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Where Do We Go From Here? The Evolving Landscape of Molecular Diagnostics

BY CATHY HUANG AND ERICA PASCAL

"Innovate or die." The adage has been in use for decades, but it holds true today. The world of molecular diagnostics is a rapidly evolving and competitive field. With the advancement in sequencing technologies and the scale of data collected and analyzed, companies and institutions strive to be at the forefront of the field and to protect their new discoveries. Yet in the past five years, the legal rules governing patent protection have shifted the landscape dramatically. Cases heard at the Supreme Court and Federal Circuit—including *Prometheus*, *Myriad*, *Ariosa*, *Virnetx*, and *Promega*[1]—have altered the scope of patentable subject matter, changed the rules for divided and induced infringement and shifted the confines of damages available for infringement. These changes present new challenges—and new opportunities—for the industry.

In this article, we report on the diverse perspectives offered by representatives from the public and private sector working in the field of how the recent evolution in case law has affected the molecular diagnostics industry and how it may impact strategies moving forward. The panel was held in San Diego on Feb. 3, 2016, as a cosponsored event by BIOCOM and DLA Piper LLP.

The panelists featured in this event were:

Lauren Nguyen-Antczak, National Cancer Institute Technology Transfer Center, National Institutes of Health

Laurie Hill, Head of Global Intellectual Property, Illumina

Phil Makrogiannis, Chief IP Counsel, Life Sciences Solutions, Thermo Fisher Scientific

Kim Kamdar, Partner, Domain Associates

Brian Sun, Patent Counsel, Hologic, Inc.

Erica Pascal, Partner, DLA Piper (Panel Moderator)

Changes in the Patent Landscape

In just five years, the Supreme Court and Federal Circuit have significantly modified the scope of protectable subject matter in *Prometheus*, *Myriad*, and *Ariosa*. In brief, laws of nature and naturally-occurring products, absent "something more," do not fall within the scope of allowable claims. Thus, methods such as adjusting drug dosage based on the drug's metabolite levels or detecting paternally inherited nucleic acid are no longer patentable subject matter, unless the methods contain one or more additional elements to transform them into an "inventive concept." Similarly, product claims to isolated genomic DNA, primers and probes are not patentable without something more to distinguish them. This two-step analysis of patent claims was formalized in *Alice v. CLS Bank* (2015)[2]. The impact of these rulings could extend itself to proteins and peptides, as well as the instrumentation for handling detection and analysis of nucleic acids, proteins and other biological molecules.

In addition to patentable subject matter, the courts have recently addressed the scope of patent infringe-

[1] *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012) ("*Prometheus*"); *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) ("*Myriad*"); *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015) ("*Ariosa*"); *Virnetx, Inc. v. Cisco Sys., Inc.*, 767 F.3d 1308 (Fed. Cir. 2014) ("*Virnetx*"); *Promega Corp. v. Life Technologies Corp.*, 773 F.3d 1338 (Fed. Cir. 2014) ("*Promega*").

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[2] *Alice Corp. Pty. v. CLS Bank Intern.*, 134 S. Ct. 2347 (2014).

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ment under 35 U.S.C. § 271. In *Limelight Networks v. Akamai* (2014)[3], the Supreme Court clarified the need for a direct infringer underlying claims of inducing infringement. The direct infringement requires that performance of each claimed step be attributed to a single party or, if the steps are carried out by multiple parties, to a single defendant exercising control or direction over the entire process. This case may raise issues for diagnostic methods claims that include steps divided among several actors, including the manufacturer, health-care provider and patient. For example, a diagnostic method might include collecting a patient's sample, sending that sample to a company for physical analysis, processing and analyzing the data using another company's software and a physician then using the results to form a diagnosis.

The importance of single versus multi-party actions was addressed with a different twist in *Promega Corp. v. Life Technologies Corp.* (Fed. Cir. 2014)[4]. The court set out two key holdings for indirect infringement: (1) A single entity can ''actively induce'' itself to infringe a patent since involvement of a third party is not required; and (2) A single commodity component sourced from the U.S. can constitute patent infringement in the U.S. for ex-U.S. manufacturing (even if that component is used within the same company). These holdings may enlarge the scope of actions that fall within induced infringement. A petition for certiorari was filed on June 26, 2015, and is currently pending.

The face of damages available for patent infringement continues to see changes as well. In *Virnetx, Inc. v. Cisco Systems* (Fed. Cir. 2014)[5], the court signaled a push toward apportionment at the smallest salable unit of a multi-component product in calculating damages. This focuses the damages calculation on the value of the infringing features, rather than the product as a whole. Given that diagnostic assays and instrumentation are often complex multi-featured products, this trend may present challenges in damages calculations as patent infringement cases move forward.

Where Do We Go From Here?

The primary focus of the panel discussion addressed the impact of these court decisions on strategies in the diagnostics field—including on patent prosecution and patent litigation—as well as effects on public-private collaborations and funding available for new and growing diagnostic companies.

In general, the panelists agreed that the law remains unsettled, and thus the impacts are not yet fully defined. Particularly because some of the case law is so nascent, patent applicants are finding a heterogeneous and somewhat unpredictable application of the case law by U.S. Patent and Trademark Office (''USPTO'') examiners. This seems particularly true in the rejection of claims for lack of patentable subject matter.

Other changes such as the prevalence of *inter partes* review (''IPR'') proceedings to challenge patents have also impacted the landscape. The IPR procedure allows post-grant challenges of patents on grounds of anticipation and obviousness. However, IPRs do not permit challenges to the patentability of subject matter; these challenges must instead be brought in federal court or in a post-grant review proceeding (''PGR''). The PGR process came into being with the America Invents Act (''AIA'') and is only available to a subset of newly issued patents. As of yet, the panelists had not yet seen any impact of PGRs in the diagnostics space. This mechanism for patent challenge thus remains largely untested.

In view of the increased activity of the courts and the uncertainty of how the law will continue to develop, the panelists discussed several strategies for protecting and maximizing the value of a patent portfolio.

1. *Diversify*. A patent portfolio is an investment, and like many other investments, a diversified approach can protect a company's portfolio against dramatic changes in law. Diversification can include pursuing a variety of system, product and method claims to cover as many aspects of the new technology as possible. Filing in both the U.S., as well as abroad, is also an important tool. In particular, different countries offer different views of patentable subject matter.

2. *Get Creative*. While it can be tempting for companies to guard their technologies as trade secrets in view of the changing patent law, this avenue has its drawbacks. It can be risky to forgo patenting and bet that a competitor won't arrive at the same solution. Patents, and particularly a well-rounded patent portfolio, can offer visible market value to a company where the value of trade secrets may be less visible.

Creative claiming strategies present an opportunity to overcome the hurdles of the new landscape. While naturally occurring products and processes are not patentable subject matter, careful consideration of the ''something more'' that can be added to distinguish products and methods can provide fruitful avenues. Interviews with the USPTO examiner assigned to the application may help reduce the amount of guesswork in ascertaining a path forward. This has been especially true in view of the lack of uniformity between examiners for Section 101 rejections.

For method claims, avoiding steps that lead to divided infringement between two parties can serve multiple purposes. The single entity claims can help strengthen the enforceability of the claims, and at the same time help insulate customers and the company from infringement liability. On the flip side, when designing diagnostic methods, a careful look at which parties perform and direct each step can help avoid potential future infringement litigation.

3. *Assess Licensing Strategies*. The shift in case law may have effected a change in the value of certain patent licenses, such as for nucleic acid sequences and diagnostic methods. An analysis of existing in- and out-licenses can be helpful in assessing whether the underlying patents are likely to remain valid and enforceable in the new landscape, and the level of value each brings to the company's business including focusing on whether the licensed patents cover only a small portion of a multi-component product.

Because the patentability of many products and methods varies from country to country, licensing worldwide IP rights can bring more value to the table. Changes in the law for indirect infringement and damages also impact licensing value. Up-front conversations with existing and potential licensors about the

[3] *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, 134 S. Ct. 2111 (2014).

[4] *Promega Corp. v. Life Technologies Corp.*, 773 F.3d 1338 (Fed. Cir. 2014).

[5] *Virnetx, Inc. v. Cisco Sys., Inc.*, 767 F.3d 1308 (Fed. Cir. 2014).

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strength of the patents protecting the licensed technology can bring focus to the real value of the negotiated license.

4. *Business-Focused Strategies*. The key focus for a company remains its customers. While patents can take a front seat for IP attorneys, clinical utility is the stronghold for the industry. To fund a new company, demonstrating the utility of the technology and its place in the competitive market is critical. The patent portfolio then backs up the technology if it can provide sufficient enforceable rights. Thus, diligence on the strengths and weaknesses of the portfolio still have a place in the assessment of business strategy.

New grants and collaborations between government agencies and industry provide additional outlets for growth in diagnostics technologies, particularly big data issues. The National Cancer Institute at the NIH, for example, has rolled out several large-volume grants to develop advances in such fields as early cancer detection, diagnostic assays, genomic analysis of tumor and microenvironment and cloud computing. The Food and Drug Administration, Department of Defense and Veterans Administration have also received accelerated funds toward similar goals under the Presidential Cancer Moonshot Initiative. As one example, the NCI Intramural Research in Biomarkers is seeking industry collaborators in three areas: predicting therapeutic outcomes, diagnostic assays (particularly for high mortality cancers, such as pancreatic and liver cancers) and assay development to monitor cancer progression.

5. *Legislative Intervention*. The question remains whether Congress will step in to swing the pendulum back from its current position on protecting patentable subject matter. Scientific advances are often based on natural phenomena, and the Supreme Court has acknowledged this[6]. Moreover, a number of effective treatments and diagnostics methodologies are at their core natural products and assess natural processes, respectively. Absent an incentive for the industry to build from and utilize what nature has provided, discoveries and patient-beneficial technologies may be lost. To this end, industry organizations can play an influential role in bringing companies and other stakeholders together to effect legislative change.

Changes in the patent law landscape over the past few years have been viewed as having a significant impact by some industry members, but not by all. However, a generally uniform consensus emerges when looking towards the future of the industry—namely a wish for clarity. Despite the collection of cases that have come from the Supreme Court and the Federal Circuit, the implementation of the holdings by the USPTO and the interpretation of the law by industry stakeholders is still quite heterogeneous. Yet established companies and entering entrepreneurs cannot wait until the dust settles. The industry remains hungry for innovative technologies that will address the numerous medical and public health needs, and so we soldier on. ''Innovate or Die'' remains the mantra.

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[6] *See Alice Corp. Pty. Ltd. v. CLS Bank Intern.*, 134 S. Ct. 2347, 2354 (2014) (''At some level, all inventions . . . embody, use, reflect, rest upon, apply laws of nature, natural phenomena, or abstract ideas.'').