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Are Human Genes Patentable?

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On April 15 2013, the US Supreme Court heard oral arguments to address the question “are human genes patentable?” and will deliver its ruling by the end of June. Thus will culminate a lawsuit that was filed on May 12, 2009 (1), in the Federal District Court for Southern New York, Judge Robert Sweet presiding. The case centers on patents underlying genetic testing for inherited risk of breast and ovarian cancer attributable to two genes, *BRCA1* and *BRCA2*. The patents enabled Myriad Genetics of Salt Lake City, Utah, to establish a US service monopoly on such testing, with rights extending to clinical research and follow-up testing in cases of ambiguous results that Myriad does not authorize or perform itself. These patents have been highly controversial for over fifteen years (2).

The lawsuit is an unusual patent case in several respects. Most patent suits pit one company or inventor against another and center on *who* will exercise their exclusive patent rights. This case is about changing the law, challenging whether patents on genes should be granted at all. The American Civil Liberties Union (ACLU) organized and litigated the case with the Public Patent Foundation affiliated with Cardozo Law School in New York. It is the ACLU’s first venture into patent law and the first public interest patent case in the United States.

The initial plaintiffs were individuals and organizations who objected to Myriad’s patents on *BRCA1/2* genes. Plaintiffs included women who wanted testing, physicians who wanted to test patients, and laboratory directors who wanted to offer *BRCA* testing. Others were organizations representing laboratory professionals, clinical geneticists, and breast cancer advocates. They sued Myriad and the US Patent and Trademark Office (USPTO; which was subsequently dropped from the suit).

In March 2010, Judge Sweet delivered a summary judgment that invalidated all fifteen claims in 7 patents held by Myriad (3). Claims are the heart of a patent, defining the intellectual property. A patent grants exclusive rights to make, use, sell, or import the claimed invention. Myriad’s patents included two general categories of claims: (1) methods for detecting “alterations” or mutations in the DNA sequence, and (2) isolated DNA molecules. The broadest method claims gave exclusive rights to any way of comparing the DNA sequence from a sample to the reference sequence of the *BRCA1* and *BRCA2* genes disclosed in Myriad’s patents. These method claims were invalidated because they were based only on “comparing” or “detecting” variations. They neither entailed a transformation nor specified a machine. The “isolated” nucleic acid molecule claims covered sequences from the two genes. The patents did not claim DNA from a person’s body, but claims were nonetheless broad—deliberately crafted to preclude others from making or using DNA molecules or detecting mutations. Judge Sweet argued that DNA is the embodiment of genetic information and claims on isolated DNA molecules in effect blocked access to that information. He ruled that the claimed molecules were not “markedly different” from corresponding naturally occurring DNA molecules simply because they were isolated. He also ruled that the plaintiffs could sue.

However, following appeal to the Court of Appeals for the Federal Circuit (CAFC), which hears appeals of patent cases from all 94 US Federal District Courts, a three-judge panel

ruled in July 2011 that only one of the plaintiffs had standing to sue, but that was sufficient (4). CAFC affirmed Judge Sweet's invalidation of five broad method patents, arguably Myriad's broadest patents, and the hardest to work around. CAFC also unanimously agreed that engineered DNA molecules, such as complementary DNA (cDNA)—DNA synthesized from a messenger RNA template, thus eliminating intron sequences—are eligible for patenting, thus reversing Judge Sweet's ruling that no DNA molecules are patent-eligible. CAFC also unanimously upheld one method patent for using BRCA in screening drugs for cancer treatment.

The panel split 2-1, however, on the matter that ultimately went to the Supreme Court—whether “isolated” DNA molecules corresponding to sequences in human genes are eligible to be patented. Judges Lourie and Moore said “yes,” although for somewhat different reasons, and Judge Bryson dissented, saying that the claimed DNA molecules were not markedly different in a way that should make them eligible to patent.

The Supreme Court returned the case to the CAFC in 2012 (5), after deciding another case, *Mayo v Prometheus*, in which it unanimously invalidated patents over a laboratory test for a metabolite used to adjust doses for thiopurine drugs (6). In August 2012, the CAFC largely reiterated its prior ruling, with the same 2-1 split (7). In November, the Supreme Court agreed to hear the case.

It is highly significant that the Solicitor General filed amicus briefs twice before the CAFC and again before the Supreme Court (8-10). The original decision to file a US Government brief in October 2010 ended a contentious process within the executive branch. Officials from the National Institutes of Health and the US Patent and Trademark Office (USPTO) disagreed. The Solicitor General is the final arbiter of the US Government position and argues cases before the higher courts. The final decision to weigh in was made at the White House. Solicitor General briefs are highly influential. In ten out of twelve patent cases in which the Solicitor General and CAFC have disagreed, the Supreme Court has ruled with the Solicitor General (11). The Solicitor General's briefs tracked with Judge Bryson's dissent arguing that engineered DNAs, including cDNAs, are patent-eligible, but DNA molecules whose sequences are found in nature are not. The most recent brief also makes quite clear that the formal US Government position was a deliberate step away from three decades of USPTO practice in granting claims on isolated DNA molecules whose sequences occur in nature.

The oral arguments demonstrated the Justices' familiarity with the Solicitor General's brief. Their questions probed arguments against the Solicitor General's logic, but they heard only feeble counter-arguments punctuated by technical gaffes. Two concerns were repeatedly aired. One was that Myriad's claims reached far upstream into research, precluding the study of *BRCA* genes. Many analogies got at this basic concern, including ingredients in chocolate chip cookies, baseball bats, and anti-cancer sap from plants in the Amazon. Other questions signaled real concern about disrupting patent rights for biotechnology products. The Justices sought assurance that barring patents on isolated DNA molecules with naturally occurring sequences could still preserve the claims on complementary DNA that undergird commercially valuable therapeutic proteins. If the questions predict an outcome, it is likely to be, “isolated genomic DNA is not patentable, but engineered DNA molecules are.”

Such a ruling would not threaten most patent claims that underlie therapeutic proteins (insulin, growth hormone, erythropoietin, etc.), but would invalidate many claims on molecules and methods for DNA molecular diagnostics, weakening companies like Myriad Genetics and Athena Diagnostics. Other companies will breathe a sigh of relief as the

shadow of infringement liability lifts, for example those offering multi-gene tests, all-exome sequencing, and whole-genome analysis.

The case might never have reached the highest court had Myriad Genetics adopted two policies it has long been urged to articulate: allowing (1) research use and (2) verification and follow-on testing after initial *BRCA* testing. Most plaintiffs would no longer have had complaints and the Supreme Court's concern about pre-empting scientific innovation would be moot. By preserving its legal options to sue over research use and verification testing, Myriad may have killed its cash cow two years before its patents began to expire.

Myriad has recently reported its best financial quarter ever, projecting over \$500 million revenues from its various *BRCA* tests in 2013 (12). It runs an efficient laboratory and secures third-party payment. Moreover, all three CAFC judges agreed that Myriad could get patents with claims on primers, probes, and DNA constructs it made and disclosed. The Supreme Court appears poised to judge that Myriad's claims reached too far, however, to secure exclusive rights on naturally occurring DNA sequences. If so, those developing molecular diagnostics will have to comport with a new rule for US patent jurisprudence: yes cDNA can be patented, but not gDNA.

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