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Denying Injunction against Ambry BRCA Testing, Utah Judge Unconvinced of Myriad's Legal Success

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By Turna Ray

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A US federal district court in Utah denied Myriad Genetics and other plaintiffs a preliminary junction that would have stopped Ambry Genetics from selling competing BRCA tests, even though the court determined this may harm Myriad's business.

According to the court's ruling, Judge Robert Shelby wasn't convinced that Myriad and other patent holders were likely to succeed on the merits of their case, which alleges that Ambry's BRCA tests infringe several of their BRCA patents claims.

"The court finds that although plaintiffs have shown they are likely to be irreparably harmed if an injunction does not issue, defendant [Ambry] has raised substantial questions concerning whether any of the patent claims at issue in plaintiffs' motion are directed toward patent eligible subject matter under 35 USC Section 101," Shelby wrote. "In light of defendant's showing, plaintiffs are unable to establish that they are likely to succeed on the merits of their claims."

Several owners of patents underlying Myriad's BRACAnalysis test sued Ambry in July, a few weeks after the company launched tests that gauge BRCA gene alterations associated with heightened risk of hereditary breast and ovarian cancer. Ambry began offering its tests immediately after the US Supreme court determined in Association for Molecular Pathology et al. v. Myriad that several of Myriad's claims on isolated BRCA sequences were patent ineligible under Section 101, because they are naturally occurring, but found cDNA used in gene cloning to be eligible because it doesn't occur in nature.

In order to grant a preliminary injunction against Ambry, Shelby had to determine whether without this action Myriad would suffer irreparable harm; which company would face more hardships, Myriad or Ambry; and whether granting or denying an injunction would be in the public interest. Myriad also had to show that it was likely to succeed on the merits of its case.

Establishing whether the plaintiffs would be "irreparably harmed" and whether they have a high likelihood of success in the case were the two most critical considerations for Shelby. While he was convinced that, facing competition from Ambry, Myriad's business would take a hit due to pricing pressure from insurers and loss of customers, the judge wasn't swayed that Myriad's asserted patent claims would stand up to the Section 101 test following the Supreme Court's rulings in AMP v. Myriad and Mayo v. Prometheus.

Shelby spends much of the 106-page ruling explaining why he doubts that Myriad's 10 asserted IP claims are patent eligible in light of older and more recent legal decisions. Myriad alleges that Ambry's testing processes infringe four of its claims covering pairs of synthetic DNA strands used as primers in amplifying or producing multiple copies of a DNA segment, and six method claims for analyzing BRCA1/2 sequences. Myriad believes that these claims are still valid after the Supreme Court's ruling in AMP v. Myriad.

"While [the] outcome was not what we had hoped for, the ruling was not unexpected because preliminary injunctions are difficult to obtain and rarely granted," Myriad spokesperson Ron Rogers told PGx Reporter. "That said, yesterday's decision is not the end of the legal case since the district court did not rule on the actual merits of the

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Allentoft, Heller, et al., Proceedings of the National Academy of Sciences
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Olson, Hartsough, et al., Nature Methods
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case. That decision will be decided in future district court proceedings."

Myriad has also taken legal action against a number of other labs performing BRCA testing, including LabCorp, Quest Diagnostics, GeneDx, and InVitae. But, Myriad and other patent holders are not seeking a preliminary injunction against these firms. While several of these labs had requested that federal district courts in their home state of California determine whether they are infringing Myriad's patent claims, these cases have been transferred to the US District Court for the District of Utah following a request from Myriad.

A few weeks earlier, Gene by Gene – another testing firm that launched BRCA testing after the Supreme Court's ruling in AMP v. Myriad and was sued by Myriad – settled the dispute out of court. Under the agreement, Gene by Gene has agreed to stop selling in North America standalone diagnostic tests that gauge BRCA1/2 genes or tests that include the genes as part of broader diagnostic panels. However, the company can continue selling and marketing these tests outside of North America. Gene by Gene can also globally provide its whole-genome and exome sequencing products that gauge BRCA genes, as well as its custom array products that assess variants for Mendelian disorders, including BRCA1 and BRCA2 variants.

Likelihood of success

Perhaps the most important aspect Shelby considered in determining whether to grant an injunction is the likelihood that Myriad would win its case in trial. In order to assess this, the judge had to analyze the claims in the post-AMP v Myriad era. "At this early stage … the court 'does not resolve the validity question,' but instead assesses 'the persuasiveness of the challenger's evidence, recognizing that it is doing so without all the evidence that may come out at trial,'" Shelby acknowledged.

In its effort to sway the judge in favor of its case, Myriad reasoned that its asserted primer claims were patent eligible because primers are derived from synthetic oligonucleotides designed in a lab. Myriad put forth that in AMP v Myriad, while the Supreme Court found that the process of extracting or isolating genomic DNA from its natural surroundings was not enough to make it markedly different from what exists in nature, it found cDNA claims patent eligible.

The order of exons in cDNA may be "dictated by nature," the court said, but "the lab technician unquestionably creates something new when introns are removed from a DNA sequence to make cDNA." However, when short strands of cDNA have the exact sequence as naturally occurring, or genomic DNA, then it is not patent eligible, according to the Supreme Court. In its ruling, the court noted as an exception "very short series of DNA" that "have no intervening introns to remove when creating cDNA."

Shelby wasn't assured by Myriad's argument that, like cDNA, primers are patent eligible just because they are synthetic. He countered this saying that it didn't matter so much whether primers were synthetic, but whether they reflected naturally occurring BRCA1/2 sequences. "The only synthetic DNA that [the Supreme] Court expressly found patent eligible was cDNA. Even then, the court held only that cDNA may be patent ineligible under some circumstances," Shelby wrote. "If cDNA – which is clearly synthetic – is sometimes patent ineligible, then implicit in the Supreme Court's decision is the conclusion that not all synthetic DNA is patent eligible."

Additionally, Shelby doesn't read the Supreme Court's decision as being solely concerned with whether cDNA was created in a lab as a definitive test for patent eligibility. "The … court was not focused simply on cDNA's origin in a laboratory – isolated genomic DNA is extracted and purified in a laboratory as well," he wrote. "Rather, the court focused on the fact that the cDNA's contiguous sequence was altered in comparison to the sequence from which it was derived."

Shelby writes that although primers and probes used in diagnostic processes can hybridize to exon-only DNA segments, which would be akin to cDNA of the gene, "primers and probes are not cDNA" and "cDNA is typically not used as a primer or a probe."

Ultimately, the deciding factor for Shelby is whether the information content of the primers – the very information that made them useful as part of a test that gauges the genetic alterations of interest – is the same as that contained in the DNA sequences in the body. "The information (emphasis Shelby's) set forth in a particular sequence of 4 nucleotides is the same whether the DNA is genomic or synthesized. Like the isolated DNA at issue in AMP, the primer claims are drawn to compositions specifically expressed in terms of the nucleotide sequences derived or isolated from the naturally occurring BRCA1 and BRCA2 genes," he reasons. Shelby finds the claimed primers to not only be structurally similar to genomic DNA, but also similar in

for programming gene expression signals in live bacteria. The team designed pre-computed light sequences based on experimentally calibrated mathematical models of light-switchable, two-component systems and used them to drive intracellular protein levels to match user-defined reference time courses. This method was used to accurately and precisely generate accelerated and linearized dynamics, sinusoidal oscillations with desired amplitudes and periods, and a complex waveform. The researchers also combined the function generator with a dual fluorescent protein reporter system — which they say is analogous to a dual-channel oscilloscope — to find that the synthetic repressible promoter linearly transforms repressor signals with about a seven-minute delay. "In principle, our method could be used to study virtually any biological process that is dynamically affected by gene expression," the researchers add.

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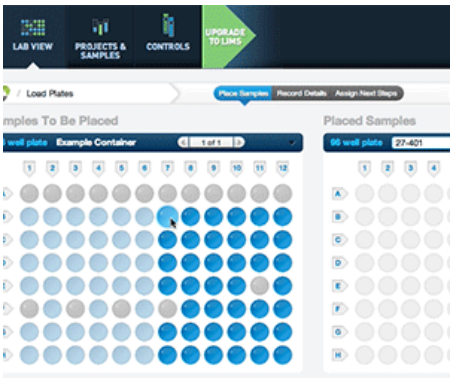

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A number of concerns have arisen regarding the recent Nature stem cell papers from a group of Riken researchers. Should the articles be retracted?

- Yes. The papers appear to be flawed and are not reproducible.
- Yes. The allegedly duplicated images are worrisome.
- Maybe. I'd need to know more details about the issues.
- No. The concerns thus far don't rise to the level of a retraction.
- No. Let the investigations take their course.

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utility since they will hybridize to complementary DNA fragments just as native DNA does. "In addition, in PCR, the primers function similarly to genomic DNA undergoing replication in the human body," he said.

Robert Cook-Deegan, director of Duke University's Institute for Genome Ethics, Law & Policy, believes that Shelby's reading of AMP v. Myriad with regard to Myriad's primer claims may be too broad, particularly in light of the US Patent and Trademark Office's recently issued guidelines to its examiners on how to apply the Supreme Court's decisions in AMP and in Mayo v. Prometheus. Both rulings have implications on what is required to transform a naturally occurring substance or abstract idea into patent eligible subject matter.

The USPTO guidance contains a number of examples to help examiners determine whether a claimed invention "reflects a significant difference from what exists in nature." One example deals with a claim on a pair of primers and another claim on a method of amplifying two sequences on two DNA strands. The USPTO found that the first claim is not patent eligible because it doesn't claim something significantly different than natural products, but held claim two as patent eligible because it "includes elements in addition to the judicial exceptions that amount to a practical application of natural products."

Cook-Deegan read this to mean that Myriad's primer claims on, for example, two DNA molecules in pairs that are selected to bracket amplicons, would stand up to USPTO's method of determining patent eligibility. "That requires human ingenuity, and they're not claiming the primers per se, but pairs of primers for PCR," he noted. "I think those same claims are very vulnerable on enablement and written description, but I do think those primer-pair claims would be eligible under Section 101."

Antoinette Konski, IP partner with the global law firm Foley & Lardner, also observed that USPTO's guidelines may have implications for the patent eligibility of testing methods and primers. "The patent office has now indicated that it will apply the Myriad analysis to purified bacteria, purified compounds, and medical methods," Konski said. With regard to primer claims, "they're really looking at the structure, and the linear sequence of the amino acids … Now, the question is, what if you modify the amino acids, you modify the backbone, then that would probably be more [akin] to cDNA, unless that sequence is found in nature."

Cook-Deegan felt Shelby's analysis of Myriad's method claims was stronger. "I do think he put not one but several nails in the coffin of the method claims, and I expect that part will stand," he said.

With regard to the six method claims at issue in this case, Myriad maintains they are patent eligible because they use primers and because these methods used in gauging BRCA1/2 sequences were not routine in the life sciences community before the company and its research collaborators sequenced and identified the location of the BRCA1 and BRCA2 genes in the mid-1990s. Shelby wasn't swayed that Myriad would win its case with this argument. Citing AMP v. Myriad and Mayo v. Prometheus, he asserted that the method claims are drawn to naturally occurring, patent ineligible BRCA1/2 sequences, and contain "no otherwise new process for designing or using these probes, primers, or arrays beyond the use of BRCA1 or BRCA2 sequences in those processes."

In Mayo v. Prometheus, the Supreme Court stated that in order to patent an application of a law of nature, the applicant "must do more than simply state the law of nature while adding the words 'apply it.'" In that case, the court also cautioned against tying up natural laws so others in the field could not make discoveries. "If allowed, plaintiffs' method claims would essentially foreclose the most widely used means to study and test for BRCA1 and BRCA2 genes," Shelby said. "To study a gene, geneticists generally must amplify a given DNA sample. The most widely used means to amplify DNA is through PCR, which requires primers."

Dan Burk, a law professor at the University of California, Irvine, and an expert in biotechnology and patent law, believes that Shelby applied the Supreme Court's AMP v. Myriad as well as he could given the court's decision was inherently flawed. "Shelby's reasoning is consistent with part of the Supreme Court opinion. There is probably no way to be entirely consistent with the Supreme Court opinion, since it is not consistent with itself," Burk said in an e-mail. "Since this is a motion for a preliminary injunction, Ambry only had to show that it can raise 'substantial questions' about Myriad's ability to win at trial. Given the incoherence of the Supreme Court's opinion, that is not hard to do."

He noted that the Supreme Court's Mayo v. Prometheus decision put "nearly all" diagnostic method claims at jeopardy. "There are parts of Judge Shelby's reasoning

that the Federal Circuit probably won't like" if Myriad chooses to appeal the lower court's decision, Burk noted. "But the question at this point isn't whether Judge Shelby is correct, it is whether Myriad has demonstrated that it is likely to win at trial."

Who will suffer more?

Without an injunction, Shelby acknowledged, Myriad will suffer irreparable harm. But in deciding whether to grant an injunction his responsibility is to weigh the facts of the case and assess how limiting competitive BRCA testing would impact not just Myriad, but also Ambry and the public.

Myriad, being the longstanding market leader in the space, is already experiencing some competition for market share and pressure to lower the price of its tests. "Simply put, in a BRCA testing market where Myriad has been the lone seller, the introduction of new competitors offering alternative testing will force Myriad to choose between lowering its test price or losing customers," Shelby wrote.

Myriad's list price for BRACAnalysis (including mutation and large rearrangement testing) is $4,040, while Ambry's price for next-generation sequencing analysis of BRCA1/2 genes has a price tag of $2,200. Having enjoyed a monopoly over the BRCA testing market since launching the test in 1996, Myriad generated between $2 billion dollars in revenues from BRACAnalysis between 1997 and 2013, according to documents filed with the court.

Myriad officials have assured investors and market analysts that competition will not significantly deteriorate its leadership position in the BRCA testing space. During its latest quarterly earnings call, company officials said that Myriad saw a "modest" share loss that "compromises approximately 15 percent of [its] total revenue" due to competition in the BRCA testing space. But in Shelby's view, even a "moderate" negative effect on Myriad's business is enough to establish a showing of irreparable harm. "This harm need not destroy Myriad in order to be irreparable," he wrote.

Meanwhile, in readying to offer BRCA testing last summer, Ambry invested $46.7 million to expand its lab and hire 110 new employees, the company revealed in court hearings and documents. The firm claimed that if Shelby issued an injunction it would put Ambry out of business.

While this in itself was not persuasive, the judge viewed favorably that Ambry waited until after the Supreme Court's ruling in AMP v. Myriad before launching its BRCA testing services. "The court finds that defendant appears to have acted with some caution in timing its BRCA testing launch," and using that decision, "cast considerable doubt on the subject matter eligibility of plaintiff's patent claims," Shelby wrote.

In the end, an injunction would harm Ambry more than it would Myriad, Shelby said, noting that the balance of hardships tip "slightly" in Ambry's favor. "Although plaintiffs will suffer economic harm without an injunction, Myriad has enjoyed an exclusive monopoly in the BRCA1 and BRCA2 testing market for nearly two decades, and its own financial forecasts show that it expects to see increased revenue growth this year," Shelby held. "Even without an injunction, plaintiffs will undoubtedly continue to benefit from Myriad's expertise, market strength, and brand name recognition."

Finally, Shelby felt that while both Myriad and Ambry showed that their positions in the case would impact public access to BRCA testing in "compelling" ways, he didn't find that the public interest mandated either issuing or denying an injunction. The judge, however, expressed concern over the fact that not all patients may be tested for BRCA mutations and large rearrangements through Myriad's service, and not all eligible patients are covered for testing. In comparison, Ambry's NGS-based test gauges mutations and large rearrangements in BRCA1/2 as part of one test, and so patients don't need to be covered for two separate tests.

Since the National Comprehensive Cancer Network in 2012 recommended that all women eligible for the BRCA point mutation test also receive large rearrangement testing, Myriad has reported that most insurers are reimbursing for its BRACAnalysis Large Rearrangement Test when the mutation test comes up negative. Still, Shelby noted that BART is "neither offered as a matter of course, nor covered by third-party payors for all patients," and that some women will have to pay out of pocket for it.

Shelby appreciated Myriad's substantial investment ($500 million) in improving its BRCA test offerings, in achieving broad reimbursement for its test through in-network contracts with more than 530 private payors, and generous patient assistance programs that have helped 35,000 women gain access to testing. "The court notes, this is not an insignificant undertaking," he said.

However, Shelby seemed to wag his finger at the company for its business practices, criticizing the firm for simultaneously using its patents and proprietary variant database to thwart advancements in the field. Myriad's proprietary variant database, in which the firm has stored data from a million patients' test results, has enabled it to boast a variants-of-uncertain-significance rate of 2 percent for BRACAnalysis. The firm recently published its first variant classification methodology paper in Clinical Genetics, but critics of the firm still maintain that the company's variant classification processes are a "black box."

"The practical result of Myriad's patents has been to hinder or halt follow-up research, data sharing, patient testing, and the creation of additional and more affordable technologies for BRCA1 and BRCA2 testing," Shelby wrote.

"For example, since about 2005, Myriad has declined to publicly share critical information regarding its classification of variants, including with its own patients. Instead, Myriad retains that information in a private database," he continued. "In so doing, Myriad distorts rather than serves the patent system's goal of public disclosure in exchange for exclusive rights. In this way, Myriad has chosen a commercial path that turns much of our patent system policy on its head."

Turna Ray is the editor of GenomeWeb's Pharmacogenomics Reporter. She covers pharmacogenomics, personalized medicine, and companion diagnostics. E-mail Turna Ray or follow her GenomeWeb Twitter account at @PGxReporter.

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Science

Through an epigenome-wide association study, researchers have linked DNA methylation at three spots in one gene to body-mass index. Investigators examined the methylation status of nearly 480 people, finding a handful of probes associated with BMI. The researchers confirmed three of those probes — all in intron one of the HIF3A gene — in two additional cohorts. They noted, though, that methylation at these HIF3A sites was likely a consequence rather than a cause of increased BMI.

Business

The FDA Microbiology Devices Panel of the Medical Devices Advisory Committee has recommended first-line use of Roche's cobas HPV test for women 25 years and older to assess their risk of cervical cancer based on the presence of clinically relevant high-risk HPV DNA. If the FDA follows through on the recommendation, the cobas HPV test, which provides genotyping information for HPV 16, 18, and 12 other high-risk HPV types, would be the first HPV test indicated for first-line screening of cervical cancer in the US.

Funding

Harvard Medical School and Columbia University have both received grants from the National Institute of Allergy and Infectious Diseases, totaling $12.3 million this year, to create translational research centers to develop molecular diagnostics technologies. Funded under NIAID's Centers of Excellence for Translational Research program, the grants will provide $6.3 million to Columbia and $6 million to HMS this year. Columbia's center could receive a total of $31 million in funding over the full term of the award.

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