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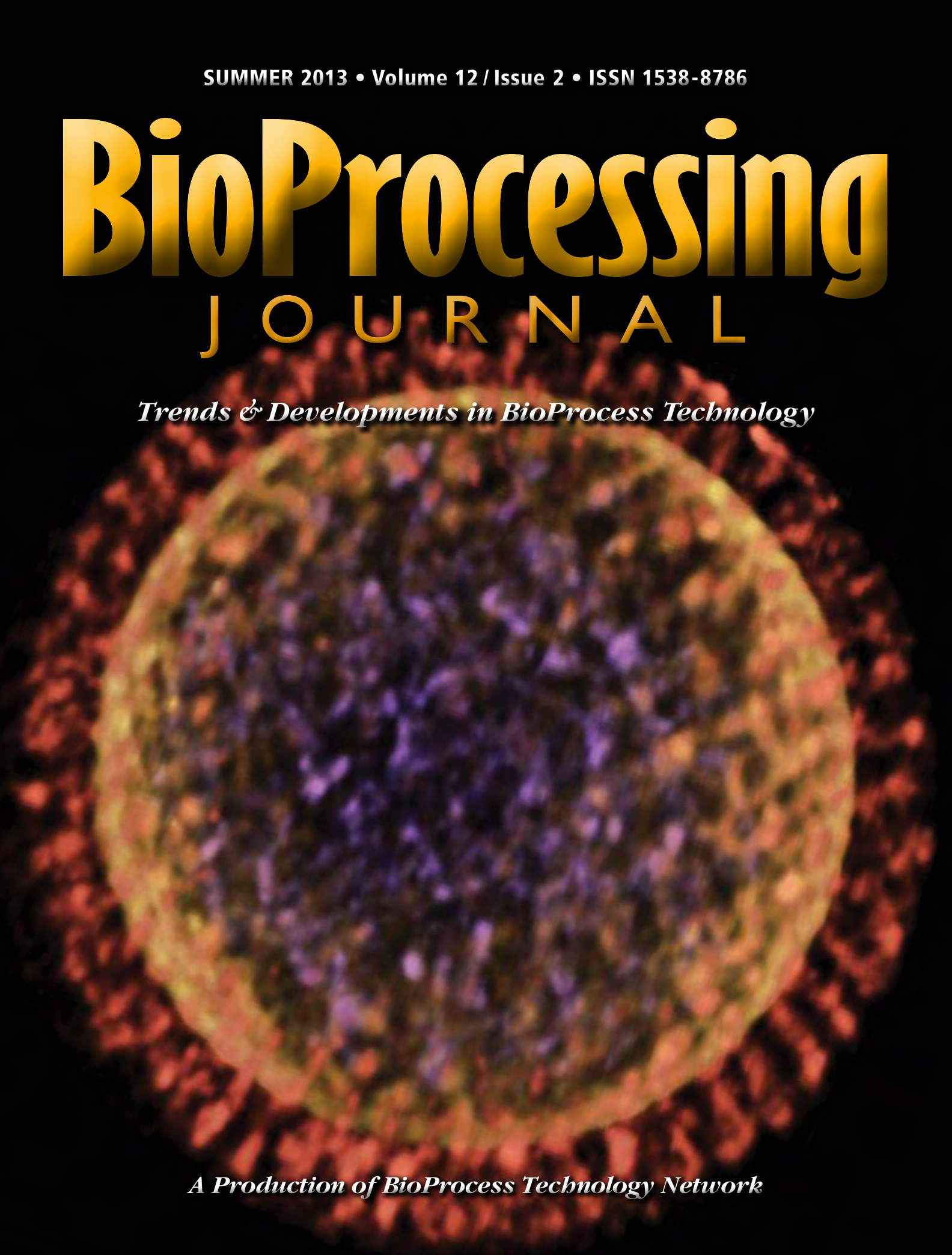

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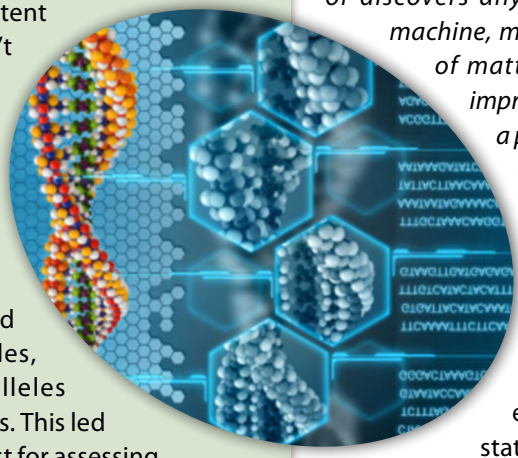
TRENDS & DEVELOPMENTS IN BIOPROCESS TECHNOLOGY

Myriad Further Limits Patent Eligibility

By WILLIAM K. MERKEL

The recent decision of the US Supreme Court in *Assoc. Mol. Pathol. v. Myriad Genetics, Inc.*, No. 12-398 (June 13, 2013) continued the Court's efforts to clarify those innovations eligible for patent protection. *Myriad* unanimously held that "isolated" BRCA1/2 DNAs were patent ineligible under 35 USC § 101 while BRCA1/2 complementary DNAs (cDNAs) were patent eligible under that statutory provision. In considering patent eligibility, the Court proposed a test for isolated DNAs that balances incentives and impediments to innovation arising from patent protection, without placing any weight on whether the innovation relates to nature or to an abstract idea. The Court concluded that the mere act of isolating DNA segments claimed in terms of their genetic information was insufficient to render the claims patent eligible. Although the full effect of *Myriad* won't be fully known for some time, it is already apparent that reliance expectations developed over 30 years have been upset.



Taking a closer look, Myriad discovered the BRCA1 and BRCA2 genes and their influence on the risks of breast and ovarian cancers.[1] Myriad also located these genes in the human genome, isolated the genes, and determined the sequences of several alleles, or versions, of these genes, with some alleles associated with higher cancer risks than others. This led Myriad to develop and market a diagnostic test for assessing breast and ovarian cancer risk, and to seek patent protection for the technology. Myriad refused to license the technology to competitors, which led to a declaratory judgment suit against Myriad. The district court granted summary judgment to the challengers, holding that Myriad's isolated BRCA1/2 DNA claims and BRCA1/2 cDNA claims were invalid for patent ineligibility under 35 USC § 101. For reasons not relevant to the patent eligibility of DNA composition claims, the Court of Appeals for the Federal Circuit (CAFC) had two cracks at this case on appeal, and both times it held that isolated BRCA1/2 DNAs and BRCA1/2 cDNAs were patent eligible. On its own second review of the case, the US Supreme Court unanimously and finally decided the appeal of summary judgment, holding isolated BRCA1/2 DNAs patent ineligible, but BRCA1/2 cDNAs patent eligible.

Legal Considerations

The US Constitution provides the basis for patent law (Art. I, Sec. 8, Cl. 8) in stating that Congress has the power to promote the progress of science and the useful arts by securing, for limited times to authors and inventors, the exclusive rights to their respective writings and discoveries. Congress has used that power to enact the patent laws found under Title 35, US Code. The statutory provision relevant to *Myriad* is 35 USC § 101, which provides that *". . . [w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."*

The Supreme Court has recognized the expansive language of this statute, but it has also recognized implicit exceptions to the broad statutory language in deeming patent ineligible a law of nature, a natural phenomenon, or an abstract idea. Justice Clarence Thomas, speaking for the *Myriad* Court, reiterated the rationale for such exceptions. The exceptions defined basic scientific tools, and allowing a patentee to exclude others from using such tools would run a risk of impeding rather than promoting technological progress.

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[1] BRCA are genes that, when mutated, are associated with BReast CAncer and ovarian cancer. Two BRCA genes are known in humans, BRCA1 and BRCA2, abbreviated herein as BRCA1/2.

Myriad relied on its precedent in applying the eligibility exceptions to the facts of the case. When initially faced with the appeal in *Myriad*, the Supreme Court remanded the case to the CAFC for reconsideration in view of *Mayo Collaborative Services, Inc. v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012), a Supreme Court decision addressing the patent eligibility of process claims that relate to a "natural law," a concept left undefined in that opinion. *Prometheus* held ineligible the patentee's claims to methods of optimizing therapeutic dosages of a known drug by analyzing a drug metabolite. The Court reasoned that the claims did not add "enough" to a recited "law of nature" to establish an inventive concept independent of that natural law. Many in the biotechnology and pharmaceutical industries were concerned that the influence of *Prometheus* would lead to another decision based on patent claim parsing (to exclude any exception to eligible subject matter), assessing whether a subset of claim elements would yield an inventive concept, importing art-based considerations into the eligibility determination, and the like. It was with some relief that many viewed the *Myriad* opinion as forging its own analytical approach rather than following *Prometheus* too closely. This outcome was not too surprising, however, because *Prometheus* had addressed method claims (which typically involve multiple active steps) and focused on the claim elements not tainted by an exception to patent eligibility, while *Myriad* concerns composition claims and most composition claims, including the DNA claims at issue in *Myriad*, contain little beyond an identification of the composition. Excluding the arguably ineligible composition from the analysis under Prometheus would leave little to no subject matter available to establish the inventive concept needed for the claim to be patent eligible.

The Court also considered, and distinguished, *Diamond v. Chakrabarty*, 447 US 303, 100 S. Ct. 2204, 65 L. Ed. 2d 144 (1980), a case deemed central to the *Myriad* inquiry. In contrast to Chakrabarty, who created a new bacterium containing four plasmids with heterologous genes conferring the new trait of oil degradation, Myriad assertedly did not create anything. The Court then summarily concluded that separating a gene from its natural surroundings is not an act of invention.

Beyond *Chakrabarty*, the Court relied on *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 US 127, 68 S. Ct. 440, 92 L. Ed. 588 (1948), a case arguably decided on grounds of obviousness. Although the claims combined nitrogen-fixing bacterial strains that the art considered to be incompatible, the claimed mixture was held to be an obvious combination of the individual strains, all of which were naturally occurring and were combined in unmodified form to yield the claimed mixture. Dicta in *Funk Bros.* has proved irresistible in rationalizing conclusions of patent ineligibility based on natural phenomena, however, as evinced by the Court's citations to it in both *Myriad* and *Prometheus*.

Factual Considerations

To provide context for a consideration of the *Myriad* facts, the Court provided an explanation of the biotechnological background. The explanation, however, revealed the Court's flawed understanding of the technology and weakens public confidence in the Court's opinion that isolated DNAs, which have been patented for decades, are not patent eligible. In characterizing the conclusions of the CAFC, Justice Thomas stated that "the cDNA nucleotide sequence listed in SEQ ID NO:1. . . codes for the typical BRCA1 gene." Slip op. (edited/printed record of the bench opinion) at 5-6. No form of DNA, including cDNA, codes for a gene; rather, SEQ ID NO:1 is the nucleotide sequence of the wild-type, or typical, coding region of the BRCA1 gene. Justice Thomas also wrote that genes are encoded as DNA, but genes are simply composed of DNA. *Id.* (concurring opinion) at 2. The Court also states that the DNA *"nucleotides are adenine (A), thymine (T), cytosine (C), and guanine (G),"* but these are the names of the bases contained in DNA nucleotides. *Id.* The explanation also refers to "each 'cross-bar' in the DNA helix", when cross-bars schematically illustrate the hydrogen bonds between nucleotides of different strands that hold two helices together in a double helix form. Continuing, the Court noted that *"nucleotides that do not code for amino acids . . . are known as 'introns,'"* but that statement overlooks the nucleotides forming stop codons that are within exons but do not encode any amino acid as well as the untranslated 5′ and 3′ regions of mRNAs that also do not code for any amino acid. The summary also describes bonds separating in the process of transcription, but bonds do not separate, they break or form. Further describing transcription, the Court states that *"the DNA helix unwinds into two single strands,"* but each DNA helix is composed of a single DNA strand. Additionally, transcription does not unwind duplex DNA into single strands, but simply unwinds portions of the DNA double helix to form single-stranded regions. In describing translation, the Court states that *"[e]ach codon . . . tells the ribosomes which of the 20 possible amino acids to synthesize. . . ." Id.* Ribosomes don't synthesize amino acids, however, they catalyze the incorporation of free amino acids into peptides forming in the process of translation. Further, codons are described as providing stop signals to end amino acid production. *Id.* Amino acids are synthesized in a variety of biochemical pathways, with each step in a given pathway enzymatically catalyzed. None of these pathways is involved in the

process of translation. The Court also discusses sequence changes, referring to the changes as mutations. Overlooked in defining the smallest mutations is the silent mutation in which the DNA sequence is changed by, typically, a single nucleotide substitution that does not lead to a change in the amino acid sequence of the encoded protein. Many of the suspect statements regarding the technology may appear to be relatively minor, but the patent eligibility, and hence patent validity, of isolated BRCA1/2 DNAs depended, in part, on the chemical differences found at each end of isolated BRCA1/2 DNAs relative to the corresponding DNA segment in the human genome. The suspect explanation of the technology by the Court leaves the reader wondering if the significance of these differences was fully appreciated. In view of the number of errors and mis-statements present in the description of the technological background, it is not surprising that Justice Antonin Scalia penned a concurring opinion solely to distance himself from the technical explanations provided in the opinion.

With respect to the facts specific to *Myriad*, the patentee expended considerable effort and resources to analyze genetic risk factors influencing rates of breast and ovarian cancers. Two genes, BRCA1 and BRCA2, were identified, mapped to particular locations in the human genome, isolated, and the nucleotide sequence of the coding regions of these genes were determined. In fact, Myriad obtained the sequences of several different alleles, or versions, of BRCA1 and BRCA2 obtained from samples of humans that had, or did not have, breast or ovarian cancer. Over time, Myriad associated the sequences of particular alleles with increased, or decreased, risks of these cancers. Recognizing the value of these results, Myriad developed a diagnostic assay for breast and ovarian cancers. Myriad also sought patent protection, ultimately obtaining a number of US patents covering the technology. At issue in the appeal were claims 1, 2, and 5–7 of US Pat. No. 5,747,282 (the '282 patent), claim 1 of US Pat. No. 5,693,473, and claims 1, 6, and 7 of US Pat. No. 5,837,492. The majority of the analysis focused on claims 1 and 2 of the '282 patent: (1) an isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2; and (2) the isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.

SEQ ID NO:1 contains the nucleotide sequence of the wild-type, or most common, allele of the BRCA1 gene. SEQ ID NO:2 contains the amino acid sequence of the BRCA1 protein encoded by the BRCA1 gene.

Analysis of Myriad and Patent Eligibility

Applying the law to *Myriad's* facts, Justice Thomas initially dismissed arguments based on the extensive efforts required to develop the isolated BRCA1/2 DNAs, noting that extensive effort alone is insufficient to satisfy § 101. Thomas then boldly stated that Myriad's claims are not saved by severing chemical bonds in the process of isolating DNAs because Myriad's claims are *"simply not expressed in terms of chemical composition . . . . Instead the claims understandably focus on the genetic information . . . ."* Slip op. at 14.

Armed with an imperfect understanding of the technology, the Court reviewed Myriad's technical accomplishments and characterized them as involving an iterative effort to localize the BRCA1/2 genes, followed by their isolation and sequence determination using conventional methods. The Court noted that the coding sequences of Myriad's isolated DNAs did not differ from the corresponding coding sequences found in the human genome. The isolated BRCA1/2 DNAs were useful in developing diagnostic tests for breast and ovarian cancer, which Myriad marketed, but which Myriad was unwilling to license to others.

The full import of Justice Thomas's statement that the claims are *"simply not expressed in terms of chemical composition"* requires a deeper look. *Myriad* does not hold that all of the claims at issue were patent ineligible, so Thomas's statement must refer only to those claims struck down by the Court. Unfortunately, the opinion never identifies by patent and claim numbers which claims are patent eligible and which claims are not. The two claims that received most of the Court's attention were claims 1 and 2 of the '282 patent. Claim 1 was a patent ineligible claim to isolated DNAs encoding the amino acid sequence of BRCA1. The structure expressly recited in the claim was the structure of the encoded polypeptide. Allowing for the degeneracy of the genetic code, in which some amino acids are encoded by more than one triplet of DNA nucleotides, the claim indirectly specified several corresponding DNA sequences, or structures, each of which encoded that protein. Most, if not all, of the sequence variants arising due to the degeneracy of the genetic code would not be expected to occur in nature.

Beyond DNAs falling within claim 1 due to the degeneracy of the genetic code, it is arguable that DNAs providing an interrupted code for the BRCA1 protein would also be embraced by the claim, at least if those interrupted coding regions could somehow give rise to the BRCA1 protein of specified sequence (*i.e.,* SEQ ID NO:2). A classic example of an interrupted code is the genomic BRCA1 gene containing introns dividing the coding region into discrete exons. Thus, claim 1 included isolated genomic DNA segments, cDNAs, and DNAs containing sequence variations due to the degeneracy of the genetic code. The inclusion of isolated genomic DNA segments in claim 1 resulted in the Court's holding that the claim was patent ineligible.

In contrast to the ineligibility of claim 1, claim 2 was

drawn to the BRCA1 cDNA sequence, which is the genomic coding region sequence for the BRCA1 protein, without any interruptions from introns. The cDNA sequence of claim 2 contained contiguous triplets of DNA nucleotides specifying each amino acid in the BRCA1 protein, with no intervening sequences or interruptions. The Court held this claim to be patent eligible as it did not occur in nature.

Justice Thomas observed that the claims, if valid, would give Myriad the exclusive right to isolate BRCA1/2 DNAs. The Court then curiously asserted that isolation is necessary to conduct genetic testing and others were conducting such testing after Myriad discovered the BRCA1/2 genes. The statement is suspect in that there is no reason that BRCA1 or BRCA2 DNAs would have to be isolated in order to use them in diagnostic testing. The statement is also confusing. Is the Court lamenting that competitors can't simply practice patented technology without a license, at least if the technology concerns the diagnostic testing of humans? Or is the Court implying that Myriad's claims embraced technologies that were known in the art prior to Myriad's invention? Given that the defining feature of a US patent is the power to exclude others from practicing the invention for a certain time, perhaps the statement reveals some hostility towards patenting technologies that could affect access to human healthcare.

Beyond asserting that the claims did not define the isolated DNAs in terms of chemical structure, Thomas stated that the DNAs of the claims were understandably defined in terms of their genetic information. A long-standing principle of patent law is that a claimed product and its properties are one and the same. The DNA compositions of claim 1 are defined indirectly in terms of their nucleotide sequence structure, and each of these compositions is inextricably bound up with its property of encoding the amino acid sequence of the BRCA1 protein (*i.e.,* the genetic information). The language of claim 1, requiring a DNA coding for a BRCA1 polypeptide of specified amino acid sequence, does not change the structural requirement for particular nucleotide sequences that encode the BRCA1 polypeptide. Thus, claim 1 is drafted in terms of chemical structure. To be sure, the claimed DNAs do contain genetic information as a salient property, but that does not change the nature of the claim as one defining a composition in terms of chemical structure. The Court's exclusive focus on genetic information under these circumstances appears strained.

Justice Thomas supported the assertion that Myriad's claims focused on the genetic information rather than chemical composition by stating that *". . . [i]f 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 (such as claims 1 and 2 of the '282 patent) by isolating a DNA sequence that included both the BRCA1 or BRCA2 gene and one additional nucleotide pair. Such a molecule would not be chemically identical to the molecule 'invented' by Myriad. But Myriad obviously would resist that outcome . . ."* Slip op. at 15.

The quoted statement is puzzling, and not just because it veers into a discussion of hypothetical patent infringement to address an issue of patent eligibility, and thereby patent validity. A claim defining its subject matter in terms of chemical composition is not limited to defining a single unique molecule. Moreover, beyond the distraction of considering infringement in the context of patent eligibility, the unique cDNA of claim 2 would be infringed, literally or under the doctrine of equivalents, by a cDNA containing one more nucleotide than found in SEQ ID NO:2. The Court seems to lose sight of the fact that a unique character of a given molecule often will confer uniqueness on any larger molecule containing the unique molecule. Given the open-ended transition terms of the Myriad claims, the Court's argument is perplexing in that the addition of a nucleotide would not avoid infringement, but this isn't probative on the issue of what constitutes a natural composition.

The Court also addressed the cDNA of claim 2 of the '282 patent, stating that *"creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring."* Slip op. at 16. The Court dismissed the argument that a cDNA sequence was dictated by nature, not by a lab technician: *"That may be so, but the lab technician unquestionably creates something new when cDNA is made."* Slip op. at 17. The Court did note that cDNAs, such as short cDNAs, made from natural DNA that lacked introns may not be patent eligible because they do not differ from natural DNA. *Id.*

Although the Myriad opinion is colored by the impression that the unanimous Court's understanding of biotechnology is suspect, the Court did mandate a balancing test for assessing patent eligibility. That test, offsetting the incentive to innovate from providing patent protection for a given advance against any impediments to progress from providing such protection, may now guide inquiries into whether claimed subject matter constitutes a law of nature, natural phenomenon, or abstract idea. In *Myriad*, the balance favored patent protection for cDNAs lacking at least some DNA (*e.g.*, an intron) found in the genome, but the balance favors denial of patent protection for simply isolating a DNA fragment. Stated in terms used in *Prometheus*, simply isolating a DNA fragment doesn't add "enough" to the natural phenomenon of the DNA.

The Court characterized the *Myriad* balancing test as a *"well-established standard,"* citing to the recent *Prometheus*

opinion. In particular, *Myriad* quoted *Prometheus* in characterizing the balancing test as striking a balance between *"'incentives that lead to creation, invention, and discovery' and 'imped[ing] the flow of information that might permit, indeed spur, invention.'"* Slip op. at 11. Continuing the second *Prometheus* quote reveals that *"imped[ing] the flow of information that might permit, indeed spur, invention, by, for example, raising the price of using the patented ideas once created . . ." Prometheus*, 566 US __. Slip op. at 23). This balancing test doesn't appear to have been used by US Patent and Trademark Office (USPTO) examiners, and it is difficult to imagine how examiners would assess the technological and economic effects of patenting, or not patenting, a given invention. Further, it would seem that the incentive to innovate provided by patents operates to induce invention whereas the impediments to broader developments operates once an invention is both realized and patented. In balancing incentives and impediments, it would seem that an argument can be made that the impediments can never exceed the incentives because there can be no impediment to further development if there is no invention to be further developed. The Court's position is reminiscent of an argument made years ago by a Medical Doctor asking whether the public would prefer one therapy in a world of patents versus many therapies in a world without. That logic is flawed in assuming the existence of the invention. The comparison should be between no therapies in a world without patents versus one therapy in a world with patents.

The Court has characterized the exceptions to patent eligibility (laws of nature, natural phenomena, and abstract ideas) as fundamental scientific tools, implying that these tools have many applications. Certainly, the Court cannot be troubled by excluding others from using a "scientific tool" that is the product of invention because that is the constitutional mandate of the patent system. If the concern is that patenting "scientific tools" will lead to impediments that exceed the incentive, is it because a claim extended beyond the scope of the invention, *i.e.*, the claim is over-broad? If so, there are statutory provisions and examination procedures in place to address improper claim breadth, but that place has never been the threshold eligibility inquiry under 35 USC § 101.

The lasting effect of *Myriad* on the bioprocessing industry remains to be seen. While *Prometheus* and its treatment of the eligibility of method claims is recognized as significant for this industry and others, the use of compositions in process-based technologies, including bioprocesses, of commercial value signals the importance of *Myriad* as well. Notwithstanding the Court's continuing efforts to clarify the law of patent eligibility, the voice of Congress may ultimately need to be heard.

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