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A Perfect Storm Is Brewing Against Personalized Medicine

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I. Introduction

While the nation debates the future of healthcare, one of the most promising hopes for curing diseases—personalized medicine—is at risk of ending before it really begins. A perfect storm is gathering force against personalized medicine. Measures in Congress affecting patent protection for personalized medicine and a number of court cases have arisen, and regulatory elements are looming on the horizon. This is particularly troubling for the biotechnology and pharmaceutical industries, which are uniquely dependent on patents. In fact, personalized medicine now faces challenges from all three branches of government, each of which could capsize and submerge this developing new area of science. In this paper we discuss these new developments in the courts, the Administration, and Congress.

II. Personalized Medicine

The sequencing of the human genome, particularly since the late 1990s, has led to advancements in medical research that can now provide the ability to pinpoint specific genes and relate them to the diseases they cause. It is now known that diseases, such as breast cancer, can occur through many different pathways (for example, pathway A versus pathway B). In fact, the drugs that cure one patient who has a disease working through pathway A may actually harm another patient who has the same disease working through pathway B. Using the patient's genetic makeup, physicians can now determine which pathway is altered, and subsequently administer the best drug for the patient.

Thus, a new industry was born, a new field that links specific genetic makeups to effective drug therapy. Personalized medicine is the development of novel diagnostic tools that allow practitioners to differentiate between various species of a disease, create new medicines tailored to particular gene mutations, and devise new methodologies to determine individual efficacy of one drug over another in a particular patient. In sum, personalized medicine is simply using the right drugs for the right person.

Indeed, personalized medicine has emerged as a competitor to the one-drug-for-most approach that has profited pharmaceutical companies for years. Yet, while some insist that the development of new blockbuster drugs cannot counteract the declining sales of legacy formulations, pharmaceutical companies seem hesitant to adopt new models.

The well known blockbuster-drug business model is based on developing drugs in hopes of cures with bell-curve success. Yet, whether a particular individual will respond positively to a blockbuster drug is generally unknown until after it is administered, and many times, a person runs the risk of not just remaining uncured, but reacting negatively. If the first drug or dosage fails, the process repeats itself, placing patients and doctors in a stressful and sometimes deadly game of trial-and-error.

While the new age of personalized medicine takes shape in the lab and the examination room, the question of whether these methodologies are protectable by patents is taking shape in the courtroom, on the Hill, and in the White House. Personalized medicine is currently at a watershed. Forces are now in place and aligned to destroy this nascent field.

III. Stirrings in the Judiciary

Under 35 U.S.C. § 101, any new and useful process, machine, manufacture, or composition of matter (or any new and useful improvement thereof) may be a patentable invention. Recently, the focus on patent eligible processes has emerged as an important debate pitting recently developed diagnostics tests resulting from years of research versus the risk of a narrow interpretation of the statute.

In three seemingly unrelated and recent law suits discussed below, an opportunity to address the limits and technical grounds of patentability has arisen. Not since the Supreme Court ruled that genetically engineered microorganisms were eligible for patent protection in 1980, has the question of patent eligible subject matter related to advanced biological research been put to this level of scrutiny. Thus, although the issue of patent eligible subject matter has been submerged for approximately 30 years, titanic changes in patent law subject matter may soon surface.

A. Bilski

In 1980, the Supreme Court ruled that genetically modified micro-organisms can be patented. *Diamond v. Chakrabarty*, 447 U.S. 303 (1980). In its ruling, the Court applied a broad interpretation of Section 101 and held that Congress had intended patentable subject matter to "include anything under the sun that is made by man." It has been presumed that such an assertion also applies to inventive methods or processes. However, it is unclear what steps beyond mere mental contemplation are necessary to lift these method claims to the level of patentability.

The U.S. Patent and Trademark Office and courts have recently struggled to define the breadth of patent eligible subject matter in the face of new technology that combines both data-gathering and mental steps. One such case that has gained attention is *In re Bilski*, which deals with a method of hedging risks in commodities trading. The link between Bilski and personalized medicine is direct because both use mental steps and data-gathering to diagnose a problem.

At the Federal Circuit, the court focused on whether Bilski's claimed methods are joined to a particular machine or apparatus, or transform a particular article into a different state or thing ("machine-or-transformation" test). *In re Bilski*, 545 F.3d 943 (Fed. Cir. 2008) (en banc) The Federal Circuit held that Bilski's method claims did not transform any article into a different state or thing, and thus are not patentable. However, Bilski is under review at the Supreme Court, and a decision is expected early in 2010.

Although the Supreme Court will focus on the facts of *Bilski* and how the machine-or-transformation test is applied to software applications, there is great potential that *Bilski* will spill over into other areas such as personalized medicine. Specifically, diagnostic claims that comprise (1) determing levels of a specific protein or gene and then (2) administering a specific drug, may be susceptible to review.

B. Prometheus

Prometheus is the most recent case from the Federal Ciruit which directly affects patentees in the medical diagnostics, therapeutic methods, and personalized medicine fields. Under the blockbuster-drug model, the prescribed dosage may negatively affect some patients, while successfully treating a majority of others. One link between optimized therapeutic efficacy and minimization of toxic side effects has been addressed by studying genetic variation of patients and comparing varying dosage treatments in an individual patient. Determining the link to a specific gene, and developing the dosage correlations can take not only extraordinary effort and time, but incredible private investment typically recouped by enforcement of patent rights to these methods. Some argue, however, that these methods are unpatentable because the determination of metabolite levels, for example, is nonstransformative requiring no more than mental processes.

In *Prometheus Laboratories Inc. v. Mayo Collaborative Services*, 581 F.3d 1336 (Fed. Cir. 2009), the Federal Circuit reversed the district court and applied the *Bilski* machine-or-transformation test to confirm patentability of method claims related to determining drug metabolite levels and using this information to adjust drug dosage. Thus, *Prometheus* did not directly deal with correlating polymorphisms with a disease, but a method for optimization of drug dosage based on metabolite levels. Specifically, the court noted that the asserted claims are in effect claims to methods of treatment, which are always transformative when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition. Furthermore, the Federal Circuit determined that the methods described in these patents went beyond simple data gathering, and the presence of a mental step in a method claim does not automatically render the claim unpatentable.

C. Myriad

According to the American Cancer Society, over 178,000 American women were diagnosed with invasive breast cancer in 2007, and another 62,000 with non-invasive breast cancer. As such, breast cancer is the most common cancer diagnosis for women after skin cancer. As of September 2008, Myriad Genetics, Inc. had

submitted over 180,000 entries for over 2600 mutations to the Breast Cancer Information Core database. Early publications estimate that as many as 19%-74% of at risk individuals who could benefit from this test were not being tested.

Myriad currently charges approximately $3,000 for a breast cancer analysis known as BRACAnalysis®, which assesses the risk of developing cancer based on detection of mutations in the BRCA1 and BRCA2 genes. Although Myriad has never enforced its patents against researchers, it does have the right to do so. Myriad has never publicly stated its de facto research exemption policy. The American Civil Liberties Union ("ACLU") believes that it is manifestly unfair to charge monopoly prices for a "natural product" that is not the effort of invention.

The ACLU, in collaboration with several other entities, has driven the debate a step further. The group brought suit against the USPTO, challenging the issuance of seven patents assigned to Myriad by the University of Utah Research Foundation. Recently, the Southern District of New York allowed the case to proceed. *Assn. for Molecular Pathology v. U.S. Patent & Trademark Office*, No. 09-CV-04515, 2009 BL 237222 (S.D.N.Y. Nov. 1, 2009) ("*Myriad*"). A decision may be based more on public policy than on technical matters of law. The ACLU wishes to prevent the patenting of all genes as well as of diagnostic methods that use gene patents. Specifically, the ACLU believes that gene patents inhibit the progress of science and stifles the innovation of potentially life-saving products.

The Supreme Court now has enough pressure from the biotechnology innovation community to appropriately address cases such as *Prometheus* and *Myriad* while reviewing *Bilski*. The court must now balance the technical requirements of patentability with the ethics of how patent rights can be enforced.

IV. Commotion on the Hill

A. Congressional Hearings

On February 9, 2007, Representative Xavier Becerra (D-CA) introduced H.R. 977, the "Genomic Research and Accessibility Act" a bill that would end the practice of gene patenting. In late October of 2007, the House Judiciary Committee Subcommittee on Courts, Intellectual Property and the Internet held a hearing on gene patents. Chairman Howard Berman (D-CA) outlined public fears towards gene patents, including: (1) fear that gene patents will be used to hinder research, (2) fear that quality of gene patents are weak because of the speculative nature of gene patents, (3) fear that patents on genetic tests are harming patient access to and stunting improvement of these tests. Suggestions to improve these patents included: (1) heightened standard of inventorship, (2) compulsory licensing of gene patents, and (3) an academic research use exemption from patent infringement.

Specifically, a 2006 study in the Journal of the American Medical Association showed that Myriad's breast cancer testing strategy missed up to 12% of large genomic deletions or duplications. These researchers argued that this was due not to technical errors, but flaws in Myriad's testing strategy. Additionally, during the October 2007

congressional testimony, Drs. Marc Grodman (a physician and founder of Bio-Reference Laboratories) and Wendy Chung (researcher at Columbia University also a named plaintiff in the *Myriad* case) noted that this testing flaw was only corrected after "considerable pressure from the scientific community." Dr. Chung also noted, "In a competitive marketplace, this delay would have never occured."

B. Bayh-Dole Act

The Bayh-Dole act established a uniform policy of allowing academic institutions to retain title to federally-funded inventions. Currently the Bayh-Dole act gives the government "march-in rights" if the invention was partly financed by government funds. Specifically, "march-in rights" give the federal agency under whose funding agreement an invention was made the right to grant a license to a response new applicant if the current licensee has failed to make the product available to the public on reasonable terms (18 U.S.C. §§ 201(f), 203(a)(1)). Additionally, "march-in rights" can be used to alleviate health or safety needs which are not reasonably satisfied by the current manufacturer (18 U.S.C. § 203(a)(2)). It is possible that this law may be amended or interpreted to give agencies the authority to require non-exclusive licensing practices.

V. Administrative Turbulence

A. Unrest at Health and Human Services

Most recently, after five years of study, a government advisory group, Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) stated its intention to recommend that the HHS Secretary support statutory regulations that would limit the practice of patenting claims on genes. Previous reports have focused on factors affecting the adequacy of genetic tests and services, and their oversight.[1] However, in its most recent report, SACGHS has recommended that no liability exist for those who develop or sell a test based on patent claims on genes for patient care or for research. Additionally, SACGHS urges industries and academia to practice ethical licensing practices specifically discouraging exclusive licenses. Finally, SACGHS suggests creation of an advisory board to assess the impact of gene patenting and licensing practices, and to clarify whether the Bayh-Dole Act gives agencies the power to influence license agreements. However, several committee members have criticized these recommendations because the recommendations were so broad they would be disruptive to the entire US patent system.

Several case studies were done on the impact of gene patents and licensing practicees on the access to genetic testing.[2] Specifically, a 2003 French study found that the "monopolitic control" of the BRCA1 gene "may prevent health care systems from identifying and adopting the most efficient genetic testing strategies."[3] Additionally, a 2005 Lewin Group study concluded that Myriad's exclusive rights to the BRCA genes had a chilling effect on further basic research. However, few empirical data support or refute this conclusion.[4]

On October 8, 2009 Dr. James Evans presented a review of gene patents and licensing practices for SACGHS. This study found that patents do not serve as a powerful incentive to conduct genetics research, to disclose genetic disoveries, or to invest in the development of genetic tests. Specifically, the committee supported: (1) exemption from liability for patient care purposes, (2) exemption from liability for research purposes, (3) promotion of more transparent licensing practices, (4) creation of an advisory board to assess the impact of gene patenting and licensing practices, (5) promotion of broad licensing and patent access (limited use of exclusive licenses), (6) limiting exclusive licenses through Bayh-Dole, and (7) working with the USPTO to develop guidelines on determinations of nonobviousness and subject matter eligibility.

In response, Mr. Tom Dilenge of the Biotechnology Industry Organization (BIO) stated that there was no evidence to link patents or licensing practices with problems associated with the quality, access, or consistent pricing problems associated with gene patents. Furthermore, BIO noted that the SACGHS committee's own studies showed that exclusive licenses often create incentives to bring genetic discoveries to market. Furthermore, BIO obvserved that universities have been more successful in managing their genetic patent portfolios to support robust technology transfer than the federal government despite its more restrictive rules. BIO also noted that the real patient access problem identified in the committee's case studies is the fact that insurers are unwilling to cover certain genetic tests.

B. Preemption at the USPTO

Fallout from these decisions could force the USPTO to independently decide to stop granting gene association patents. Currently, the USPTO only allows naturally occurring genes to be patented if they are "isolated from their natural state and purified." However, the *Myriad* court, in its motion to dismiss opinion, acknowledged that "the information dictated by the gene is identical whether it is inside or outside the body, and an 'isolated and purified' human gene performs the same function as the human gene in a person's body." *See Myriad*, 2009 BL 237222, at *26.

VI. Conclusion

This is a dangerous time for personalized medicine. Many events that loom on the horizon could jeopardize this fledgling industry. Indeed, a tempest is brewing against personalized medicine in all three branches of government. However, if personalized medicine is able to successfully navigate and weather this storm, it has the potential to revolutionize health care and the way we practice medicine.

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[1] SACGHS 2006 and 2008 reports. http://oba.od.nih.gov/sacghs/sacghs_documents.html.

[2] Prepared for SACGH by the Duke University Center for Genomic Ethics, Law & Polic. February 2009.

[3] Sevilla, C. et al. Impact of gene patents on the cost-effecitve delivery of health care: the case of BRCA1 genetic testing. International journal of Technology Assessment in health care 2003. 19:287-300.

[4] The Lewin Group. The Value of Diagnostics: Innovation, Adoption, and Diffusion into Health Care. 2005, 62–3.