AMP v Myriad: driving or disrupting innovation?

Anne Paxton

February 2017—The Association for Molecular Pathology belongs to a small and exclusive club of plaintiffs on the winning side of a unanimous U.S. Supreme Court decision. Such a ruling was issued in 2013 in the case of *AMP v Myriad Genetics*, a suit sponsored by the American Civil Liberties Union with the AMP as lead plaintiff.

The high court's finding against Myriad Genetics—that the company's patents on the *BRCA1* and *BRCA2* genes are invalid because products of nature cannot be patented—expanded the message of another momentous Supreme Court decision in 2012 in *Mayo Collaborative Services v Prometheus Laboratories, Inc.*

Molecular pathologists hailed the AMP's victory in 2013. And more than three and a half years later, robust and rapid developments in molecular diagnostics have seemed to justify the belief that limiting patents on genes would encourage, not dampen, innovation in the field.

At the AMP annual meeting in November last year, Roger D. Klein, MD, JD, chair of the AMP professional relations committee, and Timothy T. Stenzel, MD, PhD, chief operating officer of Invivoscribe in San Diego, presented contrasting perspectives on whether *Myriad* is opening new doors or wreaking harm. In interviews with CAP TODAY, they explain why they see *Myriad* as a pivotal decision, but for different reasons.

At issue in the *Mayo v Prometheus* case, which laid the groundwork for *Myriad*, was a patent on the relationship between metabolites of thiopurine drugs and their therapeutic responses, both efficacy and side effects. "Basically Prometheus received a patent on a reference range, but there was no specific test that the company invented," Dr. Klein says. "What they did was take a relationship and frame it as a method for purposes of patenting it." Prometheus' patent's "artful drafting," as Supreme Court justice Stephen Breyer termed it in his opinion, "was really taking a natural law and framing it as though the company was actually doing or discovering something."

Under the patent, the mere act of physicians thinking about the relationship between these thiopurine metabolites and the drug's effect would be an infringing activity, and the Supreme Court fundamentally found in Mayo that these test types of biological relationships are not patent-eligible, Dr. Klein says.

But a method patent that involved a biochemical relationship was at issue in *Mayo*, while the claims before the Supreme Court in *Myriad* were composition of matter claims on DNA. So the court's view of Myriad's *BRCA* patents was not necessarily predictable.

Because the patent office had issued many gene patents under precedents that had allowed the patenting of isolated, purified chemicals, few in patent prosecution thought the Myriad case would go the way it did—and certainly not in a unanimous opinion. But justice Clarence Thomas, who wrote the opinion, made it plain that the court linked the two patent challenges and their rulings. Quoting from justice Breyer's opinion in *Mayo*, Thomas reaffirmed that "'laws of nature, natural phenomena and abstract ideas' are 'basic tools of scientific and technological work' that lie beyond the domain of patent protection." The court held that the *BRCA1* and *BRCA2* genes, though isolated by Myriad, are raw materials, not inventions.

"From our perspective as pathologists and molecular diagnosticians, these cases are two sides of the same coin," Dr. Klein says. "One gives ownership of testing through method claims, and the other is composition of matter on the genes themselves. But they're both addressing different types of gene patents." The most important practical ramification of the *Mayo* and *Myriad* cases (the CAP was a co-plaintiff in Myriad) is that they eliminated infringement for large-scale gene sequencing (next-generation sequencing), he says.

While *Myriad* was pending, a number of companies developed their own *BRCA* tests and were ready to

launch them as soon as the decision came down, Dr. Klein said. But since, under patent law, Myriad's existing, unchallenged patents relating to BRCA1 and BRCA2 gene testing, such as primer patents, were presumed valid, Myriad filed lawsuits against several of the companies, among them Ambry Genetics, LabCorp, BioReference Laboratories, and a small company called Gene by Gene.

Some or all of the companies were using next-generation sequencing to do BRCA tests, so the potential threat to NGS was not a theoretical concern, Dr. Klein points out. Myriad sued for a preliminary injunction to stop Ambry and the others from performing the tests, which required Myriad to show it had a likelihood of success on the merits, there was an immediate threat, and it would be subject to irreparable harm if the injunction were not granted. Gene by Gene settled right away; other companies went to trial.

Dr. Klein

Before the trial court, Myriad argued that it created the primers, the short RNA sequences that serve as a starting point for synthesis. "PCR primers work by hybridizing to one strand of the double-stranded DNA molecule, so a primer contains a sequence that is identical to that of a segment of the complementary strand," Dr. Klein explains. "However, a primer is synthetically generated DNA that was created to form a PCR reaction, and in that narrow sense it did not exist in nature."

The idea that primers were patent-eligible didn't fly at the trial court (*University of Utah Research Foundation v Ambry Genetics*). The appeals court also went against Myriad, denying the preliminary injunction and finding that Myriad would not win on the merits. That was "pretty strong stuff," Dr. Klein says, "and was consistent with the Supreme Court's opinion in *Myriad*." The Supreme Court had found in *Myriad* that natural DNA sequences are not patent-eligible and that separating a gene from its natural environment is not an act of invention (though cDNA is patent-eligible because it is not naturally occurring). The high court also found that the techniques used to isolate *BRCA1* and *BRCA2* were in routine use at the time of discovery.

Opponents of the *Myriad* decision felt it was a destructive decision that would eliminate property rights and crush invention. Supporters saw the ruling as important for the advancement of molecular technology and the ability of laboratory service providers to offer it.

Dr. Klein sides with the latter. "I think the ruling was essential to our ability to perform exome, genome, and next-generation sequencing panels. Moreover, it is better to have multiple testing companies than one provider who basically owns the subject of testing." And test providers have multiplied as predicted, he found. When he recently checked the National Institute of Health's Genetic Testing Registry, he turned up 185 listings of companies that were offering *BRCA1.* "They may not all have been in the U.S., and there may have been duplication, but there are a lot of entities or companies out there testing," he says.

Prices also dropped precipitously, from the $3,000 that Myriad was charging to as little as $500 for panels containing as many as 30 to more than 100 genes, including *BRCA1* and *BRCA2.* "So what *Myriad* did was usher in this dramatic change," Dr. Klein says. "I think people with a free market bent would say this is great; this is what competition does. It's opened more and more testing with more genes at lower and lower prices. Opponents might say that quality suffers and that this basically commoditizes everything, but I don't know that we have evidence that quality has been harmed."

Far from having an adverse impact on genetic testing, the Supreme Court's decision has had the opposite effect, he believes. This clear benefit, he contends, makes it extremely unlikely that Congress would disrupt the enormous

advances made in clinical sequencing with legislation to counteract the ban on patenting of DNA sequences, even though biotechnology companies are free to request such a bill. “My guess would be that any changes made would be more directed to other types of technology products. The odds of this being reversed are very low because of the revolution in clinical sequencing that would not have happened without this case.”

AMP meetings have reflected the explosion of genetic testing, with a record 300 vendors exhibiting last year. “Exhibitors continue to rise substantially, especially vendors of the core products, which are the sequencing instruments. However, I had at least one vendor tell me that the existence of gene patents continued to inhibit their ability to put out a particular product because they can still be sued for it.” Nevertheless, Dr. Klein adds, “We’re seeing a surge of innovation in molecular diagnostics because it’s freed up the ability of labs to test.”

The impact of *Myriad* on biotechnology and the pharmaceutical industry is less clear. In talking with several intellectual property law experts, Dr. Klein says, he is hearing concerns about the weakening of patent protection and the increased difficulty of obtaining patents in the nondiagnostic realm. For example, one opponent of the decision complained of the following, he says: “At the U.S. Patent and Trademark Office, one can no longer claim a patent on naturally occurring substances, whether isolated or not, whether synthesized or not. If you can’t patent isolated DNA from a fungus, for example, why would you be able to patent an enzyme or an additional molecule that came from the same fungus?”

In comments to the United States Patent and Trademark Office, the AMP argued against barring patents on isolated, purified chemicals in general. “We felt that DNA was different,” Dr. Klein says. “It’s not just a chemical but a unique molecule that primarily acts as a store of a great deal of information. So although we did not support patents on isolated, purified DNA because of DNA’s unique role as an informational molecule, we supported patents on natural isolated, purified pharmaceutical products.” Some drugs, he says, are made this way, and experts have pointed to natural products that would have weaker patent protection—for example, medicinal molecules from plants and microbes (some of them possible antibiotic candidates), bacterial enzymes for laundry detergents or grain ethanol production, and fermentation products for nutritional or industrial use.

Although such products may continue to receive some patent protection, patent law experts contend that the *Myriad* decision has diminished this protection. “Some are saying you may be able to get only a method patent, which tends to be less strong,” Dr. Klein said. For example, instead of obtaining a claim to “an isolated lipase having amino acid SEQ ID1,” the applicant gets a claim to a method of washing laundry in a washing machine using a detergent composition containing that new lipase. But with such method patents, “the allowable claims are much narrower and harder to enforce, so the patents are viewed as commercially less meaningful. So one could argue that, over time, this could adversely affect the investment people are willing to make in these types of products.”

Some policy analysts have expressed fear that, despite the ability to sequence the patient’s genome, there might not be patent protection for companies developing therapies to treat the patient’s condition. “I don’t know the answer to that,” Dr. Klein says. “We’re seeing huge numbers of drugs in the pipelines, for example, for targeted therapy, so it isn’t clear that there has been an adverse impact in that way. But people have been discouraged from looking at natural sources from which to isolate a drug, for example. I don’t know how much of that work has been taking place in recent years.” He is confident, however, that few if any of the plaintiffs in *AMP v Myriad* wanted to get rid of patents on drugs. “We really were just concerned with diagnostics.”

He believes next-generation sequencing could not have become widespread without the *Myriad* decision. “If people were enforcing gene patents, then when somebody did a hereditary cancer panel, if it included *BRCA1* and *BRCA2*, you’d have to eliminate that and any other patented genes. How could you do an exome? And any specific variants could also have been patented in the way that the *JAK2* V617F variant was.” He adds: “When anybody found a genotype-phenotype relationship, there would have been a risk that they would patent that relationship. The result would have been a highly problematic fragmentation of testing.”

Complex royalty schemes would have to have been set up, he says. “And it seems like negotiating that—because of the large number of players—would have been enormously challenging and potentially impossible. People wouldn’t even have known when they were infringing because there would have been so many valid patents out there.”

As it is, he sees the ruling as having eliminated some of the huge obstacles to doing large-scale sequencing and lowered barriers to entry. “NGS is getting relatively easy for labs to do, and there are many, many participants engaged in it.”

But uncertainty remains. “There are some labs that won’t test for *BRCA1* and *BRCA2*—and maybe still won’t because Myriad could sue them,” he says. Not all of Myriad’s claims have been tested in the courts, he adds, and thousands of other patents have already been granted and are not automatically invalidated by the *Mayo* and *Myriad* decisions. “And the *Ambry* decision was on the preliminary injunction, not on the merits.”

Nevertheless, the continued rapid growth and advances in molecular diagnostics suggest Myriad has not impeded innovation, “and there don’t seem to be any data to support the notion that there is decreased investment because of this decision,” Dr. Klein says. “In fact, if you start looking at large-scale sequencing, it’s quite the opposite.”

From his standpoint at in vitro diagnostics manufacturer Invivoscribe, COO Dr. Stenzel perceives the molecular diagnostics industry as having many constraints that pharmaceutical companies don’t have to contend with—a factor he says is holding the field back.

Almost four years after the *Myriad* decision, “we’ve seen some new things. But the biggest issue for our field—and I consider molecular diagnostics still a young field, especially in the area of cancer—is that there just aren’t that many FDA-approved cancer molecular tests.”

Reimbursement for these technologies, sometimes even below the cost of testing, is abysmal, he says. “It has gotten really unacceptable, especially given all the things that labs and IVD manufacturers are required to do to provide quality testing.” By contrast, “Pharmaceutical companies have been well rewarded for their innovation, and reimbursement for their new drugs is very high. In the oncology space in the U.S., it’s not uncommon to be able to charge $100,000 for a single patient for a full course of treatment, versus diagnostic testing that may be very necessary to determine the treatment costing less than $100.”

Dr. Stenzel

The *Myriad* decision should get some of the blame for that, in his view. Getting Food and Drug Administration approval for a companion diagnostic can cost up to $20 million. Myriad spent millions to produce a companion diagnostic for a patentable drug, yet as a result of the *Myriad* decision, other companies not connected to the drug can come in and copy that diagnostic with a laboratory-developed test and get the same reimbursement, Dr. Stenzel says.

No other area of medicine allows this degree of unapproved instrumentation or other products, he says, and he is opposed to this sidestepping of the regulatory process. In fact, he left a post at Duke University to work on getting diagnostics through the FDA. “I thought that was what I could do to really help our field. In my lab, except for HPV, there weren’t any approved tests I could offer. I had to do LDTs, which was always a concern because I did not

have the funding to do the same level of test development and validation as IVD companies."

Dr. Stenzel questions the argument that NGS would not have developed at the speed it did without the *Myriad* ruling. "First, if there were a requirement to take things through the FDA, there wouldn't be a ton of genes that would get approval because the FDA looks at genes one by one. So any panel cleared would only have specific genes that were FDA cleared." Other products, such as cell phones and computers, contain multiple patented inventions and could not be produced without licensing deals in which different companies each get a cut of the action. "Other industries have been able to figure this out. Why couldn't we?"

The *Myriad* decision "hurt our field," he contends. "*Myriad* went against years of precedent. The patent office had determined that gene patents were patentable, many licenses were given out, and many companies spent time and effort based on those patents, and it was like pulling the rug out from under their feet."

By way of contrast with the U.S., Europe accepts gene patenting, and numerous decisions have defended manufacturers' exclusive rights. Nucleic acid sequences are patentable, and gDNA and cDNA are patentable, as long as the sequence is isolated. "Europe is totally different," Dr. Stenzel says. "I think they see the ability to reward innovation as necessary for stimulating development of new products."

Despite the *Myriad* decision's downsides for the diagnostics industry, Dr. Stenzel says, Invivoscribe and Myriad are finding success now with their focus on oncology. Invivoscribe has launched a suite of 11 genetic assay kits, even though it also has CLIA labs offering the testing around the world. The NGS technology employed in these kits is "phenomenal," he says, and can provide so much more information and benefit to patients and the clinicians taking care of them. "But it is a lot more complicated and costly technology."

His company also has contracts with pharmaceutical companies Novartis and Astellas to develop companion diagnostics. "Pharma usually pays the bills, because most of the companies developing companion diagnostics don't do it unless pharma funds the work. We don't know if a drug is going to get approved, so we would be taking a huge risk spending $10 to $20 million on a drug that failed, while our diagnostic might work just fine."

Some companies are starting to pressure pharmaceutical companies to share in the upside of the drug development, Dr. Stenzel adds, and most pharma companies so far are refusing. "But I'm hearing that some early-stage pharma companies are opening up to that possibility," especially in partnering with companies that have a strong track record of developing companion diagnostics.

For its part, Myriad continues to do well with *BRCA1* and *BRCA2* testing. "They have seen a lot of patients and have built up a knowledge base over time, and can figure out what the mutations mean in a large number of patients." Most of the new laboratories that have begun *BRCA* testing haven't developed the same database and can't be as helpful to patients, he says; it's for this reason he advises patients needing *BRCA* testing to go to Myriad.

But the majority of new companies are struggling, he says. "I would say 90 percent of the startups in the last five years in laboratory services that have focused entirely on molecular diagnostics, if not entirely on NGS, are losing money." Foundation Medicine, for example, is a company that is growing its revenue, "but if you look at their profitability, they are growing a loss faster than their revenue."

The complexity of sequencing should not be underestimated, Dr. Stenzel says, nor should the challenges that new laboratories offering *BRCA* testing, for example, must confront. "How deep is your coverage? What is your error rate, your sensitivity, your limit of detection? We've seen the deeper the coverage, the more accurate the testing. But it also costs more to do that. And the larger the gene, the more it costs to sequence it at a deep level. Large deletions or insertions are very challenging for an NGS system to be able to assess."

He is baffled that some BRCA tests are being offered at $250. "I just don't understand how you can do quality testing and all the development work and things to ensure patient safety in a way that you can still support a company at $250 a patient," Dr. Stenzel says. "We all know about Theranos and the lesson that some companies

are too good to be true."

In addition, he notes, "you're probably relying on bioinformatics to be able to interpret all the data that comes off NGS." In the past, molecular pathologists could look at sequencing and make visual calls. "With NGS, we're entirely dependent on medical informatics tools, and some of them are very poor at detecting large deletions." Invivoscribe uses a minimum of 1,000× coverage (average reads per base pair) for anything it does in NGS, and sometimes the minimum has to be 10,000×. "But there are companies out there doing testing at a much lower level—maybe 30× or lower. So there's this huge difference in how you do testing, and the price of sequencing reagents for these platforms is dependent on how deep you go. Companies that are trying to cut costs might do lower coverage, and then the accuracy of the test goes down."

Interpretive challenges must be added to complete the picture. "Since we started discovering genes and mutations, there are certain mutations that are clearly deleterious—mutations that generate a new stop codon, so if it were to make a protein, the protein would be truncated well before the end of the gene. Or with a frameshift mutation, the insertion or deletion is out of frame, then oftentimes leads to a premature stop and starts generating a random protein sequence, not the true protein."

But other mutations may be benign, he says, and it takes a lot of time and effort, expertise, and building a good database of every base in the genes to figure that out. Determining which genes are deleterious is important. "Variant of unknown significance" is a common test result, even for a company like Myriad in an initial report before an extensive workup is done with the family, Dr. Stenzel notes. On one hand, there is pressure not to leave patients hanging, and on the other, not to invite lawsuits. "The labs that come to this genetic testing new, that haven't developed the kind of expertise they need, unfortunately cannot serve patients as well."

He cites BCR-ABL—testing that is important for some chronic myelogenous leukemia patients—as an object lesson in why responsible patent holders with FDA-approved tests are necessary. Imatinib (Gleevec) was approved for CML more than a decade ago, but there was no international harmonization of BCR-ABL testing. As a result, for many years testing was "all over the place." As CAP proficiency tests have shown, "you cannot compare BCR-ABL testing from site to site." It was only in 2016 that an FDA-cleared 510(k) product was launched, Dr. Stenzel says.

"If there had been a single responsible patent holder for BCR-ABL testing, it is quite likely this situation would have been rectified long ago—or better yet, addressed from the start."

Similar concerns apply to PD-L1, which is required for some drugs but not others. "Multiple tests are on the market but do not agree with one another because there is no international harmonization. So laboratories have a huge dilemma as to which approved testing to perform."

Dr. Klein and Dr. Stenzel agree the data are not all in, and several important legal questions await resolution in the wake of *Myriad*. Funding has dried up for many new startups, Dr. Stenzel says, because of the uncertainty. "If you file a patent now and it's unsuccessful, it goes public. And everybody knows the genes you were looking at, without any protection. It's a real challenge in the U.S. Until we know exactly what we can and cannot do with the patent office or until the pendulum swings back, it will be hard to raise the capital to take new molecular diagnostics all the way to the FDA"—which he says is critical for the field to advance.
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Anne Paxton is a writer and attorney in Seattle.