

Gene Patents on the Line

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Whoever 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. Patent Statute (USC 35, Part II, Chapter 10, Section 101).

On May 12, 2009, two teams of patent lawyers squared off in U.S. District Court for the Southern District of New York in the potentially precedent-setting *Association for Molecular Pathology et al. v. United States Patent and Trademark Office et al.* The suit was filed by the American Civil Liberties Union (ACLU) and the Public Patent Foundation (PUBPAT), a not-for-profit patent reform organization affiliated with the Benjamin N. Cardozo School of Law in New York.

Even the plaintiffs' lawyers admit that this is an unusual case, because it seeks nothing less than the abolition of all gene patents, which, they argue, are unconstitutional.

Approximately 20 percent of the human genome is already patented, so if *Association for Molecular Pathology et al.* prevail, something like 5,000 gene patents could become invalid. Patents on genes encoding therapeutic proteins have been litigated, but patent disputes on genes for diagnostic purposes have so far been settled out of court. What may be at stake now is how patent claims affect diagnostic and risk prediction uses of DNA sequences. Either way, a ruling in this case will have consequences for employers, payers, and healthcare consumers.

Represented by the ACLU and PUBPAT, the plaintiffs include prominent scientific organizations and researchers and six women diagnosed with either breast or ovarian cancer. The defendants include the United States Patent and Trademark Office, Myriad Genetics, and 10 directors of the University of Utah Research Foundation, which owns some of the patents in question.

PRODUCTS OF NATURE?

At issue are Salt Lake City-based Myriad Genetics' seven patents on the BRCA1 and BRCA2 genes. Certain mutations in these genes confer an increased risk of breast and ovarian cancer in women and breast and prostate cancer in men. The BRACAnalysis test detects the presence of these mutations.



Together with a family history and other medical information, a BRACAnalysis report can help a medical geneticist or a genetic counselor provide critical guidance about prevention and treatment options to a patient who may be considering a prophylactic mastectomy or oophorectomy. That's why this molecular diagnostic test is widely acknowledged as a significant advance in personalized medicine.

Just to be clear, the Myriad Genetics patents do not cover its BRACAnalysis test, which involves the DNA sequencing of each gene. Rather, the company controls the patents on the BRCA1 and BRCA2 genes. That means Myriad Genetics can legally prevent anyone in the United States from doing any research involving these genes until the first of its patents expires in 2015.

"The more we discover that the crucial factors in genetics have to do with the interaction of genes, not with the action of a particular gene, the more gene patents get in the way of research and treatment," says Christopher Hansen, an ACLU staff attorney and lead attorney in this suit.

The alleged stifling of research — which could lead to diagnostic tests that detect other harmful mutations known to exist in the BRCA1 and BRCA2 genes — is only one of the "wrongs" plaintiffs seek to redress. The Statement of Material Facts submitted to the court claims, in part, that Myriad Genetics' monopoly inflates the price of the BRACAnalysis test, prevents other laboratories from using newer and potentially better testing methods such as microarray analysis, reports test results that read "genetic variant of uncertain significance" disproportionately for minority groups, and that women cannot verify BRAC-

Analysis results with another laboratory before undergoing major surgery. They also point out that discovery of the BRCA1 and BRCA2 genes was funded in part by the National Institutes of Health.

The suit also alleges that the gene patent claims violate the First Amendment by limiting thought and knowledge. For example, a medical professional or researcher who mentally compared two genetic sequences would be infringing on a gene patent. Because they represent information, plaintiffs contend, patenting genes limits information “in a manner far different from patents on true inventions, such as carburetors.”

The real question in this case is whether genes are patentable in the first place.

“It has long been the rule in American patent law that you cannot patent laws of nature or products of nature,” says Hansen. “ $E=mc^2$ took an enormous amount of effort to discover, but it’s not patentable, because all Einstein did is figure out what nature herself is doing.”

“Isolating and purifying” has been a successful strategy in gaining patent protection for substances such as epinephrine and vitamin B12, but isolating and purifying a gene—that is, converting it into complementary DNA or cDNA—so that it can be sequenced is simply copying it into another format, the plaintiffs argue. Similarly, sequencing a gene does not change the informational content of that gene.

“Human genes are products of nature and patents on them should never have been granted in the first place,” declared co-counsel and PUBPAT Executive Director Daniel B. Ravicher in an August ACLU news release (ACLU 2009). “Genes are not inventions, and patenting genetic sequences is like patenting blood, air, or water.”

That same news release announced that the American Medical Association, the March of Dimes, and the American Society for Human Genetics (ASHG) each have submitted friend-of-the-court briefs in support of a motion for summary judgment in favor of the plaintiffs.

When asked to comment on this article, Susan Barton, Myriad Genetics’ director of investor relations and assistant to the CEO, replied, “I am sorry that I cannot be more helpful, but Myriad has a policy of not commenting on pending litigation matters.” Brian M. Poissant, partner and chair of the intellectual property practice at the New York law firm Jones Day, who leads the defense, also declined to comment for this article.

“EITHER SIDE COULD WIN”

Don’t short your stocks in biotechs and pharmas with gene patents just yet. Even a ruling in favor of the plaintiffs may have a limited impact on other gene patents and even on the BRCA1 and BRCA2 patents.

“If the court were to find that gene patents are always

patents on products of nature and, therefore, are not patentable, it would put a lot of other gene patents at risk,” says Hansen. “But every gene patent is written differently and a ruling might not necessarily affect all of them.”

Robert Cook-Deegan, MD, director of the Center for Genome Ethics, Law & Policy at the Duke Institute for Genome Sciences & Policy, agrees.

“People use the term ‘gene patent’ quite loosely, but it can refer to all kinds of different things, depending on the precise language in the claims section of a patent,” says Cook-Deegan. “Myriad could still have some intellectual property on the BRCA1 and 2 genes even after this case is decided. Either side could win this case, and we would still have a fair amount of uncertainty.”

The difference between producing a therapeutic protein and sequencing DNA for diagnostic purposes may provide just such an opportunity for the court to rule in a way that doesn’t disrupt a patent system that seems to be working reasonably well—at least for therapeutic gene sequences.

“With a diagnostic, you’re taking a sequence that is in somebody’s body, but you’re not going to make a copy of the full-length cDNA,” Cook-Deegan explains. “You’re going to be making a copy of a PCR [polymerase chain reaction] segment. That’s how Myriad does its BRCA-*Analysis* test. So the courts may decide that you can patent a gene to make a therapeutic protein, but that you cannot patent a method that blocks another person from figuring out what the sequence is in somebody’s body.”

Cook-Deegan is one of several authors of a compendium of case studies on the impact of gene patents (NIH 2009), which includes a case study of Myriad Genetics’ BRCA test. The authors conclude that there is insufficient empirical evidence that the company’s patents raise the price of its test or inhibit consumer access to BRCA testing. The compendium is now in the “for public comment” phase, but the conclusions were reported in a commentary published in *Nature* (Cook-Deegan 2009).

AN “ATTENTIVE CONSTITUENCY”

How Myriad Genetics managed to become the target of this unusual lawsuit is a long and tortured tale of miscommunication, mixed signals, and mistrust detailed by Edward Gold and Julia Carbone in a paper published online (Gold 2008). An earlier content analysis study (Caulfield 2007) found mostly negative media coverage of Myriad Genetics.

According to Cook-Deegan, the company made a lot of enemies in the international scientific community early on by creating the impression—perhaps unintentionally—that any attempt by other researchers to work with BRCA1 and BRCA2 genes would be regarded as an infringement of its patents. Today, many clinical and research professionals give Myriad Genetics high marks for quality, turn-

This is a complicated case. Whatever the outcome, it is unlikely to nullify all intellectual property rights where specific genes are concerned.

around, and even price, but “There’s still a residue of resentment,” says Cook-Deegan. Another important reason why Myriad became a target may be that breast cancer has “a very attentive constituency,” as Cook-Deegan puts it.

Meanwhile, a decline in the cost of whole genome sequencing may pose a bigger threat to Myriad Genetics’ business model and that of similar molecular testing companies.

“The list price for the BRCA*Analysis* test is \$3,120, but by the end of this calendar year, you’re going to be able to get a whole genome sequence for \$5,000,” Cook-Deegan points out. “That suggests that you won’t use sequencing as your screening tool anymore. Instead, you’ll look for very specific mutations in a particular patient. So even if Myriad’s patents weren’t going to expire in 2015, by then nobody’s going to be doing tests like this, because you can get way more information [with whole genome and other testing] for the same money.”

Within weeks of this conversation with Cook-Deegan, Complete Genomics, in Mountain View, Calif., cut the cost of sequencing a human genome to \$4,000.

NO MERE TECHNICAL MATTER

“The inventive effort that goes into discovering, characterizing, and patenting a gene is the same or even greater as in other technologies,” says Hans Sauer, PhD, JD, associate general counsel for intellectual property with the Biotechnology Industry Organization. “And once you’ve discovered it, it can be the basis for a whole technology backbone, which requires huge investments and many years of development before it can come to the market in the form of a useful medicine or diagnostic test.”

Sauer has an insider’s perspective on what’s involved. He was a research scientist with Genentech and other pharmaceutical companies before entering patent law and becoming a registered patent attorney in 1999. He notes that the lawsuit has attracted attention among BIO members, many of whom have patented genes, but emphasizes that Myriad Genetics is not a BIO member nor is BIO directly involved in this litigation.

Encouraging that inventive effort is precisely the function of the patent system, asserts patent attorney Kate H. Murashige, PhD, JD, partner with the law firm of Morrison & Foerster, in San Diego. “I doubt if anybody would develop these tests if they didn’t have some assurance of exclusivity,” she adds.

But, Murashige also criticizes Myriad Genetics for not being “a good citizen.” She thinks Myriad should grant li-

censes to researchers, even if it’s not legally required to do so. The way to fix that, she says, is for the United States to adopt a research exemption — a provision many other countries include in their patent systems.

“My own view is that we’re making a big mistake in this country by not having a research exemption and compulsory research licensing,” says Murashige, “but I think patent holders should be compensated for it.”

As for the plaintiff’s alleged inability to access medically indicated BRCA testing, Murashige observes, “The problems that these people are experiencing aren’t necessarily the result of the fact that Myriad has these patents or that Myriad’s making a profit. The problem is that we don’t have a healthcare system that recognizes that people are entitled to have sensible healthcare.”

Which underscores what Gold and Carbone wrote in the conclusion of their paper:

If nothing else, this study has shown that the patent system is not a mere technical matter: It has a significant impact on health delivery, the biotechnology industry, and public debate. To avoid another crisis such as the one that erupted over Myriad’s patents, countries need to first set out their goals with respect to science and technology – is it to maximize innovation, maximize access to innovation, develop a scientific infrastructure – and then adapt their patent laws to best facilitate those goals.

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