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Legal Affairs

Enforceable Diagnostic Method Patents

Though ITC Provides Some Protection Abroad, States Can Trample Rights Here at Home

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Molecular biomarkers, such as variations in genetic sequences, protein levels, or combinations of specific biochemical changes, are increasingly important to the emergence of personalized medicine. Biomarkers are used to detect cancers and other diseases, to predict the risk or progression of diseases, or to choose among therapeutic options. Diagnostic methods involving biomarkers have long been patentable in the U.S., and are important value drivers for companies, and a revenue source for universities.

Recent developments threaten the scope and enforcement of diagnostic method patents in the U.S., forcing innovators to plan carefully to protect their biomarker inventions.

Patent protection for diagnostic methods will fail unless the patent claims, which define the enforceable scope of the patent, are sharper than a scalpel. The claims must be focused on the key, inventive step. Extra steps in a claim permit competitors to avoid infringement while appropriating the value of the diagnostic.

For example, if a method includes multiple steps, such as (step 1) drawing blood from a patient and (step 2) detecting the presence or absence of a biomarker, no one infringes the claim unless one party performs each step of the method. Thus, if a clinician draws the blood, and a different diagnostic company detects the biomarker, there is no patent infringement.

Even properly focused diagnostic method claims forfeit their value if they are unduly narrow. Most biomarker inventions relate not to a new method of detecting a biomarker, but to the information that a detected biomarker provides about a patient's current or future status. Claims that are limited to one method of detecting the biomarker are of little value, as competitors can select a different method, avoiding infringement.

As sequencing costs plummet, some individuals are having their complete genomes sequenced, and this trend should accelerate. **Knome** (www.knome.com) already provides whole genome sequencing, delivering a copy of a customer's personal genome. Diagnostic method patents that require inspection of a sample may be of little value once a computer program can scan a personal digital file for a genetic biomarker without resorting to a biological sample. As technology evolves, patent claims that are too narrow will not effectively protect diagnostic methods.

Problems with Narrow Claims

Narrow patent claims for diagnostic methods on genetic biomarkers also encounter the proxy allele problem. A researcher may identify a specific polymorphism (Polymorphism P) that

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provides information about disease risk or progression. The resulting patent application may claim methods of assessing risk by detecting the presence or absence of Polymorphism P. Importantly, though, no human polymorphism exists in isolation—each exists on a chromosome among other polymorphisms, many of which are in linkage disequilibrium with each other. Rather than sequencing Polymorphism P, a competitor could instead detect the presence of a different, proxy polymorphism that is tightly linked with Polymorphism P.

In this way, the competitor obtains the same diagnostic benefit but avoids infringement of a claim narrowly drawn to sequencing Polymorphism P. More effective patent protection would be available from a broader diagnostic method claim that is open to detecting either Polymorphism P or a polymorphism in linkage disequilibrium with it.

A similar problem arises when a research effort finds that 20 specific blood proteins are elevated in Alzheimer's patients. The diagnostic is most informative when it includes all 20 proteins, but testing for 19 or 10, may still be informative. While a claim that requires detecting all 20 proteins would be too constricting, the U.S. Patent and Trademark Office (USPTO) often resists examining more than one combination of proteins in a patent, creating a serious dilemma for diagnostic innovators.

The patentability of some broad method claims is currently under attack in U.S. courts and the USPTO. Recent decisions have invalidated method claims that were not tied to a particular machine and did not transform an article, as discussed in the February 1 issue of *GEN* (Court Ruling May Impact Life Science Patents: Innovation Could Be Hampered by "Machine or Transformation" Test Adopted in *Bilski*).

Today, diagnostic innovators are caught between the courts, which are invalidating broad method claims; the USPTO, where examiners seek to divide diagnostic inventions into ever-smaller slices; and the pace of technological advancement, which permits competitors to rapidly outflank narrow claims.

Inventors of diagnostic methods must follow a layered patent strategy, pursuing 1) method claims that are tied to a particular reagent, composition, or machine, 2) method claims that transform an article or transform data representing an article, 3) claims to valuable diagnostic reagents such as antibodies or nucleic acids for detecting a molecular biomarker, and 4) broader method claims whose final fate may depend on a more favorable wind from the courts or from Congress.

Cross-border shipments of diagnostic samples present important enforcement issues for diagnostic method patents. For example, if a diagnostic method is patented in the United States, but not in Mexico, a competitor can ship a sample from a U.S. patient to Mexico for detection of the biomarker. The competitor can't be sued for using the claimed method in the U.S. if the steps are performed in Mexico. Selling a patented invention in the U.S. would also infringe the patent—but U.S. courts have questioned whether selling applies to methods, or only to products.

U.S. companies facing competition from infringement abroad often can enlist the involvement of the International Trade Commission (ITC). The ITC can block the importation of articles made by a process patented in the U.S. If a competitor performs diagnostic tests abroad and attempts to import the resulting reports, the ITC may be able to intervene if the reports are articles produced by a process protected by a U.S. patent.

The ITC has the additional power to intervene to prevent unfair methods of competition that "destroy or substantially injure" a U.S. industry. If a foreign competitor is taking unfair advantage of a company's technology and threatening the viability of the U.S. industry, the ITC can and should be asked to intervene.

If a U.S. state or state agency decides to practice a patented method, a patentee may have no recourse. Patents cannot be enforced against any U.S. state unless the state waives its sovereign immunity under the Eleventh Amendment of the U.S. Constitution.

Recently, a patentee sued the California Department of Health Services for infringing upon a method for screening birth defects [*Biomedical Patent Management Corp. v. California, Department of Health Services* (Fed. Cir. 2007)]. The suit was dismissed because California had not waived its immunity from suit.

Regardless of the diagnostic market served, protecting the value of the underlying inventions requires a patent strategy that simultaneously outpaces new technologies for detecting molecular biomarkers and navigates the ever-shifting shoals of U.S. law. Today, successful diagnostic companies continually readjust their patent strategies to reflect changing opportunities and obstacles in the courts and the marketplace. GEN