

Personalized Medicine and the Changing Intellectual Property Landscape: Updating the Freedom to Operate Analysis

Paul W. Radensky, MD, Esquire

Dov Greenbaum, Esquire

McDermott Will & Emery

Washington, DC, and Silicon Valley, CA

New Rules, Different Risks

The past couple of years have brought substantial innovations and changes in genomic science and the relevant patent law. Combined, these shifts will globally change the risk analysis of those in the personalized medicine space.

The business decisions raised as we march inevitably toward the \$1,000 genome are beyond this article's scope.¹ However, this article does attempt to show how recent changes in the patent laws will protect and affect those business decisions. This paper outlines how recent Federal Circuit and Supreme Court rulings change the freedom to operate analysis—the ease in which to bring in outside innovation, and its corollary, the ability to defend in-house intellectual property from outside threats. These legal changes will serve both to broaden and weaken patents in the personalized medicine field and should inform companies as to how to optimally develop, prosecute, and litigate their intellectual property.

The Science of Personalized Medicine

Personalized medicine promises to transform the way healthcare is delivered. Although definitions vary, this term often refers to the method whereby a therapeutic product or service is prescribed and/or titrated (or potentially even developed) to a particular patient subset as determined by the molecular features (genetic make-up, gene or protein expression pattern) of the individual.

Currently, most drugs are selected or dosed based on the patient's age, weight, and presence or absence of various co-morbid conditions, such as kidney or liver disease. These relatively gross levels of distinction unfortunately fail to take into account many highly relevant biological features specific to the individual patient such as patient pharmacokinetics, including the absorption, distribution, metabolism, and excretion of drugs that affect their safety and effectiveness in each individual.

Personalized medicine provides added value to the healthcare system. Taking advantage of the growing expanse of genomic data, medical product companies and treating doctors can make more refined patient distinctions that will enhance a therapy's efficacy and limit adverse reactions. For example, reasonably large percentages of patients who are treated with the antidepressant paroxetine and the hormonal therapy tamoxifen cannot

activate the pro-drugs because of mutations in the CYP2C19 and CYD2D6 genes respectively; as a result, they have substantially poorer clinical outcomes.²

Personalized medicine also may radically change the way clinical trials are conducted by enabling the stratification of patients into subgroups representing those who are expected to experience a greater or lesser effect from the treatment based on their genetic make-up or gene or protein expression profiles. Using this information to stratify patient subgroups, the industry is looking to make clinical trials more successful and presumably less costly. Further, personalized medicine may be used to identify in otherwise unsuccessful drugs that failed to show efficacy among a broad group of patients a particular subset of patients where the drug was effective (e.g., NitroMed's BiDil).³ These "rescued" drugs could perhaps minimize the lost sunk costs of failed drugs—costs that are factored into and account for a significant portion of successful drug pricing.

Stagnation in the Development of Personalized Medicine?

It is unclear how many biotech companies currently are taking advantage of the targeted therapy business model, reviving drugs from failed phase-two drug trials. The cost of the data analysis and directed trial follow-up should be relatively low compared to industry's sunk costs in these failed drugs.

Notwithstanding Food and Drug Administration (FDA) encouragement,⁴ personalized medicine is far from being broadly adopted among products under development within the industry. Currently, only .5% of the \$550 billion annual pharmaceutical industry reflects the knowledge provided by these and/or other genes in prescribing and dosing medications.

Key components of the personalized medicine revolution are the genetic/biochemical assays, biomarkers, and diagnostic tests that can be used to stratify the patient population and establish optimal usage of a particular drug. The tests often rely on knowledge of a particular gene and its disease-related mutations, and the correlations between the different mutations and disease phenotype. Alternatively, the gene may be related to drug metabolism, and a correlation may be known between the different alleles and the metabolism of the drug. Other models compare gene or protein expression with the biological behavior of disease, such as recurrence of cancers or benefit from therapy. Personalized genomics patents in this context may protect the sequence of the gene and its mutations, the correlations between the genetic mutations or alleles with the disease or drug metabolism, methods for treating the disease or delivering the drug based on this knowledge, or any combination of these innovations.

Genetic diagnostic technologies are unusual within the context of intellectual property in that unlike other fields, it may be difficult to invent around the patented gene-drug-disease relationship, leaving the patentee able to control access to that gene's diagnostic powers. As this market grows and opportunities to monetize genetic information becomes clearer, we can assume that more genetic diagnostic tests will be licensed or litigated.

But, current case law suggests that these diagnostics may face risks under patent law. Without the protection of intellectual property rights, there are concerns that among other impediments to research, valuable venture capital funding will dry up and effectively impede innovation in these fields.

Do Personalized Medicine Innovations Fall Under Patentable Subject Matter?

Patentable Subject Matter

Under current patent doctrine, “anything under the sun made by man” is patentable but patents are excluded from laws of nature, natural phenomena, abstract ideas, and mental processes.⁵ The Supreme Court reiterated this broad stance on patentable subject matter in *J.E.M. Ag supply Inc.*⁶

Business Method Patents

The Federal Circuit’s decision in *State Street* further expanded the Supreme Court’s scope of patentable subject matter by allowing for business method patents when those innovations “produce a useful, concrete and tangible result.” In *State Street*, Signature Financial Group’s patented method that transformed data was patentable under this new doctrine.⁷

Subsequently, many processes and methods, including methods for correlating genetic information with disease states or drug metabolism, became patentable subject matter if they could produce a “useful, concrete and tangible result.”⁸

Reversing the Trend?

Notwithstanding the decades of general expansion, there now have been a number of recent cases that attempt to refine and narrow patentable subject matter. Whether or not there is patentable subject matter is a question of law—a threshold criterion making the use of this lever all the more powerful in limiting patentability.⁹

Justice Stephen Breyer’s dissent in the Supreme Court’s reversal in the *Lab Corp* case arguably set off this recent focus on patentable subject matter.¹⁰ *Lab Corp*, which raised the issue of patentable subject matter *de novo* and generated twenty amici briefs on that topic, involved a process patent for helping to diagnose vitamin deficiency through correlating the patient’s homocysteine level with the deficiency.

Breyer noted the strong policy reasons for limiting these types of process patents, as they threaten “to leave the medical profession subject to the restrictions [. . . that] may force doctors to spend unnecessary time and energy to enter into license agreements . . . [that] may raise the cost of health care while inhibiting its effective delivery.”¹¹

Bilski—A New Test for Patentable Subject Matter

Although Breyer’s dissent is not law, the Federal Circuit’s *Bilski* decision currently is law.¹² And, *Bilski* may have effectively accomplished what Breyer’s dissent in *Lab Corp* advanced, overruling *State Street*.¹³



In *Bilski*, the patentee’s process patent on a method of arbitrage was found to fall outside of the realm of patentable subject matter. In outlining the boundaries of the subject matter clause of the Patent Act,¹⁴ the court ruled (*en banc*) that a patentable method claim must be either tied to a particular machine, or must transform an article. Further, a specific machine’s use and/or an article’s transformation must impose meaningful limits on the claim’s scope to impart patent-eligibility; i.e., involvement of the machine or transformation in the claimed process must not merely be insignificant extra-solution activity. The prior *State Street* and *AT&T* tests requiring only a useful, concrete, and tangible result were considered too vague and potentially too broad according to the current court’s understanding of patentable subject matter.

Overall, *Bilski* has created substantial uncertainty and concern within many industries, including the personalized medicine industry. It is hoped that the Supreme Court, in granting certiorari, can reinstate some certainty and create law that is supportive of the current direction of biotechnology in general and personal genomics in particular.

Bilski and Biotech

To this end, amici have generated more than forty briefs, including many from the diagnostics and therapeutics industry, generally opposing the Federal Circuit’s position in *Bilski* or taking a neutral stance but supporting the patentability of personalized diagnostics. In suggesting that the Federal Circuit misquotes and misunderstands the Supreme Court precedence, many amici—noting the importance and centrality of *Bilski*-like tests for the pharmaceutical industry—suggest that the court create a broader rule that will acknowledge the practical application of scientific principles

represented in most diagnostic patents. This would allow for broad reading of the subject matter section of the Patent Act, 35 U.S.C. § 101, maintaining only the very narrow historical exceptions.

Until *Bilski* is decided, however, the Federal Circuit, district courts, and the United States Patent and Trademark Office (USPTO) (92% affirmation rate by the Board of Patent Appeals and Interferences of § 101 rejections) continue to apply the *Bilski* machine or transformation test.¹⁵

Applying the new *Bilski* test, the Federal Circuit affirmed, without an opinion, the district court's *Classen* decision.¹⁶ Channeling *Diamond v. Diehr*,¹⁷ the court found *Classen*'s patented methods for evaluating and improving the safety of immunization schedules through examining the correlation between vaccination schedules and the risk of developing chronic immune-mediated disorders to be simply a discovery of natural phenomenon and unpatentable. The correlation process described and patented was found to be indistinguishable from the idea itself.

Prometheus: Bilski Applied to Personalized Medicine

Most recently, the Federal Circuit applied *Bilski* in *Prometheus Labs, Inc. v. Mayo Collaborative Services*.¹⁸ Prometheus is the exclusive licensee of patents that claim a process of measuring metabolized azathioprine and other thiopurine drugs to determine an optimal patient dosage. The Federal Circuit reversed the district court ruling that struck down a method claim for “optimizing therapeutic efficacy for treatment of an immunomediated gastrointestinal disorder”:

(1) administering synthetic thiopurine drugs to a patient; (2) determining the levels of certain metabolites from a bodily sample, such as blood; and (3) based on the metabolite levels, adjusting the dosage up or down. In applying *Bilski*, the Federal Circuit found that the method of treatment was an application of a natural process by way of a series of transformative steps of both the pro-drug and the body. The Court noted that tying the correlative step to a therapeutic treatment protocol made steps (1) and (2) not insignificant under *Bilski* and, as such, patentable subject matter.

Prometheus points to a potential work-around for genomic diagnostics fearful of losing protection: tying the claims to an actual treatment method. *Prometheus* shows that the courts will acknowledge drug metabolism that occurs naturally in the body as transformative events within the *Bilski* model.

Notwithstanding *Prometheus*' win, in the words of Judge Randall Rader, *Bilski* may prove to have a substantial negative impact on biotechnology research and development as it “inadvertently advises investors that they should divert their unprotectable investments away from discovery of scientific relationships within the body to diagnose breast cancer, or Lou Gehrig's disease or Parkinson's or whatever.”¹⁹

Other Hurdles to Patenting Personalized Medicine Innovations

Subject matter is only one of the bars to patentability, and the personalized genomics industry currently is being challenged with respect to other parts of the Patent Act as well, including novelty,²⁰ non-obviousness,²¹ and the written description requirement.²²

If *Bilski* potentially prevents the patenting of a procedure to find actionable genomic correlations, the recent Federal Circuit rulings in *Kubin*²³ and *Gleave*²⁴ (discussed below) may further limit the patentability of the underlying genes that are being correlated.

Kubin: Non-Obviousness

Many have viewed the Federal Circuit's *Kubin* decision as a significant change in the law of obviousness regarding biotechnology. *Kubin*'s patent application dealt with the isolation and sequencing of a human gene that encoded a known protein. The Board of Patent Appeals had rejected the application as obvious under the new standard, from *KSR Intl. Co. v. Teleflex, Inc. (KSR)* as one skilled in the art would be motivated to use conventional methodologies to isolate the gene.²⁵ The public owns the innovation, but the inventor of the prior art in *Kubin* could not.

In upholding the Board's decision, which found that the determination of the gene encoding the relevant protein was routine, the Federal Circuit focused on the methodology of acquiring the claimed compound and not on the compound's novelty itself, affirming that the determination of the gene was obvious under the *KSR* standards. *Kubin* effectively overruled the Federal Circuit's 1995 *In re Duel* decision²⁶ and broadened *KSR* to include the unpredictable science of biotechnology. Fortunately, *Kubin*'s facts make it easy to distinguish most cases, hopefully leaving many gene patents as still non-obvious.

Gleave: Novelty/Anticipation

The Federal Circuit put further constraints on biotechnological innovations' patentability in *In re Gleave*. Decided only days apart from *Kubin*, *Gleave* held that anticipation of a oligonucleotide may occur when the sequence merely exists in the prior art, even without any disclosed usefulness. *Gleave*'s antisense oligos, designed to specifically bind to insulin dependent growth factor proteins, were found to be anticipated given a prior art listing of every fifteen base pair oligonucleotide string of that particular gene. Thus, although the sequences in the prior art could not be enabled without any usefulness characterization, the same sequences could anticipate *Gleave*'s innovation.

Although the court did leave open the possibility of patenting a method of use for *Gleave*'s antisense sequences, with the human genome fully sequenced and new genomes coming online daily, gene sequence composition patents may become more difficult to obtain.

Ariad: Written Description Requirement

Biotechnology has had a relatively heightened written description requirement compared with other technologies. This requirement, however, has been fairly consistent and reliable since the Federal Circuit's decision in 1997 when Judge Lourie set out his bright-line rule requiring a “precise definition . . . by structure, formula, chemical name or physical properties . . .,” separate and distinct from 35 U.S.C. § 112's relatively weaker enablement requirement.²⁷

The written description requirement as currently applied to biotechnology also makes it difficult to sufficiently describe a subset of species to claim the entire genus. Most recently in *Carnegie Melon* and subsequently in *In re Alonso*,²⁸ the Federal Circuit emphasized a per se, formulaic approach to the written description requirement in biotechnology, requiring the recitation of all the known sequences in order to afford protection for the entire genus.

Whereas the enablement requirement mandates only that the patent shows how one of ordinary skill in the art could go about acquiring the sequence, as it stands, the high bar set for a biotechnology written description makes it easier to invalidate patents on summary judgment.

Until now, the alternative for biotechnology inventors was to narrow their claims to a subset of a genus, something often easy to design around and hard to protect. The Federal Circuit in its upcoming *en banc* review of its April *Ariad* decision, which invalidated *Ariad's* patent for failing to adequately disclose the sequences of the molecules that inhibited NF-κB activity (nuclear factor kappa-light-chain-enhancer of activated B cells)—the claimed invention—will examine whether the statute supports both a written description and enablement requirement, potentially changing substantially how gene patents are prosecuted and litigated.

ACLU v. Myriad: Targeted Attack on Gene Patents

Finally and perhaps of most significant concern to those developing personalized genomic inventions is *ACLU v. Myriad*.²⁹ The ACLU, in conjunction with several research associations and other interested parties, filed a lawsuit against Myriad Genetics arguing that Myriad's intellectual property rights over the BRCA genes for predicting genetic predispositions to breast and ovarian cancer violates both the Constitution and the Patent Act. Myriad's patents claim the gene coding for the BRCA2 peptide, methods for detecting mutations in the BRCA gene, and methods for detecting changes in the BRCA gene.

The American Civil Liberties Union (ACLU) argues that both the genes and asserted correlations exist in nature and should be outside the scope of patentable subject matter. The ACLU further argues that the USPTO's position on gene patents—in that purified genes do not exist in nature and as such are patentable, supported by nearly of century of case law³⁰—violates the constitution; as a First Amendment issue, patenting genes also undermines the free flow of information and scientific information, notwithstanding evidence to the contrary.³¹

Many amici have already stepped up to comment on this case, which could decide the future of gene patenting.

IP Protection of Personalized Medicine—Is It All Moot?

Even if diagnostic tests are protectable subject matter, the Federal Circuit may have provided a viable work-around, further weak-

ening the intellectual property protection that can be provided to the developers of personalized medicine genomic diagnostics. U.S. patent laws only protect patentees from domestic infringements. 35 U.S.C. § 271(g) extended this protection, allowing a patentee to sue for infringement against parties importing and selling products made by U.S. patented processes outside the United States. But recently in *Bayer v. Housey*, the Federal Circuit limited this reach of Section 271(g) and effectively sanctioned the offshoring of United States patent-protected diagnostic testing by allowing the transmission of the results of those protected tests back into the United States without fear of civil liability.³² With the limited and relatively mobile infrastructure necessary to set up diagnostic testing, patentees would have to obtain patents in every country to foreclose the possibility of offshoring entirely.

Back to the Science

Ironically, as this perfect legal storm continues to grow and swirl around personalized medicine, the underlying science continues to thrive. Computational power, as per Moore's Law, continues to march forward, doubling every eighteen months. Concurrently, the cost of computational storage has been constantly dropping. At the same time, the Human Genome Project has opened up much of the human genome. And, outpacing even Moore's law, DNA sequencing technology has substantially brought down the cost of genomic sequencing. Finally, genome-wide association studies (GWAS) take advantage of gene chip technology that allow practitioners to test hundreds of thousands of gene and gene fragments simultaneously. Combined, these technologies allow therapeutic product developers to determine what genomic complements are most relevant for a particular therapeutic product. The net effect of all of these technological innovations working in concert has been a boom in relatively cheap actionable genetic information that can now be mined for pharmaceutical innovation.

Risk Analysis: What Should I do?

Personalized medicine with its promises of lowering health-care costs and reducing adverse drug reactions is clearly in the best interest of the public health. At the same time, personalized medicine provides an opportunity for a business model for therapeutics and diagnostics that can be profitable. However, the changing patent protection regime, particularly as it applies to biotechnology, can support or hamper development of personalized medicine. In-licensing innovations may become easier as the courts work to narrow the ability to patent genes and globally weaken biotech patents under *Bilski*, *Gleeve*, *Kubin*, and *Housey*. At the same time intra-circuit disagreements could do away with the written description requirement entirely, leaving only an enablement requirement effectively making it harder to invalidate biotechnology patents while at the same time granting those patents broader protection over larger areas of technology may better protect in-house innovation.

In the end, independent of the actual protection afforded to personalized medicine patents, those who grasp how these laws

will affect their particular portfolios will be best positioned to take advantage of these changes.

- 1 Robert F. Service, *The Race for the \$1000 Genome*, 311 SCIENCE 1544 (2006).
- 2 See also the National Institutes of Health (NIH) public repository of pharmacogenomics data linking genotype with phenotype data at www.pharmgkb.org/.
- 3 See, e.g., Food and Drug Administration (FDA) News Release, FDA Approves BiDil Heart Failure Drug for Black Patients, June 23, 2005, available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108445.htm.
- 4 See, e.g., FDA Guidance for Industry on Pharmacogenomic Data Submissions.
- 5 *Diamond v. Chakrabarty*, 447 U.S. 303 (U.S. 1980).
- 6 *J.E.M. Ag supply Inc. v. Pioneer Hi-Bred Int'l Inc.*, 534 U.S. 124 (2001) (once again emphasizing the expansive "product of man" requirement for patentable subject matter).
- 7 *State Street Bank & Trust v. Signature Financial Group*, 149 F.3d 1368 (Fed. Cir. 1998) (*en banc*).
- 8 *In re Alappat*, 33 F.3d 1526 (Fed. Cir. 1994); *AT&T Corp. v. Excel Commun. Inc.*, 172 F.3d 1352 (Fed. Cir. 1999) (a physical transformation was not required to create patentable subject matter).
- 9 *In re Comiskey*, 2009 U.S. App. LEXIS 400 (Fed. Cir. Jan. 13, 2009).
- 10 *Laboratory Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 125 (2006).
- 11 *Id.*
- 12 *In re Bilski*, 2008 U.S. App. LEXIS 22479 (Fed. Cir. Oct. 30, 2008) (*en banc*), cert. granted 129 S. Ct. 2735 (2009).
- 13 *CyberSource Corp. v. Retail Decisions Inc.*, 2009 WL 815448 (N.D. Cal. Mar. 23, 2009) ("Without expressly overruling *State Street*, the *Bilski* majority struck down its underpinnings.").
- 14 35 U.S.C. § 101.
- 15 See, e.g., *King Pharm v. Eon Labs*, 593 F. Supp. 2d 501 (EDNY 2009) (summary judgment of invalidity against a patentee claiming methods for informing patients about and administering a particular muscle relaxant. For preemption and lack of transformation concerns); *In re Ferguson*, 558 F.3d 1359 (Fed. Cir. 2009) (seemingly superfluously invalidated claims under Section 101, even though examiner limited invalidity to non-Section 101 issues).
- 16 *Classen Immunotherapies, Inc. v. Biogen IDEC*, 304 Fed. Appx. 866 (Fed. Cir. 2008).
- 17 450 U.S. 175 (1981) (patentability for a process to cure synthetic rubber required tying to a machine or a transformation).
- 18 *Prometheus Labs., Inc. v. Mayo Collaborative Servs.*, 2009 U.S. App. LEXIS 20623 (Fed. Cir. Sep. 16, 2009).
- 19 *In re Bilski*, 545 F.3d 943, 1014 (Fed. Cir. 2008).
- 20 35 U.S.C. § 102.
- 21 35 U.S.C. § 103.
- 22 35 U.S.C. § 112.
- 23 *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009).
- 24 *In re Gleave*, 560 F.3d 1331 (Fed. Cir. 2009).
- 25 *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007).
- 26 *In re Deuel*, 51 F.3d 1552 (Fed. Cir. 1995).
- 27 *University of Cal. v. Eli Lilly & Co.*, 1995 U.S. Dist. LEXIS 19003 (S.D. Ind. Dec. 11, 1995).
- 28 *In re Alonso*, 545 F.3d 1015 (Fed. Cir. 2008).
- 29 *Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, Myriad Genetics, et al.*, 09-cv-04515-RWS (S.D.N.Y.).
- 30 See, e.g., *Parke Davis v. H K Mulford & Co.*, 189 F.95 (S.D.N.Y. 1911) (allowing for the patentability of purified adrenaline).
- 31 See, e.g., *Effects of Intellectual Property Protections on the Conduct of Scientific Research: Results of a Survey of U.S. AAAS Members* (Jan. 16, 2007).
- 32 *Bayer AG v. Housey Pharms., Inc.*, 340 F.3d 1367, 1373 (Fed. Cir. 2003) vacated and remanded on other grounds. 128 Fed. Appx. 767, 2005 U.S. App. LEXIS 5419 (Fed. Cir. 2005).

Life Sciences Practice Group Leadership

Seth D. Levy, Chair

Davis Wright Tremaine LLP
Los Angeles, CA
(213) 633-6869
sethlevy@dwt.com



Jennifer S. Geetter, Vice Chair – Educational Programs

McDermott Will & Emery LLP
Washington, DC
(202) 756-8205
jgeetter@mwe.com



Karen A. Gibbs, Vice Chair – Publications

Applied Medical
Rancho Santa Margarita, CA
(949) 713-8313
kgibbs@appliedmedical.com



Thomas J. Quinlan, Vice Chair – Membership

Reed Smith LLP
San Francisco, CA
(415) 659-5979
tquinlan@reedsmith.com



Marc B. Wilenzick, Vice Chair – Strategic Activities

Pfizer Inc.
New York, NY
(212) 733-4210
willenm@pfizer.com



Jayson S. Slotnik, Vice Chair – Research and Website

Foley Hoag LLP
Washington, DC
(202) 223-1200
jslotnik@foleyhoag.com



Copyright 2009 American Health Lawyers Association, Washington, DC

Reprint permission granted.

Further reprint requests should be directed to

American Health Lawyers Association

1025 Connecticut Avenue, NW, Suite 600

Washington, DC 20036

(202) 833-1100

For more information on Health Lawyers content, visit us at www.healthlawyers.org.