nature genetics

Testing times

Belief in the value of DNA sequence led to investment in the technology that made the Human Genome Project possible. But DNA sequences are not in themselves inventions, and gene variants and the conditions in which they cause disease are discovered and held by many stakeholders. So, if patents are to continue to provide incentives of benefit from genomics, they must be licensed for competition that is not a zero-sum game.

These are difficult times for those looking to turn the laws of nature into an exclusive right to make money. In March, the US Supreme Court ruled that a diagnostic made by Prometheus Laboratories was ineligible for patenting (*Mayo Collaborative Services v. Prometheus Laboratories*, No. 10-1150) and also returned *Association for Molecular Pathology v. Myriad Genetics,* No. 11-725, to the Court of Appeals for the Federal Circuit for reconsideration. The appeals court had upheld Myriad Genetics' patents on isolated DNA from the *BRCA1* and *BRCA2* genes and its method patent for screening cancer therapeutics, reversing a previous decision by a district court that had ruled that the genes were non-patentable subject material under 35 U.S.C. § 101 (*Association for Molecular Pathology v. U.S. Patent and Trademark Office*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010)).

The crux of understanding how heritable mutations in these two genes confer a 50–80% cumulative lifetime risk of breast cancer and ovarian cancer to an individual woman is the genetic method that compares inherited variants to the normal sequences of the genes. Claims to this method were not considered worthy of intellectual property protection, and the appeals court decided to "affirm the [district] court's decision that Myriad's method claims directed to 'comparing' or 'analyzing' DNA sequences are patent ineligible," as "such claims include no transformative steps and cover only patent-ineligible abstract, mental steps" (http://www.genomicslawreport.com/wp-content/uploads/2011/07/Decision-in-USPTO-vs-MYGN.pdf).

Although clinicians wanting immediate and inexpensive tests for their patients may have a legitimate grievance against patent holders with inflexible licensing, the case in research is more complicated, with isolated gene patents providing a stimulus, along with the irritation and fear of litigation that many researchers and research subjects express. It can be argued that patents with licensing for noncommercial research use have stimulated discovery. In the years since Myriad and its collaborators published their discoveries, the corresponding papers (*Science* **266**, 66–71, 1994; *Science* **265**, 2088–2090,1994; *Nat. Genet.* **12**, 333–337, 1996) have been used by thousands of researchers and clinicians, with the numbers of citations to them exceeding even those to the first mapping of the *BRCA1* gene (*Science* **250**, 1684–1689, 1990). Some see an obstacle, but Myriad has become a nucleus for the curation and interpretation of variants at cancer risk loci.

The identification of *RAD51C* as a cancer predisposition gene by Alfons Meindl and colleagues (*Nat. Genet.* **42**, 410–414, 2010) was a substantial discovery that provides an important lesson for clinical use of the human genome. It is not sufficient to identify variants in a gene associated or segregating with a disease and then make probes to test for disease-causing mutations. Risk variants of lower penetrance than those in *BRCA1* and *BRCA2* require an even wider evidence-gathering net before they can be useful. Accurate assessments of the genotypic risks of both breast cancer and ovarian cancer must be made on properly ascertained populations, and segregation in families with cancers must be systematically investigated, as discussed by Chay Loveday and colleagues in this issue (*Nat. Genet.* **44**, 475–476, 2012).

The appeals court has already given much thought to the role of the courts in redressing grievances and in clarifying the operation of legislation. The court also explained its decisions in light of the expected effects of intellectual property claims on the operation of the biotechnology industry. In the concurring opinion of Judge Moore, "isolated DNA claims… represent crucial and exceedingly valuable property rights," such that "disturbing the biotechnology industry's settled expectations now risks impeding, not promoting, innovation." Judge Bryson partially dissented, stating that, "as Judge Moore's concurring opinion explains, Myriad has failed to credibly identify new uses for the isolated BRCA genes as probes or primers." Judge Bryson also states: "broad claims to genetic material present a significant obstacle to the next generation of innovation in genetic medicine—multiplex tests and whole-genome sequencing. New technologies are being developed to sequence many genes or even an entire human genome rapidly, but firms developing those technologies are encountering a thicket of patents."

In our opinion, it is not new judgments or legislation that are needed but more innovation. In the era of whole-genome sequencing of highly variable genomes, it is increasingly hard to justify exclusive ownership of particularly useful parts of the genome, and method claims must be more carefully described. It should even be possible to draft a patent on a method for assessing the pathogenicity of naturally occurring variants. But the key area for change is not in patenting, but in licensing. Business as usual will not be enough, because the utility of genomic information requires iterations of updating with current information from multiple stakeholders: other biotech companies, affected families, clinicians, informaticians and researchers. Success will be determined not by who owns the most property but by who can best keep track of the parts and make them work together. ■