Gene patents and capital investment

The consequences of the revocation of Myriad's patents on the *BRCA* genes on venture capital investment in the life sciences

Howard Wolinsky

Three years ago, Noubar Afeyan, managing partner and CEO of Flagship Ventures, an early-stage venture capital firm in Cambridge, Massachusetts, USA, was working with a biotech start-up company developing techniques for *BRCA* gene testing for breast cancer risk that avoided the patents held by Myriad Genetics, a molecular diagnostics company in Salt Lake City (Utah, USA) and the only operator in the field. However, despite the promise of the start-up's techniques, investors were put off by Myriad's extensive patent portfolio and fiercely defensive tactics: "A lot of investors were simply not willing to take that chance, even though our technology was superior in many ways and patentably different," Afeyan said. The effort to launch the start-up ultimately failed.

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Afeyan believes the prospects for such start-ups improved on the morning of 13 June 2013 when the US Supreme Court ruled in an unanimous vote that Myriad's fundamental patents on the *BRCA1* and *BRCA2* genes themselves are invalid, opening up the field to new competitors. The court's ruling, however, validated Myriad's patents for *BRCA* cDNA and methods-of-use.

The court's decision comes at a time when venture capital investment into the life sciences is projected to decline in the years ahead. Some believe that the court's decision sets a precedent and could

provide a boost for products, diagnostics and other tests under development that would have been legally difficult in the light of existing patents on human and other DNA sequences.

The US Patent Office issued the original patents for the *BRCA 1* and *BRCA2* genes in 1997 and 1998 for the US National Institute of Environmental Health Services, the University of Utah and Myriad Genetics. One year earlier, Myriad had launched its first diagnostic test for breast cancer risk based on the two genes and has since aggressively defended it against both private and public competitors in court. Many universities and hospitals were originally offering the test for a lower cost, but Myriad forced them to stop and eventually monopolized *BRCA*-based diagnostics for breast cancer risk in the USA and several other countries.

"Myriad did not create anything," Justice Clarence Thomas wrote in the Supreme Court's decision. "To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention." Even so, the court did uphold Myriad's patents on the methodology of its test. Ron Rogers, a spokesman for the biotech firm, said the Supreme Court had "affirmed the patent eligibility of synthetic DNA and underscored the importance and applicability of method-of-use patents for gene-based diagnostic tests. Before the Supreme Court case we had 24 patents and 520 claims. After the Supreme Court decision, we still have 24 patents. [...] [T]he number of our patent claims was reduced to 515. In the Supreme Court case itself, only nine of our 520 patent claims were at issue. Of the nine, the Supreme Court ruled that five were not patent-eligible and they ruled that

four were patent-eligible. We still have strong intellectual property protection surrounding our *BRCA* test and the Supreme Court's decision doesn't change that."

Within hours of the ruling, capitalism kicked into high gear. Two companies, Ambry Genetics in Aliso Viejo, California, and Gene by Gene Ltd in Houston, Texas, USA, announced that they were launching tests for the *BRCA1* and *BRCA2* genes for less than the US\$3,100 Myriad has been charging privately insured patients and US\$2,795 for patients covered by Medicare—the government health plan for the elderly and disabled. Several other companies and universities also announced they would be offering *BRCA* testing.

Entrepreneur Bennett Greenspan, a managing partner of Gene by Gene, explained that his company had been poised to offer *BRCA* testing if the Supreme Court ruled against Myriad. He said, "We had written a press release with our PR firm a month before the release of the Supreme Court with the intention that if the Supreme Court overruled the patent or invalidated the patent that we would launch right away and if they didn't, we would just tear up the press release." His company had previously offered *BRCA* gene testing in Israel based on guidelines from the European Union.

Myriad Genetics has not given up defending its patents, however. On 9 and 10 July 2013, it slapped Ambry and Gene by Gene with lawsuits in the US District Court in Salt Lake City for allegedly infringing on patents covering synthetic DNA and methods-of-use related to the *BRCA1* and *BRCA2* genes. Rogers commented that the testing processes used by the firms "infringes 10 patents covering synthetic primers, probes

and arrays, as well as methods of testing, related to the *BRCA1* and *BRCA2* genes."

On 6 August 2013, Ambry counter-sued Myriad, arguing that the company "continues a practice of using overreaching practices to wrongfully monopolize the diagnostic testing of humans' *BRCA1* and *BRCA2* genes in the United States and to attempt to injure any competitor [...] Due to Myriad's anticompetitive conduct, customers must pay significantly higher prices for Myriad's products in the relevant market, often nearly twice as high as the price of Ambry's products and those of other competitors" [1].

Just as the courts will have to clarify whether the competitors in this case infringe on Myriad's patents, it is also not clear how the Supreme Court's ruling will affect the biotech and diagnostics industry at large, now that one of the most contested patents for a human gene has been ruled invalid. In recent years, venture capital investment into the life sciences has been in decline. The National Venture Capital Association and the Medical Innovation & Competitiveness Coalition reported from a survey that, "An estimated funding loss of half a billion dollars over the next three years will cost America jobs at a time when we desperately need employment growth" [2]. The survey of 156 venture capital firms found that 39% of respondents said they had reduced investment in the life

sciences during the previous three years, and the same proportion intended to do so in the next three years. "[US Food and Drug Administration] FDA regulatory challenges were identified as having the highest impact on these investment decisions," the report states, adding that many investors intended to shift their focus from the US towards Europe and the Asia/Pacific region.

Another report from the same groups explains how public policy involving the FDA and other players in "the medical innovation ecosystem"—including the US patent system, public agencies, tax policy, securities regulation, immigration laws and private groups such as insurers—affect the decisions of investors to commit to funding medical innovation [3].

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Some investors think that the court decision about the patentability of human DNA will increase confidence and help to attract investors back to the life sciences. "The clarity is helpful because for the longest time people didn't do things because of ambiguity about whether those patents would be

enforceable," Afeyan said. "It's one thing to not do something because of a patent, it's another to not do something because you know that they have patents but you're not sure what it's going to stop you from doing because it hasn't been really fully fleshed out. Now I think it is reasonably well fleshed out and I think you will see more innovation in the space."

Others also appreciate the clarification from the Supreme Court about what is a patentable invention in regard to human genes and DNA. "The Myriad decision was a very solid reading of the underlying purpose of our patent law, which is to reward novel invention," commented Patrick Chung, a partner with New Enterprise Associates, a venture capital firm in Menlo Park, California, which invested in 23andMe, a personal genomics company based in Mountain View (California, USA), and who serves on the 23andMe board.

But not everyone agrees that the Supreme Court's decision has provided clarity. "You could spin it and say that it was beneficial to create some certainty, but at the end of the day, what the Court did was reduce the scope of what you're allowed to get patent claims on," said Michael Schuster, a patent lawyer and Intellectual Property Partner and Co-Chair of the Life Sciences Group at Fenwick & West LLP in San Francisco, California, USA. "It's going to be a continuing dance

between companies, smart patent lawyers, and the courts to try to minimize the impact of this decision."

Kevin Noonan, a molecular biologist and patent lawyer with McDonnell Boehnen Hulbert & Berghoff LLP in Chicago, Illinois, USA, commented that he does not expect the Supreme Court decision will have much of an impact on venture investments or anything else. "This case comes at a time fortunately when biotechnology is mature enough so that the more pernicious effects of the decision are not going to be quite as harmful as they would if this had happened ten, 15 or 20 years ago," he said. "We're now in the 'post-genomic' era; since the late '90s and turn of the century, the genomic and genetic data from the Human Genome Project have been on publicly available databases. As a consequence, if a company didn't apply for a patent before the gene was disclosed publicly, it certainly is not able to apply for a patent now. The days of obtaining these sequences and trying to patent them are behind us."

Noonan also noted that the Myriad Genetics patents were due to expire in 2014–2015 anyway. "Patents are meaningless if you can't enforce them. And when they expire, you can no longer enforce them. So it really isn't an impediment to genetic testing now," he explained. "What the case illustrates is a disconnect between scientists and lawyers. That's an old battle."

George Church, professor of genetics at Harvard Medical School (Boston, Massachusetts, USA) and Director of the Personal Genome Project, maintains that the Supreme Court decision will have minimal influence on the involvement of venture capitalists in biotech. "I think it's a non-issue. It's basically addressing something that was already dead. That particular method of patenting or trying to patent components of nature without modification was never really a viable strategy and in a particular case of genes, most of the patents in the realm of bio-technology have added value to genes and that's what they depend on to protect their patent portfolio—not the concept of the gene itself," he said. "I don't know of any investor who is freaked out by this at all. Presumably there are some, because the stock oscillates. But you can get stock to oscillate with all kinds of nonsense. But I think the sober, long-term investors who create companies that keep innovating are not impacted."

Church suggests that the biggest concern for Myriad now is whole-gene sequencing, rather than the Supreme Court's decision. "Myriad should be worrying about the new technology, and I'm sure they've already considered this. The new technology allows you to sequence hundreds of genes or the whole genome for basically the price they've been charging all along for two genes. And from what I understand, they are expanding their collection to many genes, taking advantage of next generation sequencing as other companies have already," he said.

Whatever its consequences in the US, the Supreme Court's decision will have little impact on other parts of the world, notably Europe, where Myriad also holds patents on the *BRCA* genes in several countries. Gert Matthijs, Head of the Laboratory for Molecular Diagnostics at the Centre for Human Genetics in Leuven, Belgium, says that even though the US Supreme Court has invalidated the principle of patenting genes in America, the concept remains in Europe and is supported by the European Parliament and the European Patent Convention. "Legally, nothing has changed in Europe," he commented. "But there is some authority from the US Supreme Court even if it's not legal authority in Europe. Much of what has been used as arguments in the Supreme Court discussions has been written down by the genetics community in Europe back in 2008 in the recommendations on behalf of the European Society for Human Genetics. The Supreme Court decision is something that most of us in Europe would agree upon only because people have been pushing towards protecting the biotech industry that the pendulum was so way out in Europe."

Benjamin Jackson, Senior Director of legal affairs at Myriad Genetics, commented that Myriad holds several patents in Europe that are not likely to be affected by the Supreme Court's ruling. "The patent situation both generally and for Myriad is a lot clearer in Europe. The European Union Biotech Directive very clearly says that isolated DNA is patentable even if it shares the same sequence as natural DNA," he said. "Right now, it's pretty uncontroversial, or at least it's well settled law basically in Europe that isolated DNA is patentable." However, while the Directive states that "biological material which is isolated from its natural environment or produced by means of a technical process" might be patentable

"even if it previously occurred in nature", the European Patent Office (EPO) in Munich, Germany, requires that the subject matter is an inventive step and not just an obvious development of existing technology and that the industrial application and usefulness must be disclosed in the application.

Myriad has opened a headquarters in Zurich and a lab in Munich during the past year, hoping to make inroads in Europe. In some EU countries, Myriad offers its *BRCA* test as part of cancer diagnosis. In other countries, *BRCA* testing is conducted at a fraction of what Myriad charges in the USA, either because institutions ignore the patents that are not enforced in their jurisdictions, or because these countries, such as Belgium, were not included in the patent granted by the European Patent Office. Moreover, in various countries *BRCA* testing is only available through the healthcare system and only as part of a more extensive diagnosis of cancer risk. In addition, as Matthijs commented, "[t]he healthcare system in Europe is very heterogeneous and that's also of course a big impediment for a big laboratory to try and conquer Europe because you have to go through different reimbursement policies in different countries and that's not easy."

Ultimately, it seems the Supreme Court's decision might turn out to have little impact on biotech firms in either the USA or Europe. Technological advances, in particular new sequencing technologies, might render the issue of patenting individual genes increasingly irrelevant.

CONFLICT OF INTEREST

The author declares that he has no conflict of interest.

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