

Diagnostics Need Not Apply¹

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Diagnostic testing helps caregivers and patients understand a patient's condition, predict future outcomes, select appropriate treatments, and determine whether treatment is working. Improvements in diagnostic testing are essential to bring about the long-heralded promise of personalized medicine.³ Yet it seems increasingly clear that most important advances in this type of medical technology lie outside the boundaries of patent-eligible subject matter.⁴

The clarity of this conclusion has been obscured by ambiguity in the recent decisions of the Supreme Court concerning patent eligibility. Since its 2010 decision in *Bilski v. Kappos*,⁵ the Court has followed a discipline of limiting judicial exclusions from the statutory categories of patentable subject matter to a finite list repeatedly articulated in the Court's own prior decisions for "laws of nature, physical phenomena, and abstract ideas,"⁶ while declining to embrace other judicial exclusions that were never expressed in Supreme Court opinions.⁷ The result has been a series of decisions that, while upending

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³ See, e.g., White House Off. of Press Sec'y, Fact Sheet: President Obama's Precision Medicine Initiative, retrieved on Feb. 4, 2015 from <http://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative>; U.S. Food & Drug Admin., Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development (2013); retrieved on Feb. 4, 2015 from <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf>

⁴ See, e.g., *Mayo Collaborative Services v. Prometheus Laboratories*, 566 U.S. ___, 132 S. Ct. 1289 (2012); *Ass'n for Molecular Pathology v. Myriad Genetics*, 569 U.S. ___, 133 S. Ct. 2107 (2013); *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation*, 2014 U.S. App. LEXIS 23692 (Fed. Cir. 2014); *Ariosa Diagnostics v. Sequenom*, 19 F. Supp. 3d 938 (N.D. Cal. 202013); U.S. Pat & Trademark Off., 2014 Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74618 (Dec. 16, 2014)

⁵ 561 U.S. 593 (2010).

⁶ E.g., *Diamond v. Diehr*, 450 U.S. 175, 185 (1981); *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980). Other Supreme Court articulations of the traditional exclusions vary somewhat, sometimes including "mental processes" and "abstract intellectual concepts," *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) and "scientific truth, or the mathematical expression of it," *MacKay Radio & Telegraph Co. v. Radio Corp. of America*, 306 U.S. 86, 94 (1939).

⁷ This is most clearly evident from the multiple opinions in the unanimous decision of the Supreme Court in *Bilski v. Kappos*, 561 U.S. 593 (2010), upholding a rejection of a patent claim to a method of hedging risks in commodities trading for lack of patentable subject matter. Although some lower court decisions had been understood to hold that "business methods" were not patent-eligible, e.g., only four justices were ready to exclude "business

a quarter century of lower court decisions⁸ and administrative practice,⁹ purport to be a straightforward application of ordinary principles of *stare decisis*.¹⁰ As the implications of these decisions are worked out, the Court's robust understanding of the exclusions for laws of nature and abstract ideas seems to leave little room for patent protection for diagnostics.

This essay reviews recent decisions on patent-eligibility from the Supreme Court and the Federal Circuit to demonstrate the obstacles to patenting diagnostic methods under emerging law. Although the courts have used different analytical approaches in recent cases, the bottom line is consistent: diagnostic applications are not patent eligible. I then consider what the absence of patents might mean for the future of innovation in diagnostic testing.

I. The Quiet Period After *Diamond v. Chakrabarty*

For three decades, beginning with the 1980 decision in *Diamond v. Chakrabarty* and ending with the 2010 decision in *Bilski v. Kappos*, the Supreme Court did not hold any patents invalid for lack of patent-eligible subject matter. Before that period, a line of Supreme Court decisions had held that patent-eligible subject matter does not include laws of nature, natural phenomena, abstract ideas, and mathematical algorithms.¹¹ Although the Court never repudiated these older cases, beginning in 1980 it seemed to take a more generous approach to patent-eligible subject matter.¹² These post-1980

methods" from patentable subject matter in so many words. See 561 U.S. at 613 (opinion of Stevens, J., concurring) and *id.* at 657 (Breyer, J. concurring). Yet the justices unanimously concluded that the particular claims at issue were an impermissible effort to patent an "abstract idea." *Id.* at 609 (opinion of Kennedy, J. for the Court; *id.* at 619-20 (opinion of Stevens, J. concurring); *id.* at 658 (Stevens, J. concurring). See also *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347 (2014) (computer-mediated method for mitigating settlement risk in a financial transaction through the use of a third-party intermediary unpatentable as an "abstract idea").

⁸ E.g., *Bilski v. Kappos*, 561 U.S. at 612 ("The patent application here can be rejected under our precedents on the unpatentability of abstract ideas. The Court, therefore, need not define further what constitutes a patentable "process," beyond pointing to the definition of that term provided in § 100(b) and looking to the guideposts in *Benson*, *Flook*, and *Diehr*. And nothing in today's opinion should be read as endorsing interpretations of § 101 that the Court of Appeals for the Federal Circuit has used in the past. See, e.g., *State Street*, 149 F.3d at 1373; *AT&T Corp.*, 172 F.3d at 1357.").

⁹ See *Ass'n for Molecular Pathology* 689 F.3d 1303, at 1333 (reviewing history of PTO allowance of patent claims on isolated DNA molecules over 30-year period).

¹⁰ See, e.g., *Ass'n for Molecular Pathology v. Myriad Genetics* 133 S. Ct. 2107 (isolated DNA molecules not eligible for patent protection because they "fell squarely within the law of nature exception," *id.* at 2117, notwithstanding past practice of Patent & Trademark Office of awarding gene patents, *id.* at 2218-19). See also *Bilski*, *supra*, at

¹¹ *Funk Bros. Seed Co. v. Kalo Inoculant*, 333 U.S. 127 (1948); *Gottschalk v. Benson*, 409 U.S. 63 (1972); *Parker v. Flook*, 437 U.S. 584 (1978).

¹² *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) (upholding patent eligibility of genetically-engineered microorganism); *Diamond v. Diehr*, 450 U.S. 175 (1981) (upholding patent-eligibility of method of curing synthetic

decisions stressed the breadth of the statutory language defining patentable subject matter¹³ and quoted legislative history indicating that patentable subject matter includes “anything under the sun that is made by man.”¹⁴ In the first decades following the creation of the Court of Appeals for the Federal Circuit (the Federal Circuit),¹⁵ the old limits on patentable subject matter seemed lost in antiquity. Biotechnology firms and universities obtained patents on discoveries in the life sciences and asserted these patents against infringers in the courts without serious challenge to their patent eligibility.¹⁶

During this period the Federal Circuit sometimes balked at the broad reach of patent claims on discoveries of basic biological mechanisms and held them invalid, but not for lack of patent-eligible subject matter. The Federal Circuit relied on other statutory provisions, including a robust interpretation of the requirement that a patent claim must be supported by an adequate “written description” of the invention,¹⁷ to prevent performers of basic research from obtaining broad patents that would dominate future work of others.¹⁸ The Federal Circuit justified this approach as reflecting a policy of confining the patent system to “useful arts” rather than basic research:

Ariad complains that the [written description] doctrine disadvantages universities to the extent that basic research cannot be patented. But the patent law has always been directed to the “useful Arts,” U.S. Const. art. I, § 8, cl. 8, meaning inventions with a practical use That is no failure of the law's interpretation, but its intention. Patents are not awarded for academic theories, no matter how groundbreaking or necessary to the later patentable inventions of others. “[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.” []. Requiring a written description of the invention limits

rubber using computer-implemented algorithm to calculate cure time); *J.E.M. Ag Supply v. Pioneer Hi-Bred Int’l*, 534 U.S. 124 (2001) (upholding patent-eligibility of corn seed).

¹³ 35 USC 101 (“Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”)

¹⁴ *Diamond v. Chakrabarty*, 447 U.S. at 309 (quoting S. Rep. No. 82-1979, at 5 (1952); H.R. Rep. No. 82-1923, at 6 (1952)).

¹⁵ Federal Courts Improvement Act of 1982, Pub. L. No. 97-164, 96 Stat. 25.

¹⁶ See Rebecca S. Eisenberg, *Wisdom of the Ages or Dead-Hand Control? Patentable Subject Matter for Diagnostic Methods After In re Bilski*, 3 J.L., TECH., & INTERNET 1, 9-10 (2011)

¹⁷ 35 U.S.C. § 112; See, e.g., *Regents of the University of California v. Eli Lilly*, 119 F.3d 1333 (Fed. Cir. 1997); *University of Rochester v. G.D. Searle*, 358 F.3d 916 (Fed. Cir. 2004); *Ariad Pharmaceuticals v. Eli Lilly*, 598 F.3d 1336 (Fed. Cir. 2010).

¹⁸ *Ariad*, 598 F.3d at 1353 (“Such claims merely recite a description of the problem to be solved while claiming all solutions to it and ... leaving it to the pharmaceutical industry to complete an unfinished invention.”)

patent protection to those who actually perform the difficult work of "invention"--that is, conceive of the complete and final invention with all its claimed limitations--and disclose the fruits of that effort to the public.¹⁹

Meanwhile the Patent and Trademark Office (PTO), facing a deluge of patent applications on newly identified DNA sequences of unknown function, limited patents on these early stage discoveries through more robust enforcement of the requirement that a patent application must disclose a specific and substantial utility for an invention.²⁰ The Federal Circuit approved of this approach in affirming rejection of claims to gene fragments of unknown function:

The claimed [DNA molecules] are not an end of Fisher's research effort, but only tools to be used along the way in the search for a practical utility. Thus, while [they] may add a noteworthy contribution to biotechnology research, ... we hold that the claimed [molecules] have not been researched and understood to the point of providing an immediate, well-defined, real world benefit to the public meriting the grant of a patent.²¹

These Federal Circuit decisions articulate concerns similar to those expressed by the Supreme Court in patentable subject matter cases about the importance of preventing premature patents on basic research discoveries, as distinguished from practical applications. But rather than holding these discoveries to be outside the scope of patentable subject matter, the Federal Circuit and the PTO used other levers in the patent system to limit the availability of broad dominant patent claims on fundamental discoveries.

The Federal Circuit approach did not prevent the issuance of patents on a new generation of diagnostic inventions. Diagnostic tests typically involve measuring one or more variables in a patient (e.g., body temperature, white blood cell count) and comparing those observations to reference values to make an inference about the patient's condition, prognosis, or treatment response. A wealth of new genomic information that became available in the wake of the Human Genome Project provided an abundant source of new biomarkers to use in diagnostic testing. Patent applicants might claim either the markers

¹⁹ *Id.*

²⁰ *Brenner v. Manson*, 383 U.S. 519 (1966); U.S. Pat. & Trademark Off., Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001). 35 U.S.C. §§ 101, 112.

²¹ *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005).

themselves (e.g., newly identified genes or gene fragments or mutations associated with disease) or a method of diagnosis that involves observing markers in patients and comparing the patients' markers to standard values or ranges (e.g., variants of a gene sequence that are not predictive of disease) to make an inference about the patient's health or condition.

The usefulness of these tests for diagnostic purposes could provide "an immediate, well-defined, real world benefit to the public" sufficient to satisfy the utility requirement.²² Yet even after identifying the disease relevance of a gene or other marker, much more work may be necessary to identify additional mutations associated with disease, to understand the disease pathway, and to develop treatments. Research scientists feared that broad patents at this early stage would interfere with this further research. Some empirical studies suggested that in fact patents rarely interfered with the work of academic researchers,²³ perhaps because researchers simply ignored whatever patents they might infringe.²⁴ Nonetheless, some notable exceptions²⁵ nurtured outspoken opposition to gene patenting among influential organizations of scientists and doctors.²⁶ Some of these organizations ultimately became plaintiffs in a lawsuit challenging the validity of patent claims related to the BRCA1 and BRCA2 genes associated with breast cancer susceptibility.²⁷

II. The Alarm Bell: *Laboratory Corporation v. Metabolite Laboratories*

²² See *supra* notes **Error! Bookmark not defined.**-**Error! Bookmark not defined.** and accompanying text.

²³ See, e.g., John P. Walsh, Charlene Cho, & Wesley M. Cohen, *View from the Bench: Patents and Material Transfers*, 309 Science 2002 (2005); Timothy Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 Nature Biotechnology 1091 (2006); AM. ASS'N FOR THE ADVANCEMENT OF SCI., INTERNATIONAL INTELLECTUAL PROPERTY EXPERIENCES: A REPORT OF FOUR COUNTRIES (2007), available at <http://sippi.aaas.org>. For a summary and analysis of the evidence see Rebecca S. Eisenberg, *Noncompliance, Nonenforcement, Nonproblem? Rethinking the Anticommons in Biomedical Research*, 45 Houston L. Rev. 1059 (2008).

²⁴ Katherine J. Strandburg, *Sharing Research Tools and Materials: Homo Scientifcus and User Innovator Community Norms* (05/23/08), available at SSRN: <http://ssrn.com/abstract=1136606> or <http://dx.doi.org/10.2139/ssrn.1136606> (visited Feb. 19, 2015).

²⁵ The most notable exception was patents on the BRCA1 and BRCA2 breast cancer genes controlled by Myriad Genetics. See E. Richard Gold & Julia Carbone, *Myriad Genetics: In the eye of the policy storm*, 12 Genetics in Medicine S39-S70 (April 2010). See also Mildred K. Cho et al., *Effects of Patents and License on the Provision of Clinical Genetic Testing Services* 5 J. Molecular Diagnostics 3-8 (2003); Jon F. Merz et al., *Diagnostic testing fails the test: the pitfalls of patents are illustrated by the case of haemochromatosis*, 415 Nature 577-79 (2002).

²⁶ See generally Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests: Report of the Secretary's Advisory Committee on Genetics, Health, and Society (April 2010) available at http://osp.od.nih.gov/sites/default/files/SACGHS_patents_report_2010.pdf (visited Feb. 19, 2015) (hereinafter SACGHS Final Report).

²⁷ Original plaintiffs in this action included the Association for Molecular Pathology, the American College of Medical Genetics, the American Society for Clinical Pathology, the College of American Pathologists, in addition to individual research scientists. See Ass'n for Molecular Pathology et al. v. US Pat. & Trademark Off. et al., 2009 U.S. Dist. LEXIS 101809 (SDNY 2009) (analyzing standing of plaintiffs).

While the litigation over BRCA gene patents was pending, three Justices gave an early signal that the broader universe of patents on diagnostic tests could be vulnerable to challenge in a 2006 dissenting opinion from a decision to dismiss *certiorari* in the case of *Laboratory Corporation v. Metabolite Laboratories*.²⁸ The patent in that case included the following broad claim to a diagnostic method:

A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:

assaying a body fluid for an elevated level of total homocysteine; and

*correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.*²⁹

The lower courts did not consider whether this claim raised a problem of patentable subject matter,³⁰ and a majority of the Court ultimately decided to dismiss the case without reaching the merits.³¹ But three dissenting Justices were ready to invalidate the patent as violating the principle that one may not patent “laws of nature, natural phenomena, and abstract ideas.”³² The dissenters recognized that the category of natural phenomena is “not easy to define,” but they were nonetheless so certain that “the correlation between homocysteine and vitamin deficiency set forth in claim 13 is a ‘natural phenomenon’”³³ that they saw no need to attempt a definition because the claim “is invalid no matter how narrowly one reasonably interprets that doctrine.”³⁴

Dissenting opinions are not law,³⁵ but this dissent was a harbinger of a significant shift in the Court’s attitude towards patent eligibility. It is worth

²⁸ 548 U.S. 125 (2006) (Breyer, J., dissenting, joined by Stevens, J. and Souter, J.)

²⁹ As set forth in *id.* at 129.

³⁰ *Id.* at 132.

³¹ 548 U.S. 124 (2006)

³² *Id.* at 125 (Breyer, J., dissenting, joined by Stevens, J., and Souter, J.)

³³ *Id.* at 135.

³⁴ *Id.* at (“...this case is not at the boundary. It does not require us to consider the precise scope of the ‘natural phenomenon’ doctrine or any other difficult issue. In my view, claim 13 is invalid no matter how narrowly one reasonably interprets that doctrine. There can be little doubt that the correlation between homocysteine and vitamin deficiency set forth in claim 13 is a ‘natural phenomenon.’”).

³⁵ The Federal Circuit explicitly declined to consider the analysis set forth in the *Laboratory Corporation* dissent and faulted the District Court for relying on that opinion in its own decisions in *Prometheus*. See *Prometheus Laboratories v. Mayo Collaborative Serv.*, 581 F.3d 1336, 1346 n.3 (“In reaching its conclusion, the district court relied heavily on the opinion of three justices dissenting from the dismissal of the grant of *certiorari* in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc*]. That dissent is not controlling law and also involved

pausing to consider just why the dissenters thought that the recited correlation between elevated levels of homocysteine and vitamin deficiency was a “natural phenomenon” that called for the same treatment as $E=mc^2$, the law of gravity, and the heat of the sun.³⁶ The opinion identifies in prior cases a clear rationale for that exclusion: that patents on “the basic tools of scientific and technological work” might do more to impede than to promote scientific and technological progress.³⁷ But the opinion does not use that rationale to clarify the distinction between natural phenomena and patent-eligible inventions in the claim at issue.³⁸

Perhaps they meant that the correlation between homocysteine and vitamin levels is an inherent regularity that exists apart from any human intervention. In other words, if one could somehow observe the levels of homocysteine, cobalamin, and folate in a set of people, one would see in individuals with elevated homocysteine levels a corresponding deficiency in cobalamin and folate; the correlation is therefore a natural phenomenon rather than a human invention.

But this framing ignores the (unnatural) technology of medical diagnosis that is necessary to give meaning to the claim. The claim language requires not only the observation of biomarker levels in a patient, but also the characterization of certain levels as elevated or deficient.³⁹ Nature does not specify when homocysteine levels are elevated and when vitamin levels are deficient. These diagnostic conclusions reflect human judgments about the difference between sickness and health that are not inherent in nature. They are human constructs that belong to the applied technology of medical diagnosis. In Justice Breyer’s paraphrase, “the process is no more than an instruction to read some numbers in light of medical knowledge.”⁴⁰ But the “medical knowledge” embedded in the claim is a technological filter that

different claims from the ones at issue here.”); *on remand, Prometheus Laboratories v. Mayo Collaborative Serv.*, 628 F.3d 1347, 1356 n.2 (“Again, with respect, we decline to discuss a dissent; it is not controlling law, and it involved different claims from the ones at issue here.”).

³⁶ *Id.* at 126.

³⁷ *Id.* at 126-127.

³⁸ *Id.* at 134 (“Nor can one easily use such abstract categories directly to distinguish instances of likely beneficial, from likely harmful, forms of protection.”)

³⁹ One might object that the claim language does not specify what counts as an elevated level of homocysteine or a deficiency of cobalamin or folate. If these levels are not defined elsewhere in the patent specification, that imprecision might make the claim invalid for indefiniteness. 35 U.S.C. § 112. The Supreme Court has fortified this statutory requirement with its decision in *Nautilus v. Biosig Instruments*, 572 U.S. ____ (2014). Ruling years before the *Nautilus* decision, the Federal Circuit considered and rejected a challenge to the validity of Claim 13 on this basis. *Metabolite Laboratories v. Laboratory Corporation*, 370 F.3d 1354, 1363, 1366 (Fed. Cir. 2004).

⁴⁰ 548 U.S. at 137.

identifies which numbers to consider, and specifies when those numbers call for medical attention.

Near the end of the opinion Justice Breyer candidly reveals a concern that patent claims might impinge on the practice of medicine, as distinguished from future research. Although the principle justification he cites for the exclusion of “natural phenomena” from patent eligibility looks to the interests of researchers,⁴¹ Justice Breyer’s justification for reaching the merits without the benefit of prior consideration of the issue in the lower courts focuses on the interests of doctors and patients:

...special public interest considerations reinforce my view that we should decide this case. To fail to do so threatens to leave the medical profession subject to the restrictions imposed by this individual patent and others of its kind. Those restrictions may inhibit doctors from using their best medical judgment; they may force doctors to spend unnecessary time and energy to enter into license agreements; they may divert resources from the medical task of health care to the legal task of searching patent files for similar simple correlations; they may raise the cost of healthcare while inhibiting its effective delivery.⁴²

Perhaps these “special considerations” motivated the dissenters not only to reach the merits, but also to interpret the traditional exclusion for natural phenomena broadly in order to limit patents on medical technologies. Patents undoubtedly increase costs and restrict utilization of patented inventions, in medicine as in other fields. But so far neither the courts nor Congress have embraced a categorical exclusion of medical technologies from patent eligibility. Instead, Congress enacted a statutory exclusion of certain remedies for patent infringement against medical practitioners and related health care entities.⁴³ Indeed, the dissenters cited this legislation as a reason to decide the case so as to “help Congress determine whether legislation is needed.”⁴⁴

⁴¹ 548 U.S. at 126-27 (“The justification for the principle does not lie in any claim that “laws of nature” are obvious, or that their discovery is easy, or that they are not useful.... The problem arises from the fact that patents do not only encourage research by providing monetary incentives for invention. Sometimes their presence can discourage research by impeding the free exchange of information, for example by forcing researchers to avoid the use of potentially patented ideas, by leading them to conduct costly and time-consuming searches of existing or pending patents, by requiring complex licensing arrangements, and by raising the costs of using the patented information, sometimes prohibitively so.”)

⁴² 548 U.S. at 138.

⁴³ These limitations were a last-minute addition to an appropriations bill and are codified at 35 U.S.C. § 287(c).

⁴⁴ 548 U.S. at 138. Just a few years later, the Court in *Bilski v. Kappos* drew a very different conclusion from a later Congressional enactment that limited the enforcement of certain patents on business methods. American

Perhaps the *Laboratory Corporation* dissenters intended to sound an alarm bell for Congress to take notice of diagnostic method patents and to address their implications for healthcare.⁴⁵ But those policy considerations are quite distinct from those that the dissenters identify in the older cases that support the exclusion of natural laws and natural phenomena from patent eligibility in order to leave “basic building blocks” free for use in future scientific and technological work.

III. Diagnostics as “Natural Laws”, not “Applications”: *Mayo Collaborative Services v. Prometheus Laboratories*

The Supreme Court returned to the issue of patent-eligibility for diagnostic methods six years later in *Mayo Collaborative Services v. Prometheus Laboratories*.⁴⁶ Justice Breyer’s opinion for a unanimous court echoed the approach of the *Laboratory Corporation* dissent, again asserting that the claim at issue set forth “laws of nature” without defining that term. The opinion followed a two-step approach to patent eligibility.⁴⁷ The first step is to identify any excluded subject matter (such as natural laws or abstract ideas) in the patent claim. The second step is to decide whether the claim adds enough beyond the excluded subject matter to be sure that it properly counts as a patent-eligible application of the excluded subject matter, rather than an impermissible claim to the excluded subject matter itself.

The Court took a very expansive approach to the identification of natural phenomena in the first step of the analysis in *Mayo*. The claim at issue recited a method of optimizing the dosage of thiopurine drugs by monitoring drug metabolite levels to make sure they remained within a specified range:

Inventors Protection Act of 1999, Pub. L. No. 106-113, 113 Stat. 1536 (1999), codified as amended at 35 U.S.C. § 273. In an opinion not signed by any of the *Laboratory Corporation* dissenters, the *Bilski* majority interpreted legislation providing a novel defense against business method patents as an indication that Congress must consider business methods to be within patentable subject matter. *Bilski v. Kappos*, 561 U.S. 593, 606-607 (2010).

⁴⁵ In fact, as part of the America Invents Act of 2011 Congress directed the PTO Director “to conduct a study on effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist” and to report the results of the study to Congress with 9 months. Leahy-Smith America Invents Act, Pub. L. No. 112-29, Sec. 27. The PTO held a public roundtable on diagnostic genetic testing in January 2013. U.S. PTO, Notice of Public Roundtable on Diagnostic Genetic Testing, 77 Fed. Reg. 71170 (Nov. 29, 2012) but has not delivered its report as of this writing.

⁴⁶ 566 U.S. ___, 132 S. Ct. 1289 (2012).

⁴⁷ Although the exclusion that the Court considered in *Prometheus* was “natural laws,” the Court drew its approach in significant part from prior decisions about the exclusion of claims reciting “mathematical algorithms,” especially *Diamond v. Diehr*, 450 U.S. 175 (1981) and *Parker v. Flook*, 437 U.S. 584 (1978), and later used a similar analysis to determine whether a business method claim was an impermissible patent on an “abstract idea” in *Alice Corporation v. CLS Bank*, 134 S. Ct. 1347 (2014).

A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

(a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and

(b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder,

wherein the level of 6-thioguanine less than about 230 pmol per 8x10⁸ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8x10⁸ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.⁴⁸

Like the claim at issue in *Laboratory Corporation*, this claim recites correlations between observed biomarker levels and diagnostic inferences. Yet a broader implicit definition of “laws of nature” is necessary to understand the Court’s application of that label to the *Mayo* claim than was necessary to make sense of its application to the *Laboratory Corporation* claim. For one thing, the biomarkers that are observed in the *Mayo* claim are formed because of a medical intervention that does not occur in nature. Elevated homocysteine levels and vitamin deficiencies may well arise in the natural world without any human intervention (although, as noted above, these diagnostic characterizations represent human technological judgments rather than mere observations of nature). But nature does not administer thiopurine drugs to patients with immune-mediated gastrointestinal disorders, nor does nature monitor the effects to determine the proper dosage for a particular patient. The claimed process to “a method of optimizing treatment” does not merely observe nature, but explicitly guides doctors on how to adjust the course of treatment in order to keep the effects within specified limits. These limits are not set by nature, but reflect human judgments about how to trade off the misery of immune-mediated gastrointestinal disorders against the misery of thiopurine side effects. This technological choice reflects human preferences that are not inherent in nature.

Plainly Justice Breyer’s understanding of what counts as laws of nature is not limited to phenomena that occur without human intervention:

⁴⁸ As set forth in 132 S. Ct. at 1295.

“Prometheus’ patents set forth laws of nature – namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm.... While it take a human action (the administration of a thiopurine drug) to trigger a manifestation of this relation in a particular person, the relation itself exists in principle apart from any human action. The relation is a consequence of the ways in which thiopurine compounds are metabolized by the body – entirely natural processes.”⁴⁹

This suggests a very broad definition of “laws of nature” that includes any prediction of the effects of medical treatment in a patient, because the Court evidently sees the body’s responses to treatment as “entirely natural processes.” It makes no difference that the response was set in motion by medical intervention.

But identifying a law of nature is only the first step in the analysis. Justice Breyer recognizes that “all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena or abstract ideas.”⁵⁰ He finds in the prior cases a limiting principle that prevents the exclusions from eviscerating patent law: although laws of nature, natural phenomena and abstract ideas themselves are unpatentable “as they are the basic tools of scientific and technological work,”⁵¹ useful *applications* of these tools may be patent-eligible. A claim to a process that uses a natural law must “also contain other elements or a combination of elements, sometimes referred to as an ‘inventive concept,’ sufficient to ensure that the patent in practice amounts to significantly more than a patent upon the natural law itself.”⁵² To count as a patent-eligible application, the claim “must do more than simply state the law of nature while adding the words ‘apply it.’”⁵³

If all inventions make use of natural phenomena, laws of nature, and abstract ideas, it might seem that the real work of distinguishing patentable applications from unpatentable “laws of nature” must occur at step two of the analysis. But a close reading of the *Mayo* opinion suggests the opposite: one must understand the scope of the exclusions at step one in order to figure out what is left in the claims that might be sufficient to confer patent eligibility. In the case of diagnostic methods, the Court’s broad understanding of what

⁴⁹ *Id.* at 1296-1297.

⁵⁰ *Id.* at 1293.

⁵¹ *Id.* at 1293 (citing *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972)).

⁵² *Id.* at 1294.

⁵³ *Id.*

belongs in the category of “natural laws” prevents the Court from recognizing diagnosis as a form of applied technology at all.

The Court concludes that the other elements of the *Mayo* claim do not “add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws” because the steps of administering thiopurine drugs to a patient and measuring metabolite levels in tissue samples were “well-understood, routine, conventional activity previously engaged in by researchers in the field.” Some commentators have criticized this analysis as improperly conflating the requirements of patentable subject matter on one hand and the requirements of novelty and nonobviousness on the other hand,⁵⁴ and some lower court decision have read the decision as limiting patent eligibility to “inventive applications” of natural laws,⁵⁵ although the PTO reads the decision more narrowly.⁵⁶ Understanding the opinion as requiring an “inventive application” of the natural laws suggests that perhaps a more innovative diagnostic method could prove patent-eligible in a future case.

But the Court stops short of resting its determination of patent ineligibility on the fact that other claim steps were too conventional:

We need not, and do not, now decide whether were the steps at issue here less conventional, these features of the claims would prove sufficient to invalidate. For here, as we have said, the steps add nothing of significance to the natural laws themselves.⁵⁷

⁵⁴ Jeff Lefstin traces this conflation to the opinion of Justice Douglas in *Funk v. Kalo*. *Inventive Application*, FLA. L. REV. (forthcoming).

⁵⁵ *Ariosa Diagnostics v. Sequenom*. 19 F. Supp. 3d 938, 950 (N.D. Cal. 2013) (“the use of the abstract idea or the natural phenomenon is the only inventive feature of the claims”); *id.* at 952 (“had the inventors ... created an innovative method of performing DNA detection while searching for paternally inherited cffDNA, such as a new method of a mplification or fractionation, those claims would be patentable. But, the claims presently before the Court simply rely on processes to detect DNA that – as Sequenom concedes – were conventional techniques by those in the field at the time of the invention.”). But cf. *Genetic Technologies v. Agilent Technologies*, 24 F. Supp. 3d 922, 929 (noting in response to argument that non-excluded claim elements consisted of “known prior art techniques” that “Agilent’s arguments conflate the analysis of patent eligible subject matter under § 101 with analysis of novelty and non-obviousness under §§ 102 and 103.”)

⁵⁶ U.S. Pat. & Trademark Off., 2014 Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74618, 74624 (Dec. 16, 2014) (“A claim directed to a judicial exception must be analyzed to determine whether the lements of the claim, considered both individually and as an ordered combination, are sufficient to ensure that the claim as a whole amounts to significantly more than the exception itselfIndividual elements viewed on their own may not appear to add significantly more to the claim, but when combined may amount to significantly more than the exception.”). See also *Myriad treatment of cDNA claims*.

⁵⁷ 132 S. Ct. at 1302.

This is the essential problem for diagnostic method claims under the Court's analysis: because the Court codes the heart of the diagnostic method – the determination of when it is appropriate to modify treatment for a particular patient – as belonging to the realm of natural laws, it does not recognize any *application* of those laws (whether “inventive” or “conventional”) in the claim at all. Despite the very specific criteria set forth in the final “wherein” clauses in the claim for determining when it is appropriate to adjust the drug dosage, the Court sees that language as reciting an excluded natural law rather than an application. The Court thus concludes that the claim merely recites natural laws followed by a general instruction to “apply it” in some unspecified way:

...the ‘wherein’ clauses simply tell a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account when treating his patient...(rather like Einstein telling linear accelerator operators about his basic law and then trusting them to use it where relevant).⁵⁸

The Einstein analogy seems fundamentally confused. The insight that $e=mc^2$ provides only the most basic starting point for “linear accelerator operators” who would need considerably more help to translate this insight into practical applications; indeed, the obvious magnitude of the remaining work and the variety of applications that subsequent innovators might pursue is what makes $e=mc^2$ a compelling example of the distinction between “natural laws” and applications of those laws. By contrast, the *Mayo* claim explains *exactly* how to apply the recited correlations in the treatment of patients. There is no distance whatsoever between the recited correlation and its practical application. Yet because the Court sees the correlation itself as a natural law, it fails to recognize that the claimed invention – as is – is an entirely practical and specific contribution to applied technology, ready for immediate use.

Perhaps the Court does not recognize diagnosis alone (as distinguished from treatment) as an application. Elsewhere the Court notes that the District Court's interpretation of the claim does not include as an element the step of actually adjusting the drug dosage, and that the claim would therefore be infringed by making the diagnostic determination that the dosage should be adjusted even without following through by modifying the course of treatment.⁵⁹ Perhaps that is why the Court sees the claim as nothing more

⁵⁸ 132 S. Ct. at 1297.

⁵⁹ *Id.* at 1296. Professor Holman explains the divided infringement problem for claims to diagnostic methods in Christopher M. Holman, *Caught Between a Rock and a Hard Place: How Limelight Compounds the Challenges*

than the recital of a law of nature followed by a general instruction to “apply the law:”⁶⁰ Perhaps it is only the therapeutic intervention that the Court would recognize as a patent-eligible application of the law. Thus the Court states,

Unlike, say, a typical patent on a new drug or a new way of using an existing drug, the patent claims do not confine their reach to particular applications of those [natural] laws.⁶¹

The Court’s lament that the claims “do not confine their reach” suggests a belief that the claims before it are broader than “a typical patent on a new drug or a new way of using an existing drug.” In fact, such a “typical patent” has a broader, not narrower, reach than the *Mayo* claim. The *Mayo* claim not only specifies a drug limitation (thiopurine) and a use limitation (treatment of immune-mediated gastrointestinal disorder), but adds the further limitations of (1) measuring a particular biomarker and (2) using a particular algorithm to determine the need to adjust the drug dosage. If the Court is worried about the impact of the *Mayo* claim on the search for future applications, it should worry more, not less, about the impact of these “typical patents” on the same type of research. The *Mayo* claim is a narrowing refinement of a particular application rather than a new scientific discovery that has not yet been reduced to a particular application.

Elsewhere the Court seems to recognize the narrow scope of the claim, but insists that this does not save it from invalidity because it follows from the narrow scope of the underlying “natural law”:

.... The underlying functional concern here is a *relative* one: how much future innovation is foreclosed relative to the contribution of the inventor.... A patent upon a narrow law of nature may not inhibit future research as seriously as would a patent upon Einstein’s law of relativity, but the creative value of the discovery is also considerably smaller. And, as we have previously pointed out, even a narrow law of nature (such as the one before us) can inhibit future research.⁶²

Of course, any patent can inhibit research. But the intuitive appeal of keeping basic building blocks such as natural laws outside the patent system is that, because they are so basic, patents on natural laws could inhibit research into

Facing Biotechnology Innovators After Mayo and Myriad, 33 *Biotechnology L. Report* 135-138 ((2014). See *infra* note 65.

⁶⁰ See *supra* note 58 and accompanying text.

⁶¹ *Id.* at 1302.

⁶² *Id.* at 1303.

many different applications. Thus the Court suggests that the danger posed by patents on “new laws of nature ... becomes acute when a patented process amounts to no more than an instruction to ‘apply the natural law,’ or otherwise forecloses more future invention than the underlying discovery could reasonably justify.”⁶³ If the underlying concern is that a nonspecific directive to “apply the natural law” could foreclose a broader range of future innovation than the underlying discovery justifies, then the specificity of the application recited in the claim would seem to address that concern directly. But because the Court sees the diagnostic inference recited in the claim as a natural law, it fails to recognize that the claim recites a very specific diagnostic application.

Perhaps the Court would have recognized the claimed invention as an application if it had included the steps of raising or lowering the drug dosage as actual claim elements (rather than merely reciting when such an adjustment is indicated in the “wherein” clauses at the end of the claim). Such a claim would look more like “a typical patent on ... a new way of using an existing drug.”⁶⁴ But diagnosis and treatment are distinct aspects of healthcare and may be performed by different actors. As diagnostic testing becomes more sophisticated, this functional separation between diagnosis and treatment is likely to become more common.

If diagnostic patent claims must include treatment steps, both the healthcare provider that performs only the treatment steps and the laboratory that performs only the diagnostic steps may avoid infringement liability.⁶⁵ A new diagnostic that guides the choice of treatment is itself a valuable contribution to healthcare that may be worthy of a patent even if the resulting treatment is entirely conventional.

The conceptual separation between diagnosis and treatment is not the same as the distinction between natural laws and specific applications of those laws. Diagnosis is itself an application.

IV. Searching for Another Rationale

a. Mental Steps and Abstract Ideas

⁶³ *Id.* at 1301.

⁶⁴ See *supra* text at note 61.

⁶⁵ When different actors perform different steps of a patented method they may each avoid infringement liability. It is easy to avoid infringement liability for a patented method are performed by different actors none of which controls the other’s behavior. See *Limelight Networks v. Akamai Technologies*, 134 S. Ct. 2723 (2014).

The distinction between diagnostic and treatment steps roughly corresponds to a distinction between observation and analysis on one hand and tangible medical intervention on the other hand. The Court mentions repeatedly that the *Mayo* claim does not include treatment steps and could therefore be infringed by mere thoughts,⁶⁶ although it does not rest its holding of patent-ineligibility on that basis. But perhaps the fact that the core diagnostic inference takes the form of analysis of information rather than tangible physical steps plays a larger role in the Court's judgment than it plays in its opinion.⁶⁷

Subsequent Federal Circuit decisions have followed the lead of the Supreme Court to invalidate diagnostic method claims, but have not relied on the exclusion of laws of nature to reach that result. Instead, they have relied upon the exclusion for "abstract ideas."

The first post-*Mayo* decision of the Federal Circuit on the patent-eligibility of diagnostic methods was *Association for Molecular Pathology v. USPTO*,⁶⁸ a case better known for its challenge to product claims associated with the BRCA1 and BRCA2 genes. A previous Federal Circuit decision in that case⁶⁹ was pending before the Supreme Court at the time of the *Mayo* decision, and was vacated and remanded to the Federal Circuit for reconsideration in light of *Mayo*.⁷⁰ The Supreme Court later reviewed the decision on the product claims only,⁷¹ leaving the Federal Circuit's analysis of the method claims as the final word on the patent-eligibility of those claims. Although the Federal

⁶⁶ E.g., *id.* at 1296 ("The District Court also accepted Prometheus' view that a doctor using Mayo's test could violate the patent even if he did not actually alter his treatment decision in the light of the test. In doing so, the court construed the claim's language, "indicates a need to decrease" (or "to increase"), as not limited to instances in which the doctor actually decreases (or increases) the dosage level where the test results suggest that such an adjustment is advisable."); *id.* at 1302 ("... the patent claims ... tell a treating doctor to measure metabolite levels and to consider the resulting measurements in light of the statistical relationships they describe. In doing so, they tie up the doctor's subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations.")

⁶⁷ Professor Kevin Collins argues that although on its "rhetorical surface" the *Prometheus* opinion is about natural laws, it might be better analyzed in terms of other exclusions from patentable subject matter for "mental steps" and "printed matter." Kevin E. Collins, *Prometheus Laboratories, Mental Steps, and Printed Matter*, 50 Houston L. Rev. 391 (2013). See also Kevin E. Collins, *The Knowledge/Embodiment Dichotomy*, 47 U.C. Davis L. Rev. 1279 (2014).

⁶⁸ 689 F.3d 1303 (Fed. Cir. 2012), *aff'd in part and rev'd in part on other grounds sub nom. Ass'n for Molecular Pathology v. Myriad Genetics*, 133 S. Ct. 2107 (2013)

⁶⁹ 653 F.3d 1329 (Fed. Cir. 2011).

⁷⁰ *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 566 U.S. , 132 S. Ct. 1794, 182 L. Ed. 2d 613 (2012).

⁷¹ *Ass'n for Molecular Pathology v. Myriad Genetics*, 569 U.S. ___, 133 S. Ct. 2107 (2013).

Circuit panel was divided on the proper analysis of the product claims to DNA sequences,⁷² there was no disagreement about the method claims.⁷³

Most of the method claims covered methods of comparing a patient's BRCA1 or BRCA2 sequence to the normal sequence to detect mutations associated with predisposition to develop cancer.⁷⁴ The panel agreed that these method claims were ineligible for patent protection. It would have been a simple matter to explain this result as a straightforward application of the Supreme Court's decision in *Prometheus v. Mayo*, given the similarities between the two cases. Yet the court explicitly based its decision instead on the reasoning in its own previous opinion⁷⁵ – the one vacated by the Supreme Court – that the claims were improperly drawn to “abstract mental processes”:

This court in its now-vacated decision of July 29, 2011, had held [the method claims] --all of which consist of analyzing and comparing certain DNA sequences--not to be patent-eligible subject matter on the ground that they claim only abstract mental processes. In light of the Supreme Court's decision in *Mayo*, we reaffirm that prior holding. The Court made clear that such diagnostic methods in that case essentially claim natural laws that are not eligible for patent. Without expressly analyzing the instant method claims in the context of the Court's reasoning, but in light of the Court's holding, and in view of our own prior reasoning, set forth herein below, those method claims cannot stand.⁷⁶

⁷² Each member of the three-judge panel wrote separately. 689 F.3d at 1308, 1325-1333 (Lourie, J.)(holding that all of the product claims are patent-eligible because neither isolated BRCA1 and BRCA2 DNA molecules nor BRCA1 and BRCA2 cDNA molecules occurs in nature); 689 F.3d at 1337, 1340-1347 (Moore, J.)(concurring in the judgment on the ground that longstanding PTO practice of allowing such claims should not be set aside without Congressional action); 689 F.3d at 1348 (Bryson, J., concurring in part and dissenting in part)(concurring in the judgment with respect to cDNA claims but not claims to isolated DNA that is not materially different from native DNA).

⁷³ 689 F.3d at 1337 (Moore, J., concurring in part) (joining the majority with respect to the method claims at issue); *Id.* at 1348 (Bryson, J., concurring in part and dissenting in part) (concurring with the portions of the court's judgment that are directed to the patentability of the method claims).

⁷⁴ For example, a representative claim recited:

A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which comprises analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or analyzing a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1.

U.S. Patent No. 5, 710, 001, claim 1 (as set forth in 689 F.3d at 1309-1310).

⁷⁵ 653 F.3d 1329 (Fed. Cir. 2011).

⁷⁶ 689 F.3d at 1333.

Although it may seem insubordinate to reject the Supreme Court’s reasoning even when it does not change the result, the Federal Circuit has continued to use the exclusions for “mental steps” and “abstract ideas” as the basis for invalidating diagnostic method claims, sometimes in decisions issued as “unpublished or nonprecedential.” For example, in *PerkinElmer v. Intema*,⁷⁷ the Federal Circuit cited both the Supreme Court’s decision in *Mayo* and its own decision in *Myriad Genetics* to invalidate claims to a noninvasive prenatal screening method to detect increased risk of having a fetus with Down’s syndrome.⁷⁸ The Court observed that the claims “recite mental processes and natural laws” and that “as in *Mayo*, there is no requirement that a doctor act on the calculated risk.”⁷⁹ In its “unpublished or nonprecedential” decision in *Smartgene v. Advanced Biological Laboratories*,⁸⁰ the Federal Circuit relied on its own prior decisions excluding “mental steps” from patent eligibility to invalidate a very broad claim to a computer-implemented “method for guiding the selection of a therapeutic treatment regimen for a patient with a known disease or medical condition.” While taking note of the Supreme Court’s decision in *Mayo*, the court did not characterize the claims before it as reciting natural laws.⁸¹

⁷⁷ 496 Fed. Appx. 65 (Fed. Cir. 2012).

⁷⁸ Representative Claim 1 reads as follows:

A method of determining whether a pregnant woman is at an increased risk of having a fetus with Down's syndrome, the method comprising the steps of:

measuring the level of at least one screening marker from a first trimester of pregnancy by:

(i) assaying a sample . . . ; and/or

(ii) measuring at least one first ultrasound screening marker from an ultrasound scan . . . ;

measuring the level of at least one second screening marker from a second trimester of pregnancy, the at least one second screening marker from the second trimester of pregnancy being different from the at least one first screening marker from the first trimester of pregnancy, by:

(i) assaying a sample . . . ; and/or

(ii) measuring at least one second ultrasound screening marker from an ultrasound scan . . . ;

and determining the risk of Down's syndrome by comparing the measured levels of both the at least one first screening marker from the first trimester of pregnancy and the at least one second screening marker from the second trimester of pregnancy with observed relative frequency distributions of marker levels in Down's syndrome pregnancies and in unaffected pregnancies.

(as quoted in 496 Fed. Appx. At 66-67).

⁷⁹ *Id.* at 70-71.

⁸⁰ 555 Fed. Appx. 950 (Fed. Cir. 2014).

⁸¹ *Id.* at 955 (“The Supreme Court in *Mayo*, though addressing a case involving the ‘law of nature’ exclusion from section 101, recognized that ‘mental processes’ and ‘abstract ideas’ (whatever may be the precise definition and relation of those concepts) are excluded from section 101.... Whatever the boundaries of the ‘abstract ideas’ category, the claim at issue here involves a mental process excluded from section 101: the mental steps of comparing new and stored information and using rules to identify medical options.”)

More recently the Federal Circuit used the exclusion for “abstract ideas” to invalidate another set of diagnostic method claims related to the BRCA1 and BRCA2 breast cancer genes that had not been at issue in the earlier *Myriad* litigation in its decision in *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation*.⁸² The defendant argued that the *Mayo* case was directly on point, but the court avoided agreeing with that characterization:

We need not decide if *Mayo* is directly on point here because the method claims before us suffer from a separate infirmity: they recite abstract ideas.⁸³

The court relied on its own prior decision in *Myriad* to conclude that the claim steps of “comparing” and “analyzing” DNA sequences recited patent-ineligible “abstract ideas,”⁸⁴ then turned to the Supreme Court’s more recent analysis in *Alice Corporation v. CLS Bank*⁸⁵ to conclude that other claim elements did not add enough to the patent-ineligible abstract ideas to make the claim as a whole patent-eligible.⁸⁶

If both natural laws and abstract ideas are patent-ineligible, and if the scrutiny of additional claim elements in the second step of the analysis is the same either way, in many cases it may not matter which of the traditional exclusions the court relies upon. Although none of these terms has been clearly defined, there is likely some redundancy in the list of exclusions.

But the exclusions may not be identical, and the choice of exclusion might therefore sometimes change the outcome. For example, consider the following claim to a method of screening cancer therapeutics, which the

⁸² 774 F.3d 755 (Fed. Cir. 2014). As set forth in the opinion, the patent claims:

A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject[,]

Wherein a germline nucleic acid sequence is compared by hybridizing a BRCA1 gene probe which specifically hybridizes to a BRCA1 allele to genomic DNA isolated from said sample and detecting the presence of a hybridization product wherein a presence of said product indicates the presence of said allele in the subject.

Id. at .

⁸³ *Id.* at 762.

⁸⁴ *Id.* at .

⁸⁵ 134 S. Ct. 2347 (2014).

⁸⁶ 774 F.3d at . This second step of the analysis was quite similar to the Supreme Court’s analysis in *Mayo*.

Federal Circuit held patent-eligible in its *Myriad* decision on remand from the Supreme Court⁸⁷:

*A method for screening potential cancer therapeutics which comprises: growing a transformed eukaryotic host cell containing an altered BRCA1 gene causing cancer in the presence of a compound suspected of being a cancer therapeutic, growing said transformed eukaryotic host cell in the absence of said compound, determining the rate of growth of said host cell in the presence of said compound and the rate of growth of said host cell in the absence of said compound and comparing the growth rate of said host cells, wherein a slower rate of growth of said host cell in the presence of said compound is indicative of a cancer therapeutic.*⁸⁸

The court considered this claim patent-eligible, emphasizing its use of a transformed host cell “derived by altering a cell to include a foreign gene, resulting in a man-made, transformed cell with enhanced function and utility.”⁸⁹ Since the claimed process was carried out in cells that are not naturally occurring,

The fact that the claim also includes the steps of determining the cells' growth rates and comparing growth rates does not change the fact that the claim is based on a man-made, non-naturally occurring transformed cell--patent-eligible subject matter.⁹⁰

In other words, although the claim recited mental steps that were excluded from patent-eligibility, because the claim also involved use of a man-made, transformed host cell, the court saw it as a patent-eligible application.

This analysis is in some tension with *Mayo*. There are notable similarities between the BRCA1 drug screening claim and the “method of optimizing therapeutic efficacy” claim that the *Mayo* Court held invalid (and in light of which it asked the Federal Circuit to reconsider its decision in *Myriad*). Both claims involve use of a drug to trigger its effects – administering thiopurine to a patient in *Mayo*, and exposing cells to a “compound suspected of being a cancer therapeutic” in *Myriad*. Both involve measuring drug effects – metabolite levels in *Mayo* and growth rate of cells in *Myriad* – and comparing resulting values to a standard – the metabolite levels set forth in the “wherein” clauses in *Mayo* and the observed growth rate of cells that have not been

⁸⁷ See *supra* notes 68-76 and accompanying text.

⁸⁸ U.S. Patent No. 5,747,282, Claim 20 (as set forth in 689 F.3d at 1310).

⁸⁹ 689 F.3d at 1336.

⁹⁰ *Id.*

exposed to the compound in *Myriad*. And both involve drawing certain inferences about the effects of the drug, recited in the “wherein” recitals at the end of the claim. Presumably in both cases the reaction of the patient or cells to the drug is “entirely natural” once you ignore the prior human intervention that set the stage for observing these entirely natural processes. And in both claims the process steps are entirely conventional apart from the excluded subject matter.

Judge Lourie’s opinion focused on the fact that the drug screening method recited the use of a transformed host cell with an altered BRCA1 gene that does not occur in nature. But patients who have been treated with thiopurine drugs also do not occur in nature. And if determining how to adjust the dosage of a drug does not count as an application of the laws of nature that determine drug effects, then surely the determination that a particular screened compound exhibits drug effects is even further removed from any practical application.

The more important difference between the two cases is not the role of nature, but rather the choice of which exclusion defined the starting points in the analysis. Judge Lourie began by excluding mental steps rather than natural laws, leaving the claim step of growing transformed host cells available for consideration as an additional element that might save the patent-eligibility of the claim overall. Framed this way, it was easy to conclude that the claim “includes more than the abstract mental step of looking at two numbers and “comparing” two host cells’ growth rates.”⁹¹ Although the opinion, which was primarily concerned with the patentability of natural products, characterized the transformed host cells as “not naturally occurring,” it seemed to matter more to Judge Lourie that the claim included physically transformative process steps in addition to mental steps:

... once one has determined that a claimed composition of matter is patent-eligible subject matter, applying various known types of procedures to it is not merely applying conventional steps to a law of nature. The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible. The fact that the claim also includes the steps of determining the cells’ growth rates and comparing growth rates does not change the fact that the claim is based

⁹¹ 689 F.3d at 1336.

on a man-made, non-naturally occurring transformed cell--patent-eligible subject matter.⁹²

It is difficult to figure out exactly how the “man-made nature of the underlying subject matter” relates to the exclusion of the mental steps of “determining” and “comparing” in this passage. Perhaps if the patent challengers in the *Myriad* case had chosen to appeal the Federal Circuit’s decision on the drug screening method, the Court would have held that claim be patent-ineligible, and would have admonished the Federal Circuit to follow its teachings in *Mayo v. Prometheus* concerning natural processes. But the Court might instead have held that, although the Federal Circuit used the wrong analytical approach, it correctly concluded that the drug screening method was patent-eligible subject matter. The correct analysis under *Mayo* might have begun by excluding as “purely natural laws” the reactions of the host cells to the candidate drugs, and then considered whether the step of growing the transformed host cells was sufficiently novel and unconventional to make the claim overall patent-eligible.

Although the Supreme Court did not review the Federal Circuit’s analysis of the method claims in *Association for Molecular Pathology v. Myriad Genetics*, its review of the product claims paid no more attention than the Federal Circuit had done to the approach set forth in Justice Breyer’s opinion in *Mayo*.⁹³ The Court held that “isolated DNA” that (apart from its isolation) was otherwise identical to naturally occurring DNA within chromosomes (gDNA) was a product of nature and therefore patent-ineligible, but that “synthetically created DNA known as complementary DNA (cDNA), which ... omits certain portions within the DNA segment that do not code for proteins” is patent eligible “because it is not naturally occurring.”⁹⁴ The *Myriad* opinion cited *Mayo* for the principle that the exclusion of “laws of nature, natural phenomena, and abstract ideas” must not be interpreted so broadly as to eviscerate patent law,⁹⁵ but it did not pursue the second step of the *Mayo* analysis to search for an additional “inventive concept” in the claim to be sure that it covered a patent-eligible application rather than the excluded matter itself. The distinction between patent-eligible cDNA and patent-ineligible gDNA instead appeared to rest entirely on the Court’s understanding that gDNA is

⁹² *Id.*

⁹³ For an interesting critical analysis of the *Myriad* decision and its inattention to *Prometheus*, see Dan L. Burk, *The Curious Incident of the Supreme Court in Myriad Genetics*, 90 Notre Dame L. Rev. 505 (2014).

⁹⁴ 133 S. Ct. at 2111.

⁹⁵ *Id.* at 2116.

naturally occurring,⁹⁶ while cDNA is made in the laboratory.⁹⁷ Had the Court subjected the claims to the second step of the *Mayo* analysis, it might have concluded that the process of creating cDNA from naturally occurring messenger RNA is as routine and conventional as the process of creating isolated genomic DNA.⁹⁸ But because the Court was satisfied that cDNA is synthetically created, it did not matter that the method of creating it was routine and conventional.

Of course, the more important outcome of the *Myriad* litigation for the patenting of diagnostics is not the patent-eligibility of some drug screening methods, but rather than patent-ineligibility of naturally-occurring biomarkers and methods of analyzing and comparing a patient's biomarker to a recited sequence. In broad terms, *Mayo* invalidates patents on diagnostic methods, while *Myriad* invalidates patents on diagnostic markers. But the survival of the drug screening method in *Myriad* left room in theory for the possibility of a that future diagnostic method will be patent-eligible if it makes use of human-made materials incorporating biomarkers.

b. Diagnostics vs. Therapeutics

The Supreme Court opinions in *Mayo* and *Myriad* share an important similarity in consequence: each has the effect of excluding diagnostic applications from patent protection, while preserving the patent-eligibility of therapeutic applications. The Court comes close to articulating this distinction in *Mayo*, when it compares the claim at issue to “a typical patent on a new drug or a new way of using an existing drug”⁹⁹ and when it points to the fact that infringement of the claim would not require that a doctor actually modify the course of treatment.¹⁰⁰ The implication is that more typical patents on drugs and methods of using drugs are patent-eligible applications, in contrast to the less typical patent at issue, which could be infringed by merely making a diagnostic inference without “applying it” to change the course of treatment.

The distinction between diagnostics and therapeutics is less obvious in the *Myriad* case, although the effect of excluding isolated gDNA from patent

⁹⁶ *Id.* at 2117 (“...Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.”)

⁹⁷ *Id.* at 2119 (“cDNA does not present the same obstacles to patenting as naturally occurring, isolated DNA segments.... the lab technician unquestionably creates something new when cDNA is made.”) For an excellent critique of this distinction, see Christopher M. Holman, *Mayo, Myriad, and the Future of Innovation in Molecular Diagnostics and Personalized Medicine*, 15 N.C.J.L. & Tech. 639 (2014)

⁹⁸ See Holman, *supra* note 97, at 655-56.

⁹⁹ See *supra* text at note 61.

¹⁰⁰ See *supra* note 66.

protection while leaving cDNA and other recombinant DNA constructs patent-eligible is to prevent the patenting of many diagnostic markers while preserving the availability of a form of patent claim that is more valuable for developers of therapeutic products. Although the Court did not explicitly say this, some amicus briefs explained it to the Court.¹⁰¹ For example, the first generation of biotechnology products were therapeutic proteins (such as insulin, human growth hormone and erythropoietin) produced in recombinant organisms that incorporated a cDNA molecule as a template for protein production. For purposes of protein production, what matters is the protein-encoding regions of a gene that are retained in the cDNA molecule. Patents on the cDNA sequence (or on recombinant constructs or host cells engineered to express the protein encoded by the cDNA sequence) were enough to allow their owners to exclude competitors from producing the therapeutic protein through recombinant DNA technology, thereby making these products profitable. Patents on human-made constructs incorporating a gene might also be valuable to a firm seeking to develop gene therapy products. But for diagnostic purposes it is necessary to compare the DNA in a patient's tissue sample to sequences that are predictive of disease. It is thus important to use markers that correspond to portions of naturally occurring variations of the sequence in order to create a valid test. If the marker for disease susceptibility is not in a coding region of the gene, the cDNA version will not do the job.¹⁰²

The United States as *amicus curiae* argued that cDNA should be patent-eligible, while gDNA should not,¹⁰³ a position that was ultimately persuasive to the Supreme Court. Professor Christopher Holman has suggested that the resonance of this distinction derives in part from the relatively compelling

¹⁰¹ See, e.g., Brief for *Amicus Curiae* Eric S. Lander in Support of Neither Party, retrieved on Feb. 25, 2015 from http://www.americanbar.org/content/dam/aba/publications/supreme_court_preview/briefs-v2/12-398_neither_amcu_lander.authcheckdam.pdf, at 28 (“The vast majority of the medically and commercially important biotechnology products developed over the past quarter century are protected by patents on ... *non-natural* compositions of matter, such as cDNA and recombinant DNA molecules – *for such uses as artificially producing therapeutic proteins*. Only a small fraction of products involve *diagnostic claims to naturally occurring genomic DNA*.”). Cf. Brief for *Amicus Curiae* 21st Century Medicine, retrieved on Feb. 25, 2015 from http://www.americanbar.org/content/dam/aba/publications/supreme_court_preview/briefs-v2/12-398_resp_amcu_c21cm.authcheckdam.pdf, at 12-17 (explaining the importance of gene patents to developers of diagnostic products).

¹⁰² If the relevant mutation is in a coding region, cDNA may be a useful marker. Thus the broadly worded BRCA1 diagnostic screening method claims held patent-ineligible in *In re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation* called in the alternative for the use in testing of “germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1cDNA.” See *supra* note 82

¹⁰³ Brief for the United States as *Amicus Curiae* in Support of Neither Party, retrieved on Feb. 25, 2015 from http://www.americanbar.org/content/dam/aba/publications/supreme_court_preview/briefs-v2/12-398_neither_amcu_us.authcheckdam.pdf.

economic case for allowing cDNA claims to provide effective patent protection for therapeutic products.¹⁰⁴

A similar *de facto* distinction appears in decisions of the Federal Circuit. For example, in its pre-*Mayo* decision in *Classen Immunotherapies v. Biogen*,¹⁰⁵ the Federal Circuit considered the patent-eligibility of several claims related to the inventor's theory "that the schedule of infant immunization for infectious diseases can affect the later occurrence of chronic immune-mediated disorders."¹⁰⁶ The court upheld the patent-eligibility of two claims that recited a two-step "method of immunizing a mammalian subject" that involved first, reviewing data on the effects of different immunization schedules to determine which schedule presents a lower risk of developing a chronic immune-mediated disorder, and second, immunizing a subject in accordance with the lower-risk schedule.¹⁰⁷ At the same time, the court rejected as patent-ineligible a claim to

¹⁰⁴ Holman, *supra* note 97 at 661-63. See *id.* at 661 ("cDNA is widely used in drug discovery and drug production, and one can suspect that the government used a distinction between cDNA and genomic DNA as a proxy for a distinction between drugs and diagnostic testing, and the Court acquiesced in this policy determination.") See also Rebecca S. Eisenberg, *Why the Gene Patenting Controversy Persists*, 77 ACADEMIC MEDICINE 1381-1387 (2002) (discussing the different roles played by DNA sequence patents in the development of therapeutics and diagnostics).

¹⁰⁵ 659 F.3d 1057 (Fed. Cir. 2011), *cert. denied sub nom.* GlaxoSmithKline v. Classen Immunotherapies, 133 S. Ct. 973 (2013). The Federal Circuit's previous decision in the case, 304 F. App'x 866 (Fed. Cir. 2008) was vacated and remanded for reconsideration in light of the Supreme Court's decision in *Bilski v. Kappos*, 561 U.S. 593 (2010). *Classen Immunotherapies v. Biogen IDEC*, 561 U.S. , 130 S. Ct. 3541 (2010).

¹⁰⁶ 659 F.3d at 1060.

¹⁰⁷ More specifically, the court set forth the following representative claim language:

1. A method of immunizing a mammalian subject which comprises:

(I) screening a plurality of immunization schedules, by

(a) identifying a first group of mammals and at least a second group of mammals, said mammals being of the same species, the first group of mammals having been immunized with one or more doses of one or more infectious disease-causing organism-associated immunogens according to a first screened immunization schedule, and the second group of mammals having been immunized with one or more doses of one or more infectious disease-causing organism-associated immunogens according to a second screened immunization schedule, each group of mammals having been immunized according to a different immunization schedule, and

(b) comparing the effectiveness of said first and second screened immunization schedules in protecting against or inducing a chronic immune-mediated disorder in said first and second groups, as a result of which one of said screened immunization schedules may be identified as a lower risk screened immunization schedule and the other of said screened schedules as a higher risk screened immunization schedule with regard to the risk of developing said chronic immune mediated disorder(s),

(II) immunizing said subject according to a subject immunization schedule, according to which at least one of said infectious disease-causing organism-associated immunogens of said lower risk schedule is administered in accordance with said lower risk screened immunization schedule, which administration is associated with a lower risk of development of said chronic immune-mediated disorder(s) than when said immunogen was administered according to said higher risk screened immunization schedule.

659 F.3d at 1060-61.

a “method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder” by using that immunization schedule in a treatment group and comparing to results in a control group.¹⁰⁸ The court explained the difference by noting that the patent-eligible methods included “the physical step of immunization on the determined schedule” and that they were therefore “directed to a specific tangible application,” while the patent-ineligible method “claims the idea of comparing known immunization results ... but does not require using this information for immunization purposes.”¹⁰⁹ In a vigorous dissent, Judge Moore disagreed with the majority’s interpretation of the claim that it held patent-ineligible. Properly interpreted, Judge Moore explained, that claim also recites an immunization step as part of the method of determining the effects of the immunization schedule.¹¹⁰ Nonetheless, the majority interpreted the word “immunizing” differently in the different patents:

The “immunizing” in the ’283 patent [held patent-ineligible] refers to the gathering of published data, while the immunizing of the ’139 and ’739 patent claims [held patent-eligible] is the physical implementation of the mental step claimed in the ’283 patent.

Whether or not this interpretation is plausible, the analysis reveals a clear view that treatment is patent-eligible, but analysis of data is not.

The Federal Circuit cited *Classen* with approval in its post-*Mayo* decision in *PerkinElmer v. Intema*.¹¹¹ In that case the court held patent-ineligible patent claims to a method of determining whether a pregnant woman is at increased risk of having a fetus with Down’s syndrome that did not include a “requirement that a doctor act on the calculated risk.”¹¹² Again, mere diagnosis without treatment steps is not patent-eligible.

¹⁰⁸ More specifically, the court set forth the claim language as follows:

A method of determining whether an immunization schedule affects the incidence or severity of a chronic immune-mediated disorder in a treatment group of mammals, relative to a control group of mammals, which comprises immunizing mammals in the treatment group of mammals with one or more doses of one or more immunogens, according to said immunization schedule, and comparing the incidence, prevalence, frequency or severity of said chronic immune-mediated disorder or the level of a marker of such a disorder, in the treatment group, with that in the control group.

Id. at 1061.

¹⁰⁹ *Id.* at 1066-67.

¹¹⁰ 659 F.3d at 1076, 1077 n.1. (Moore, J. dissenting).

¹¹¹ See *supra* notes 77-79 and accompanying text.

¹¹² 496 Fed. App’x at 71.

None of these decisions purports to rest on a policy decision that therapeutics should be patentable and diagnostics should not. Quite the contrary, both the Supreme Court and the Federal Circuit insist that patent policy decisions are the domain of Congress, and that they are merely applying longstanding principles of patent law to the cases before them.¹¹³ Yet a distinction between therapeutics and diagnostics seems to lurk beneath the surface of decisions that rest more explicitly on other distinctions. Whether the courts talk about laws of nature versus applications of those laws, or natural products versus man-made materials, or abstract ideas versus physically transformative processes, or mental steps versus tangible applications, the result is remarkably consistent: diagnostic applications do not count as patent-eligible subject matter.

V. Policy Implications

Although the courts have not purported to decide on policy grounds to exclude diagnostic applications from the patent system, they have made their decisions against the backdrop of a lively debate about the impact of such patents on innovation and patient access to testing. Much of this debate has focused on patents related to genetic discoveries.¹¹⁴ As the Human Genome Project got underway in the 1990s, an increase in gene patents¹¹⁵ caused concerns about the impact of patents on biomedical research and on the availability of genetic testing services.¹¹⁶ Some empirical studies showed fewer

¹¹³ See, e.g., *Mayo Collab. Serv. v. Prometheus Laboratories*, 132 S. Ct. at 1305 (“we must hesitate before departing from established general legal rules lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another. And we must recognize the role of Congress in crafting more finely tailored rules where necessary. [] We need not determine here whether, from a policy perspective, increased protection for discoveries of diagnostic laws of nature is desirable.”); *Ass’n for Molecular Pathology v. USPTO*, 689 F.3d at 1324 (“...patents on life-saving material and processes, involving large amounts of risky investment, would seem to be precisely the types of subject matter that should be subject to the incentives of exclusive rights. But disapproving of patents on medical methods and novel biological molecules are policy questions best left to Congress....”).

¹¹⁴ See, e.g., SACGHS Final Report, *supra* note 26; National Research Council, *Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health* (2006) [hereinafter NRC Study]; Timothy Caulfield, Robert M. Cook-Deegan, F. Scott Kieff & John P. Walsh, *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 Nat. Biotechnol. 1091-1094 (2006); David B. Resnik, *Owning the Genome: A Moral Analysis of DNA Patenting*; David Korn & Stephen J. Heinig, eds., *Public versus Private Ownership of Scientific Discovery: Legal and Economic Analyses of the Implications of Human Gene Patents*, *Academic Medicine* 77:12 (2002)

¹¹⁵ NRC Study, *supra* note 114, at 100-116.

¹¹⁶ See, e.g., Ontario Ministry of Health, *Genetics, Testing and Gene Patenting: Charting New Territory in Healthcare* (2002); Nuffield Council on Bioethics, *The Ethics of Patenting DNA: A Discussion Paper* (2002); Organization for Economic Cooperation and Development, *Genetic Inventions, Intellectual Property Rights, & Licensing Practices: Evidence and Policies* (2002); U.K. Public Health Genetics Unit, *Intellectual Property Rights and*

effects on research than had been feared,¹¹⁷ but other studies showed significant negative effects of patents on the development of diagnostic tests and availability of testing services.¹¹⁸

The Secretary's Advisory Committee on Genetics, Health and Society (SACGHS), chartered in the fall of 2002 to provide advice and recommendations to the Secretary of Health and Human Services on issues raised by developments in human genetics, conducted a study of the role of gene patenting and licensing practices in patient access to genetic tests as one of its first priorities.¹¹⁹ The final report of the SACGHS study was published in 2010, shortly before the decisions of the Supreme Court in *Mayo* and *Myriad*, and was cited in many briefs submitted in those cases.¹²⁰

The primary focus of the report was on access to clinical testing rather than on incentives for research. Nonetheless, recognizing that access to testing depends on adequate incentives to conduct basic genetic research and to develop tests, the Committee also undertook to study the effects of gene patents on R&D incentives.¹²¹ Although acknowledging “[s]trongly held opposing viewpoints ... expressed throughout the Committee’s inquiry,”¹²² the Committee concluded that “patent-derived exclusive rights are neither necessary nor sufficient conditions for the development of genetic test kits and laboratory-developed tests.”¹²³ The Committee also found “that the patenting and licensing of genetic tests has limited the ability of clinical laboratories to

Genetics (2004); Australian Law Reform Commission, Report 99 – Genes and Ingenuity: Gene Patenting and Human Health (2004); Danish Council of Ethics, Patenting human genes and stem cells (2004); World Health Organization, Genetics, Genomics, and the Patenting of DNA: Review of Potential Implications for Health in Developing Countries (2005); NRC Study, *supra* note 114; SACGHS Final Report, *supra* note 26. See also *supra* note 45 (Congressional directive to PTO to study “effective ways to provide independent, confirming genetic diagnostic test activity where gene patents and exclusive licensing for primary genetic diagnostic tests exist and to report back to Congress).

¹¹⁷ For a summary of the evidence see Eisenberg, *supra* note 23; Caulfield et al., *supra* note 23

¹¹⁸ E.g., Cho et al., *supra* note 25; Merz et al., *supra* note 25.

¹¹⁹ SACGHS, *supra* note 26, at ix-x.

¹²⁰ See briefs submitted in *AMP v. Myriad* by National Women’s Health Network; Canavan Foundation; American Medical Association; Academics in Law, Medicine, Health Policy & Clinical Genetics; International Center for Technology Assessment et al.; Genformatic; AARP; Professor Eileen M. Kane; Knowledge Ecology International; Coalition for 21st Century Medicine; and briefs submitted in *Mayo v. Prometheus* by American College of Medical Genetics et al. and Roche Molecular Systems et al. These briefs were retrieved of Feb. 28, 2015 from scotusblog.com

¹²¹ *Id.* at 1.

¹²² *Id.* at 8.

¹²³ *Id.* at 35.

offer genetic testing” with detrimental effects on “patient access, the quality of testing, and efforts to innovate.”¹²⁴

The Committee recommended that Congress provide an exemption from patent infringement liability “for anyone who infringes a patent on a gene while making, using, ordering, offering for sale, or selling a genetic test for patient care purposes.”¹²⁵ This “narrowly tailored” exemption would not eliminate gene patents, which “would remain available and enforceable for therapeutic uses.”¹²⁶ Three of the eighteen members of the Committee dissented, noting that “the increasing complexity of development and clinical testing for genetic tests and higher evidentiary standards and regulatory hurdles such test must meet require increasing levels of investment.”¹²⁷

Although the SACGHS Final Report does not propose limits on patent-eligibility, the views and evidence set forth in that Report provide some support for curtailing patent rights on diagnostic inventions. The study was limited to the specific field of genetic testing, and is thus more directly relevant to patents on genetic biomarkers such as those at issue in *Myriad* than it is to patents on diagnostic methods of the sort at issue in *Mayo*. Nonetheless, the report points to considerations that may have relevance in weighing the policy consequences of excluding diagnostics from patent eligibility.

First, in its consideration of the possible incentive benefits of patents, the report notes that patents on diagnostics are not the only way to motivate research on the genetic basis of disease and development of related diagnostic products.¹²⁸ Biomedical research in general, and genomics research in particular, have benefited from significant government subsidies that provide direct support for research that has facilitated the development of diagnostic tests.¹²⁹ The report focused on past and current government subsidies as a reason to doubt the need for patent-based exclusive rights as a further incentive to develop genetic tests. But in the wake of the decisions in *Mayo*

¹²⁴ *Id.* at 39. The Committee was particularly concerned about the effects on access and quality when patent holders licensed their rights exclusively to a single provider. *Id.* at 44, 48.

¹²⁵ *Id.* at 94.

¹²⁶ *Id.*

¹²⁷ The dissent is set forth at the end of the report following the appendices in unnumbered pages.

¹²⁸ *Id.* at 90. See generally Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 Texas L. Rev. 303 (2013) (providing a taxonomy of ways that the state can promote research and development, including through research funding, tax benefits, and prizes in addition to intellectual property).

¹²⁹ See Lisa Larrimore Ouellette, *Patentable Subject Matter and Non-Patent Innovation Incentives*, U.C. Irvine L. Rev. at pp. 13-21 (forthcoming).

and *Myriad*, policy-makers could also consider increased research subsidies as an alternative mechanism to fortify incentives to develop personalized medicine¹³⁰ without having to restore patent eligibility.

The report also notes that private investors in genetics research “appear to be rarely focused exclusively on diagnostics,”¹³¹ but instead are simultaneously pursuing therapeutic product development. The expectation of patents on future therapeutic products may therefore motivate research that yields diagnostic innovations along the way, even if only the therapeutic products are patent-eligible. Although the SACGHS Report focused on genetic discoveries made prior to identifying therapeutic products, patent incentives to develop therapeutics may also motivate firms to develop diagnostics in other contexts as well. One example is companion diagnostics that are developed and submitted for FDA approval in tandem with a drug to identify patients for whom the drug is likely to be safe and effective.¹³² So long as the drug itself is patented, the firm may not need separate patent protection on the companion diagnostic, especially if the diagnostic helps the firm to get FDA approval and to market the drug. On the other hand, in some circumstances the holder of a drug patent may worry that use of the diagnostic will diminish profits by excluding some patients from the market for the drug.¹³³ In other words, if we rely on the value of patents on therapeutic products to provide an incentive to develop unpatentable diagnostics, incentives are likely to be skewed towards those diagnostics that enhance profits on therapeutics and away from diagnostics that threaten those profits.

Second, the report notes the importance of development costs, including regulatory costs, in assessing the need for patents. For many of the laboratory-developed genetic tests (i.e., tests designed, manufactured and used within a single laboratory rather than sold for use by others) considered by the SACGHS, development costs had been quite low, although development costs for FDA-regulated test kits were more substantial.¹³⁴ On the basis of a small

¹³⁰ See White House, Office of the Press Sec’y, Fact Sheet: The President’s Precision Medicine Initiative (Jan. 30, 2015) (proposing \$215 million in federal funding for precision medicine research), retrieved on Mar. 1, 2015 from <http://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative>.

¹³¹ SACGHS Final Report, *supra* note 26, at 26.

¹³² See FDA, In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff (Aug. 6, 2014), retrieved on Mar. 1, 2015 from <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>.

¹³³ See Mark R. Trusheim & Ernst R. Berndt, *Economic challenges and possible policy actions to advance stratified medicine*, 9 *Personalized Medicine* 413-427 (2012).

¹³⁴ SACGHS Final Report, *supra* note 26, at 34.

number of case studies,¹³⁵ the committee concluded that exclusive rights from patents were not necessary for either laboratory-developed tests or test kits, although the report acknowledges that regulatory costs might increase in the future.¹³⁶ Indeed, since the release of the SACGHS Report FDA has announced its intention to regulate more laboratory-developed tests than it has done in the past,¹³⁷ making increased development costs likely in the future. Increased FDA regulation is also likely to further enhance the role of drug companies in selecting which diagnostics are developed and brought to market.

These considerations are complex, involving not only patent law but also government research funding and FDA regulation. One can understand why the courts would hesitate to address explicitly the policy implications of their opinions on patent-eligibility. Yet those opinions have reshaped the expectations of diagnostics innovators. Congress may be in a better position than the courts to adjust the various levers at its disposal to rebalance the system of resources, incentives, and costs. If it wishes to accelerate the development of personalized medicine, it may have little choice.

VI. Conclusion

Recent opinions from the Supreme Court have profoundly reshaped the expectations of diagnostics innovators. These opinions use the ambiguous vocabulary of old cases excluding “laws of nature, natural phenomena, and abstract ideas” from patenting without defining these terms, leaving some confusion about just how far they exclude modern molecular diagnostics. Different courts invoke different exclusions in cases that seem otherwise indistinguishable. Yet as more cases are decided, for all the inconsistencies in their reasoning, a consistent bottom line is emerging: diagnostic technology is not patent-eligible.

Although they have drawn considerable criticism, these decisions follow on the heels of policy recommendations from around the world to curtail the effects of patents in the field of genetic diagnostics, and they have been encouraged and celebrated by organizations of eminent doctors and scientists.

¹³⁵ The principal example noted in the Report is the willingness of multiple firms to develop a test kit for cystic fibrosis without exclusive rights. *Id.*

¹³⁶ *Id.* at 35

¹³⁷ Food & Drug Admin., Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: FDA Notification and Medical Device Reporting for Laboratory-Developed Tests (LDT's) (Oct. 3, 2014), retrieved on Mar. 1, 2015 from <file:///C:/Users/rse/Documents/Research%20materials/FDA%20LDTs.pdf>.

One can only hope that the celebration is justified, and that the exclusion of diagnostics from patent-eligibility will do more to enhance future innovation than it does to suppress it. It would be difficult for Congress to undo the rulings in the face of so much support. Other moves are available to Congress if it wishes to promote diagnostics innovation, including increased federal research funding, although Congress has shown little willingness to increase discretionary spending in recent years.

Perhaps a more likely outcome is that future diagnostics innovation will depend increasingly on pharmaceutical industry sponsorship. If so, we can expect to see more companion diagnostics that help to sell new patent-protected drugs, but we may be unlikely to see the development of tests that identify which of us should forego costly treatments.