab. Corp. of Am. Holdings*, 2014 U.S. Dist. LEXIS 122780 (D. Del. Sept. 3, 2014); *Genetic Techs. v. Bristol-Myers Squibb*, 2014 U.S. Dist. LEXIS 154443 (D. Del. Oct. 30, 2014); *Genetic Techs. v. Agilent Techs.*, 24 F. Supp. 3d 922 (N.D. Cal. 2014); *Ariosa Diagnostics v. Sequenom*, 19 F. Supp. 3d 938 (N.D. Cal. 2013).
6. 133 S. Ct. at 2116.
7. 35 U.S.C. §101 (2012).
8. 133 S. Ct. at 2116.
9. Id.
10. See *Univ. of Utah Research Found. v. Ambry Genetics*, 3 F. Supp. 3d 1213, 1266 (D. Utah 2014), aff'd, 774 F.3d 755, 761 (Fed. Cir. 2014). The claim at issue recited:

> A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

11. 3 F. Supp. 3d at 1260-62.
12. 774 F.3d at 760.
13. Id. at 761.
14. *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1310 (Fed. Cir. 2012) aff'd in part, rev'd in part sub nom. *Ass'n for Molecular Pathology v. Myriad Genetics*, 133 S. Ct. 2107 (2013).
15. Id. at 1336.
16. 750 F.3d 1333 (Fed. Cir. 2014). A claim at issue recited: "A live-born clone of a pre-existing, non-embryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats."
17. 2015 WL 728501, at *26 (W.D. Wis. Feb. 19, 2015). The claim at issue recited:

> A method for quantifying at least one metabolite in a biological sample comprising the steps of … providing one biological sample … providing one set of known normative data specific to a reference metabolite … contacting the biological sample with an analytical device … detecting the presence of at least one test metabolite in the biological sample with the device … normalizing the biological sample … and quantifying the concentration of at least one test metabolite in the biological sample by comparing a ratio between the concentration of the test metabolite from the patient to the set of known normative data specific to the reference metabolite concentration.

18. 689 F.3d at 1309.
19. Id. at 1334.
20. 496 F. App'x 65, 66 (Fed. Cir. 2012).
21. Id. at 71.
22. 2014 U.S. Dist. LEXIS 122780, at *40-41. A claim at issue recited:

> A method to predict potential sprinting, strength, or power performance in a human comprising: … predicting the potential sprinting, strength, or power performance of the human, wherein the presence of two copies of the 577R allele is positively associated with potential sprinting, strength, or power performance.

23. *Ariosa Diagnostics v. Sequenom*, 19 F. Supp. 3d 938, 941 (N.D. Cal. 2013). A representative claim at issue recited:

> A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample."

24. 24 F. Supp. 3d 922 (N.D. Cal. 2014).
25. 2014 U.S. Dist. LEXIS 154443 (D. Del. Oct. 30, 2014).
26. 24 F. Supp. 3d at 926. The claim at issue recited:

> A method for detection of at least one coding region allele of a multi-allelic genetic locus comprising … amplifying genomic DNA with a primer pair that spans a non-coding region sequence … and … analyzing the amplified DNA sequence to detect the allele.

27. 3 F. Supp. 3d at 1269. The claim at issue recited:

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