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Myriad diagnostic concerns

The Myriad decision to overturn human gene patents is the least of concerns for a diagnostic sector struggling to attract investment.

Last month's US Supreme Court's ruling to outlaw patents on human genes has been hailed as a blow against the commoditization of life and a victory for the freedom to operate in academic research. But from a commercial standpoint, it is just the latest of a series of reverses to the intellectual property (IP) foundations needed to support innovative diagnostics enterprises. What's more, continued calls from the US Food and Drug Administration (FDA) to increase regulatory scrutiny of *in vitro* diagnostic tests and radical changes to test reimbursement underway at the US Centers of Medicare and Medicaid Services (CMS) are adding unnecessary uncertainty to the diagnostics business and potentially could discourage development of innovative tests.

The Supreme Court's decision in the *Association for Molecular Pathology et al. v. Myriad Genetics, Inc., et al.* brings to an end the long-running and contentious debate on the patentability of unmodified human genes. The court ruled that the unmodified sequences of breast cancer–associated genes *BRCA1* and *BRCA2* are a product of nature and therefore are ineligible for patenting. The decision draws a bright line under the types of nucleic acid sequences that cannot be patented.

The ruling also opens up patent monopolies like Myriad's $3,000 BRCAnalysis test, thereby introducing price competition; indeed, Ambry Genetics, Bio-Reference Laboratories, Pathway Genomics and Gene by Gene all announced lower-priced *BRCA1*/*BRCA2* tests within 24 hours of the ruling—good news for patients. Overturning unmodified gene patents may also untangle patent thickets that previously would have encumbered companies developing new multiplex DNA assays.

The bad news is there remains uncertainty as to how much modification of a natural human DNA sequence is needed to get a patent (although the ruling did explicitly confirm the patentability of "cDNA" and of other forms of DNA "in which the order of the naturally occurring nucleotides has been altered"). Put together with last year's decision in *Mayo Collaborative Services v. Prometheus Laboratories* casting doubt on the patentability of a gene mutation and its use in guiding clinical decision making, these uncertainties in the interpretation of patent law mean that diagnostic firms will need to carefully fashion use and method claims in their patents to circumnavigate these strictures.

The other way of looking at this is that perhaps the days of traditional diagnostic ventures built around IP covering individual gene tests are numbered. Certainly, with the increasing adoption of next-generation sequencing and multiparallel gene signature assays, innovative diagnostic ventures may instead turn to trade secrets to protect fundamental IP and resort to patenting only to protect algorithms needed to interpret test results.

The growing trend of diagnostic test complexity is one of the reasons that the FDA has been making noises about exerting more authority over home-brew tests; currently, CMS regulates these tests by assuring the competence of diagnostic laboratory service processes and protocols under the Clinical Laboratory Improvement Amendments (CLIA). In June 2010, FDA posted a notice in the *Federal Register* stating that today's home-brew laboratory tests are moving from "relatively simple, well-understood pathology tests" to high-complexity, high-risk tests. Just a few weeks ago, as part of a speech at the annual meeting of the American Society of Clinical Oncology, FDA commissioner Margaret Hamburg stated, "The agency is working to make sure that the accuracy and clinical validity of high-risk tests are established before they come to market," adding that FDA is developing a "risk-based framework" to do just that. The new system will provide "medical professionals with a critical baseline for confidence in the tests they order for their patients."

At the same time, changes are being made in the way Medicare and private insurers pay for diagnostics. Late last year, CMS announced it was letting its local state contractors figure out the prices of different diagnostic codes assigned to each of the 1,000 or so home-brew tests on the market. With little time and no direction from CMS, the solution that these contractors have come up with is to pay for only a few hundred well-established tests and cut payment rates across the board by an average of ~20% (and as high as 80% in some cases) from 2012 levels. Worse still, many of the newer, innovative and multiplex assays that do not fit the new codes simply aren't being paid for at all. The only hope they have for coverage is to provide evidence of clinical validity.

There is no doubt that everyone would love every test to be clinically validated before market entry. The problem is that the vast majority of diagnostics are supported by analytical performance data alone, not by clinical data. The low-margin diagnostic business model does not provide sufficient funds to support clinical trials; it is academic clinicians that validate diagnostics (like *KRAS* for epidermal growth factor receptor inhibitors) in medical practice after market entry.

Thus, the diagnostic sector finds itself increasingly pincered by legal, regulatory and reimbursement challenges. The courts are eroding IP protection. FDA is seemingly taking a regulatory sledgehammer to crack a nut, asserting authority over CLIA tests and requiring clinical data for approval. And payers are only reimbursing established tests (at discounted prices) and also insisting on clinical validation for new tests.

This sounds like the death knell for diagnostic innovation. Certainly, investors think so—according to Silicon Valley Bank, $17 million in Series A funding went into diagnostics in 2011 compared with $357 million in 2005. Fewer investors means less funding for trials. And fewer trials means only a fraction of tests will ever make it to market. In such an environment, one has to ask: Where are the innovative diagnostics for the new era of precision/personalized medicine going to come from?