Myriad stands alone

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Myriad took no prisoners on its way to the top of the molecular diagnostics field. That strategy is unlikely to endure.

Myriad Genetics began in 1991 as a small University of Utah startup interested in the then-novel arena of diagnostic genetic testing. After winning a highly publicized race to sequence the BRCA1 and BRCA2 breast cancer genes, the company obtained patents on the gene sequences and methods of using them to determine cancer risk. The patents were broad and interlocking, covering BRCA genomic DNA, cDNA, methods of diagnosis and systems detecting mutations. Myriad also filed for diagnostic 'toolbox' patents, including two claiming any DNA primer or probe sharing 15 nucleotides with the wild-type BRCA1 or BRCA2 it first sequenced. These patents became the heart of the company.

Since then, the decision to aggressively assert this intellectual property (IP) has become synonymous with the Myriad name. Unlike other diagnostic companies that pursued cross-licensing opportunities, Myriad was voraciously litigious, sending cease-and-desist letters to competitors, clinicians and researchers. It also developed a proprietary database of rare mutations in the two genes—"variants of uncertain significance"—that it closed to outside researchers in 2004. Access to healthcare was another flashpoint. It charged as much as $4,000 for its flagship test BRCAnalysis—not uniformly covered by health insurers—where similar, unpatented tests cost as little as $100. Civil libertarians, bioethicists and advocacy groups argued that this squeezed patients seeking BRCA sequencing into a single, high-priced option. From a business perspective, however, Myriad's strategy paid off handsomely. Between 1997 and 2013, Myriad sold around one million tests and generated $2 billion in revenue, 80% of it coming from its BRCAnalysis product.

In 2009, these business practices led a group of patients, physicians and public interest groups to challenge Myriad's patents in court. In response, the US Court of Appeals invalidated Myriad's patents' method claims in 2012. And in June 2013, the US Supreme Court invalidated several claims on the genes themselves. The Court reasoned that isolated BRCA fragments were unpatentable "products of nature," even though they were "isolated and purified" from the surrounding genome. However, the Court upheld Myriad's claims on BRCA1 and BRCA2 cDNA on the grounds that such molecules were not naturally occurring.

Following the ruling, several companies immediately started offering tests for mutations in BRCA1/2; Myriad promptly sued them for patent infringement. In March, a Utah federal court denied Myriad a preliminary injunction that would have stopped its competitors from selling diagnostic tests, accusing Myriad of thwarting advancements in the field.

Critics of the company expected a death rattle. But Myriad remains very much alive. Although its initial patents expire in 2016, market inertia still provided $613 million in annual revenue to the company last year (a 23% increase from 2012). Indeed, Myriad has been busy expanding its footprint; it has stepped up its companion diagnostic program, and the recent $270-million purchase of Crescendo Biosciences signals a move away from gene-based to protein-based diagnostics. Yet Myriad has also continued to stock its patent portfolio, licensing almost a dozen university patents on methods of cancer screening, similar to those invalidated by the US Court of Appeals for the Federal Circuit.

Meanwhile, the diagnostics landscape has dramatically changed. Several companies (InVitae, Ambry and Counsyl) offer multiplex, whole-exome and whole-genome sequencing for comparable prices. But two companies stand out in comparison: GeneDx and Illumina.

GeneDx, founded in 2000 and one of Myriad's litigation adversaries, specializes in rare-gene diagnostics. Today, it offers diagnostic sequencing for hundreds of disorders, as well as limited multigene panel and whole-exome screening, using mostly next-generation sequencing technology, at approximately half of Myriad's per-gene cost. Its parent company, Bio-Reference Laboratories, has reported about $700 million in annual revenues, with much of that from GeneDx. GeneDx also has good relationships with all commercial insurers and Medicare. In contrast to Myriad, GeneDx does not rely on gene or diagnostic patents it uses in testing, and even filed an amicus brief against Myriad in its Supreme Court case. Rather, many of GeneDx's testing protocols come from freely available, publicly funded research—'open source' genetic testing.

Illumina, meanwhile, has developed a strong IP portfolio and enforced it aggressively. It is currently engaged in a number of patent lawsuits over sequencing technology, including one involving noninvasive prenatal genetic diagnostics for Down syndrome. But the company—with >$400 million in quarterly revenues and almost 400% growth in the past five years—has mostly steered clear of patenting genes or methods of testing specific disorders. Rather, it has focused on its sequencing platform. As a consequence, it is constantly attempting to better—and outsell—its rivals.

These examples suggest that the genetics diagnostic marketplace is moving in two directions. The first, like GeneDx, is 'commodities sequencing' in which companies—armed with advanced and faster technologies developed elsewhere—sequence genes or test for genetic disorders, picking up market share at ever-decreasing rates. Patent protection contributes little, if anything, to commodities-type sequencing, and consumer attraction is largely based on reputation, branding, cost and insurance coverage.

The other path, illustrated by Illumina, is to patent technology rather than genes—the hardware and software behind running the sequencers once patients' samples come in the door. Because advancing sequencing costs a great deal in upfront engineering—and is easily copied—sequencing companies, like Illumina, have largely relied on their patent estate to police competitors. But they have also mostly forgone patenting disease-specific applications of their products. The goal is pure innovation: faster, more accurate and cheaper sequencing per nucleotide.

Myriad's current market position, however, captures neither of these streams. It has not, despite its patent losses, come to terms with single-gene sequencing as a commodities business. Nor has it developed its own sequencing platform, relying instead on the old-school Sanger method. The purchase of Crescendo suggests again that Myriad is attempting to corner a single diagnostic market on shaky IP. In sum, litigation and ever-evolving technological and business landscapes are killing monopoly-priced, single-gene sequencing. As neither a commodities sequencer nor a sequencing innovator, Myriad stands alone as the last IP-forward, single-gene company in a multigene, multiplex world.

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COMPETING FINANCIAL INTERESTS
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