

DIAGNOSING PATENTABLE SUBJECT MATTER

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Holders of diagnostic method patents attempt to claim an exclusive right to the correlation between a patient's medical data and a medical prognosis. These patents are a major source of controversy in the courts, with three prominent unresolved cases currently in litigation. The key question is whether diagnostic correlations are patentable subject matter under 35 U.S.C. § 101. Although the ultimate resolution of these cases is unclear, this Note argues that in light of recent scientific advances, the public interest supports granting patents on diagnostic correlations.

Part I reviews the origins of patentable subject matter doctrine and the basis for the current controversy. Part II provides a tutorial on modern diagnostic medicine and explains that data gathering is becoming increasingly standardized and affordable. Part III discusses the public policy concerning patents on diagnostic correlations. Finally, Part IV concludes that granting patents on diagnostic correlations is in the public interest.

I. THE LEGAL CONTROVERSY OVER DIAGNOSTIC METHOD PATENTS

The doctrine governing diagnostic method patents is in flux. Since 2006, three cases have reached the Supreme Court and a fourth is rising through the courts. Although unique issues of medical fact and policy may influence the outcome of the pending cases, the doctrine remains rooted in more general Supreme Court precedent on methods as patentable subject matter.

A. PATENTABILITY OF PRINCIPLES

The U.S. Supreme Court has long held “[l]aws of nature, natural phenomena, and abstract ideas” unpatentable.¹ The earliest published case

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1. Diamond v. Diehr, 450 U.S. 175, 185 (1981).

articulating this doctrine was *Boulton v. Bull*,² a 1795 English case concerning a method patent related to the steam engine, which set forth the general rule that a “principle” could not be patented.³ The basis for the rule was unclear, conflating issues of reduction to practice, novelty, improvement patents, and statutory interpretation.⁴ Walker, in his classic treatise on U.S. patent law, noted the general rule that a principle cannot be patented, but observed that no cases on point existed in the United States until the mid-nineteenth century.⁵

Walker identified five nineteenth century Supreme Court cases that evaluated patents claiming use of a “principle” or “law of nature” to accomplish an end, independent of any specific apparatus.⁶ In *O'Reilly v. Morse*, a claim for “electro-magnetism, however developed for [communicating]” was unpatentable for claiming all use of electromagnetism for communication, regardless of the machine or process for actually effecting the communication.⁷ Yet in four other cases, inventors had their patents upheld.⁸ Walker reasoned that the key distinction was that these other inventors claimed all the natural laws required for their invention, applied in a specific order and manner.⁹ Morse claimed the application of only one of the many natural laws necessary to accomplish his end.¹⁰ Walker reasoned that allowing patents to claim a single natural law would invite inventors to preclude all invention in their field, by correctly guessing which natural law would prove indispensable.¹¹

As new fields of useful discovery and invention have emerged, the Supreme Court has refined its jurisprudence on the patentability of principles. For example, the Court held genetically altered bacteria patentable

2. (1795) 126 Eng. Rep. 651 (P.C.).

3. *Id.* at 651, 656.

4. See *id.* at 656. At the time, monopolies in England were prohibited except for patents on “the sole working or making of any manner of new manufactures within this realm . . .” *Id.* at 661. The scope of patents in England was therefore potentially narrower than the Constitutional scope of U. S. patents. See U.S. CONST. art. I, § 8, cl. 8 (“The Congress shall have power . . . to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.”)

5. ALBERT HENRY WALKER, TEXT-BOOK OF THE PATENT LAWS OF THE UNITED STATES OF AMERICA § 7 (4th ed. 1904).

6. *Id.* §§ 8–12.

7. 56 U.S. 62, 113 (1854).

8. WALKER, *supra* note 5, § 12.

9. *Id.* § 13.

10. *Id.*

11. *Id.* § 14.

in *Diamond v. Chakrabarty*, because they were made by man, though the Court held that “laws of nature, physical phenomena, and abstract ideas” were unpatentable.¹² The Court has reasoned that such patents would impede rather than promote science, by blocking off whole fields of endeavor,¹³ and commentators have noted that it might be impossible to avoid practicing a law of nature.¹⁴

B. METHOD PATENTS THROUGH BILSKI

Method patents have been a source of controversy since the early days of the Information Age.¹⁵ Classic cases created a pattern of restrictions on algorithm and software patents that were gradually eased. The first Supreme Court case to address software patents was *Gottschalk v. Benson*, in which the Court held that an algorithm for converting numbers between binary encoded decimals and true binary was unpatentable because the patent wholly preempted the use of the algorithm.¹⁶ This formula may be an unpatentable abstract idea, but it is not necessarily comparable to the law of gravity (a law of nature) or the trade winds (a natural phenomenon), which act and can be useful even before any human mind has conceived of them.

The similarities between laws of nature, physical phenomena, and abstract ideas seem to lie in their potential preclusion of diverse unimagined applications. Thus, in *Diamond v. Diehr*, basic thermodynamic principles expressed in the Arrhenius equation were suspect as patentable subject matter.¹⁷ The patent was held valid only because the equation was coupled to a machine for curing rubber.¹⁸ Narrowing the scope of the method patent by coupling it to a specific “structure or process” within the scope of patent-

12. 447 U.S. 303, 309 (1980).

13. See, e.g., *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972) (explaining that “[p]henomena of nature, . . . mental processes, and abstract intellectual concepts are not patentable” because “they are the basic tools of scientific and technological work”).

14. See, e.g., Alan Durham, *Natural Laws and Inevitable Infringement*, 93 MINN. L. REV. 933, 949 (2009) (“Humanity had enjoyed the benefits of fire long before understanding the role of oxygen in combustion; the discoverer of oxygen could not have monopolized the use of fire.”).

15. See, e.g., *Gottschalk*, 409 U.S. at 64 (describing controversy over the patentability of a mathematical method).

16. 409 U.S. at 67–68 (“Here, the ‘process’ claim is so abstract and sweeping as to cover both known and unknown uses of the BCD to pure binary conversion.”).

17. 450 U.S. 175 (1981).

18. *Id.* at 188, 192–93 (1981).

eligible subject matter minimized the danger that patents would cover pure knowledge of the world and hinder harvesting the fruits of such knowledge.¹⁹

The chain of cases relaxing process patent standards culminated in *State Street Bank & Trust Co. v. Signature Financial Group, Inc.*²⁰ In *State Street Bank*, the Federal Circuit held that a method could be patentable if it had a “useful, concrete, or tangible result.”²¹ In practice, this essentially reduced the patentable subject matter analysis to a utility analysis.²² Lowering the § 101 subject-matter bar led to a proliferation of new method patents,²³ including many claiming allegedly shoddy business methods, like the *Bilski* patent, which attempted to claim commodity price hedging.²⁴

The *Bilski* patent served as the basis for the courts to reconsider the scope of patentable subject matter under § 101. The Federal Circuit used *In re Bilski* to rein in the proliferation of method patents by constructing the “machine-or-transformation” test while hewing closely to Supreme Court precedent.²⁵ This test required that a method be tied to a specific machine or transform a physical object from one state to another to be patentable under § 101.²⁶ The Supreme Court held that the Federal Circuit’s machine-or-transformation test is not necessarily dispositive, but referred to the test as a “useful and important clue, an investigative tool.”²⁷ Many observers have

19. See *id.* at 192 (holding that a mathematical formula can be implemented as part of an otherwise patent-eligible process without rendering the process ineligible). But see *id.* at 191–92 (noting that mere limitation of an abstract mathematical formula to a specific context would not confer patent-eligibility).

20. 149 F.3d 1368 (Fed. Cir. 1998).

21. *Id.* at 1373.

22. See Ebby Abraham, Note, *Bilski v. Kappos: Sideline Analysis from the First Inning of Play*, 26 BERKELEY TECH. L.J. 15, 36 (2011).

23. See John Bagby, *Business Method Patent Proliferation: Convergence of Transactional Analytics and Technical Scientifis*s, 56 BUS. LAW. 423, 445–46 (2000).

24. *Bilski v. Kappos (Bilski II)*, 130 S. Ct. 3218, 3220 (2010) (“Petitioners’ patent application seeks protection for a claimed invention that explains how commodities buyers and sellers in the energy market can protect, or hedge, against the risk of price changes.”).

25. *In re Bilski (Bilski I)*, 545 F.3d 943, 959–60 (Fed. Cir. 2008).

26. *Id.* at 961.

27. *Bilski II*, 130 S. Ct. at 3227 (2010). The Court stated:

The machine-or-transformation test may well provide a sufficient basis for evaluating processes similar to those in the Industrial Age—for example, inventions grounded in a physical or other tangible form. But there are reasons to doubt whether the test should be the sole criterion for determining the patentability of inventions in the Information Age. As numerous amicus briefs argue, the machine-or-transformation test would create uncertainty as to the patentability of software, advanced diagnostic medicine techniques, and inventions based on linear programming, data compression, and the manipulation of digital signals.

since noted that the Court gave little guidance to lower courts, other than general statements that prior Supreme Court cases are still good law.²⁸

C. MEDICAL METHOD PATENTS

Medical method patents have been a source of controversy for over one hundred years,²⁹ starting in the mid-1800s, when Dr. William Morton patented the use of ether as a surgical anesthetic.³⁰ This ignited more than a decade of controversy until Morton's patent was held invalid on the grounds that his new use of ether was not a patentably novel improvement over the prior art.³¹ The Patent Office relied on this judicial invalidation to block subsequent patents on medical methods and modes of treatment,³² but then removed the block in 1954.³³ In 1996, public discomfort with patents on medical procedures led to Congressional action that severely limited the remedies available for patent infringement by medical practitioners.³⁴ The liability limitations—codified in 35 U.S.C. § 287(c)—covered surgical procedure patents, but not the use of patented machines and pharmaceuticals.³⁵ “Biotechnology patents” are also exempt from these limitations, though the term “biotechnology” is not defined in the statute.³⁶

Id. (emphasis added).

28. See, e.g., Abraham, *supra* note 22, at 41 (citing Douglas J. Levy, *U.S. Patent Attorneys Say Bilski's Ruling Didn't Give Necessary Guidance*, Michigan Lawyer's Weekly (Feb. 5, 2010, 10:04 PM), <http://www.allbusiness.com/legal/trial-procedure-decisions-rulings/14825834-1.html>; Dennis Crouch, *Bilski v. Kappos*, PATENTLY-O, Jun. 28, 2010 WLNR 13013837, available at <http://www.patentlyo.com/patent/2010/06/bilski-v-kappos-business-methods-out-software-still-patentable.html>).

29. See generally ROBERT P. MERGES & JOHN F. DUFFY, *PATENT LAW AND POLICY: CASES AND MATERIALS* 182–86 (4th ed. 2007) (reviewing patentability of medical techniques); Joseph Reisman, *Physicians and Surgeons as Inventors: Reconciling Medical Process Patents and Medical Ethics*, 10 HIGH TECH. L.J. 355 (1995) (discussing the debate over medical technique patents shortly before passage of 35 U.S.C. § 287(c) (2006)).

30. See *Morton v. N.Y. Eye Infirmary*, 17 F. Cas. 879, 879 (S.D.N.Y. 1862).

31. *Morton*, 17 F. Cas. at 884 (S.D.N.Y. 1862) (considering the patent as “nothing more, in the eye of the law, than the application of a well-known agent, by well-known means, to a new or more perfect use, which is not sufficient to support a patent”). Under the 1952 Patent Act this basis for rejection would not be under 35 U.S.C. § 101 for patentable subject matter, but under § 102 for novelty or § 103 for obviousness. See 35 U.S.C. §§ 101–103 (2006).

32. See Reisman, *supra* note 29, at 378 (citing, for example, *Ex parte Brinkerhoff*, 24 Dec. Comm'r Pat. 349 (1883)).

33. *Ex parte Scherer*, 103 U.S.P.Q. (BNA) 107, 110 (B.P.A.I. 1954).

34. 35 U.S.C. § 287(c) (2006); see also *Pallin v. Singer*, 36 U.S.P.Q.2d (BNA) 1050, 1054 (D. Vt. 1995) (the proximal cause of Congressional action).

35. See § 287(c).

36. *Id.*

Diagnostic method patents have generated controversy in recent years.³⁷ For example, throughout the 1990s, Dr. M.H. Bogart asserted his method patent on Down's syndrome diagnosis against medical providers.³⁸ This created substantial backlash.³⁹ Though he lost an enforcement action against a state healthcare provider on sovereign immunity grounds, the validity of his patent was never litigated to conclusion on patentable subject matter grounds.⁴⁰ A recent clutch of cases on the patentability of diagnostic methods has risen through the courts, driven by hostility to business method patents and a growing cultural skepticism towards intellectual property generally.⁴¹

1. *Laboratory Corp. of Am. Holdings v. Metabolite Laboratories, Inc.*

The recent wave of cases addressing diagnostic correlations as patentable subject matter began with *Laboratory Corp. of Am. Holdings v. Metabolite Laboratories, Inc. (LabCorp)*.⁴² The patent at issue claimed a method for detecting vitamin B deficiencies by measuring amino acid levels in a patient's blood and then correlating those amino acid levels with vitamin B levels.⁴³

Though LabCorp argued for invalidity on a variety of grounds in the lower courts,⁴⁴ it did not raise the issue of whether diagnostic correlations were patentable subject matter under § 101 until it appealed to the Supreme Court.⁴⁵ The Court initially granted certiorari,⁴⁶ possibly because the justices were interested in the patentable subject matter issue. The Court then dismissed the writ of certiorari as improvidently granted,⁴⁷ possibly due to LabCorp's failure to raise the patentable subject matter issue prior to appeal.

37. See generally MERGES & DUFFY, *supra* note 29, at 182–86; Reisman, *supra* note 29.

38. U.S. Patent No. 4,874,693 (filed Oct. 10, 1986); see Seth Shulman, *Cashing in on Medical Knowledge*, TEC. REV. (March 1998), <http://www.technologyreview.com/business/11659/>. The '693 patent expired on Oct. 17, 2006.

39. Shulman, *supra* note 38.

40. See *Biomedical Patent Mgmt. Corp. v. Cal., Dept. of Health Servs.*, 505 F.3d 1328, 1343 (Fed. Cir. 2007).

41. Gaia Bernstein, *In the Shadow of Innovation*, 31 CARDOZO L. REV. 2257, 2262–64 (2010) (reviewing “the intellectual property wars”).

42. 548 U.S. 124 (2006).

43. U.S. Patent No. 4,940,658 (filed Nov. 20, 1986).

44. *Metabolite v. Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1365–69 (Fed. Cir. 2004).

45. Brief for the United States as Amicus Curiae at 15–19, *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124 (2006) (No. 04-607), 2005 WL 3533248.

46. *Lab. Corp. of Am. Holdings v. Metabolite Laboratories, Inc.*, 546 U.S. 999 (2005).

47. *LabCorp*, 548 U.S. 124, 125 (2006) (per curium).

Three justices dissented from the dismissal.⁴⁸ The dissenting justices argued that diagnostic correlations are mere descriptions of nature, not patentable subject matter.⁴⁹ Specifically, Justice Breyer argued that the patent claimed the natural relationship between vitamin B compounds and certain amino acids.⁵⁰ Although the diagnostic was certainly useful, Justice Breyer rejected the *State Street Bank* “useful, concrete, or tangible” doctrine.⁵¹ Though not binding on lower courts, this facet of the dissent guided the Federal Circuit’s *Bilski* decision.⁵²

Justice Breyer also reasoned that inclusion of a transformation step should not necessarily qualify a method for patentability under § 101.⁵³ Metabolite argued that amino acid measurement in fact requires transformation of a blood sample, but Justice Breyer noted that this measurement step is not the core of the patent.⁵⁴ He reasoned that the inclusion of a non-novel step involving transformation does not alter the overall subject matter.⁵⁵ The patent, in Justice Breyer’s view, covers the relationship between amino acids and B vitamins—the transformation needed to measure the amino acids is immaterial.⁵⁶

There is no majority or plurality opinion that might countervail Justice Breyer’s substantive dissent, which has proven persuasive to at least one district court deciding diagnostic method patentability.⁵⁷ In contrast, the Federal Circuit has rejected or declined to discuss his reasoning.⁵⁸

2. Classen Immunotherapies, Inc. v. Biogen IDEC

In *Classen Immunotherapies, Inc. v. Biogen IDEC*,⁵⁹ the Federal Circuit considered the patentability of method patents for discovering optimal immunization schedules.⁶⁰ The district court had held that the method

48. *Id.* at 125 (Breyer, J., dissenting).

49. *Id.* at 138.

50. *Id.* at 135.

51. *Id.* at 136–37.

52. *In re Bilski (Bilski I)*, 545 F.3d 943, 959–60 (Fed. Cir. 2008).

53. *LabCorp*, 548 U.S. at 135–36 (Breyer, J., dissenting).

54. *Id.*

55. *Id.* at 136.

56. *Id.*

57. See *Prometheus Labs., Inc. v. Mayo Collaborative Servs. (Prometheus I)*, No. 04-CV-1200 JAH (RBB), 2008 WL 878910, at *8 (S.D. Cal. Mar. 28, 2008).

58. *Prometheus Labs., Inc. v. Mayo Collaborative Servs. (Prometheus II)*, 581 F.3d 1336, 1346 n.3 (Fed. Cir. 2009); *Prometheus Labs., Inc. v. Mayo Collaborative Servs. (Prometheus IV)*, 628 F.3d 1347, 1356 n.2 (Fed. Cir. 2010).

59. 304 F. App’x 866 (Fed. Cir. 2008).

60. See, e.g., U.S. Patent No. 6,420,139 col. 52 l. 40 (filed July 6, 2000) (claim 1).

patents were not connected to a specific vaccine; instead, the patents' holders had attempted to patent the *idea* of a possible connection between vaccination schedules and immune disorders.⁶¹ In a brief, non-precedential opinion, the Federal Circuit held that the patent failed the machine or transformation test.⁶² The Supreme Court granted certiorari, vacated without comment, and remanded the case for reconsideration consistent with *Bilski*.⁶³

Several commentators have noted that vaccinations transform a patient by conferring immunity.⁶⁴ However, the *Classen* vaccination step is not performed on an actual patient to protect him or her from a specific disease.⁶⁵ Instead it is performed on a generic research subject.⁶⁶ Indeed, the *Classen* patent seems to claim merely the performance of a controlled experiment in the field of minimizing vaccine-induced autoimmune reactions.⁶⁷ Thus, the *Classen* transformation might be judged ancillary, insignificant, extra-solution activity.⁶⁸ This centrality standard might serve to distinguish processes that produce a direct patient benefit from those that are research tools.

3. Ass'n for Molecular Pathology v. U.S. PTO

A coalition of advocacy groups has recently brought suit against Myriad Genetics, seeking to invalidate patents relating to the *BRCA* breast cancer genes.⁶⁹ Although much of the media attention has focused on the “composition” patents claiming the isolated DNA sequence of the *BRCA* genes,⁷⁰ stakeholders also dispute several diagnostic method claims.⁷¹ These

61. *Classen Immunotherapies, Inc. v. Biogen IDEC*, No. WDQ-04-2607, 2006 WL 6161856, at *5 (D. Md. 2006).

62. *Classen*, 304 F. App'x at 866.

63. *Classen Immunotherapies, Inc. v. Biogen IDEC*, 130 S. Ct. 3541 (2010).

64. See e.g., Angela D. Follett, *The Problem with Bilski: Medical Diagnostic Patent Claims Reveal Weaknesses in a Narrow Subject Matter Test*, 7 U. ST. THOMAS L.J. 229, 247 (2009).

65. See, e.g., '139 Patent col. 52 l. 40 (claim 1).

66. *Id.*

67. *Id.* The claim thus raises significant questions of novelty and obviousness.

68. See *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989) (finding a generalized method of medical diagnosis unpatentable).

69. *Ass'n for Molecular Pathology v. U.S. PTO*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010). Certain versions of Breast Cancer Susceptibility Genes 1 and 2 (*BRCA* genes) place women at increased risk for breast cancer. *Id.* at 184–185.

70. See, e.g., John Schwartz & Andrew Pollack, *Judge Invalidates Human Gene Patent*, N.Y. TIMES, Mar. 30, 2010, at B1, available at <https://www.nytimes.com/2010/03/30/business/30gene.html>; Danny Townsend, *Myriad Genetics Can't Patent a Human Gene: The Wise Judicial Ruling in a Lawsuit Over a Test for Breast Cancer*, SLATE (Apr. 7, 2010), <http://www.slate.com/id/2250082/>.

71. See *Ass'n for Molecular Pathology*, 702 F. Supp. 2d at 234–35.

method claims generally cover “analyzing” the *BRCA* sequence and then inferring breast cancer risk based on the sequence data.⁷²

The Southern District of New York heard the case while the “machine-or-transformation” test was still dispositive,⁷³ and held the *BRCA* diagnostic methods claims invalid because they failed to meet that test.⁷⁴ Because the claims were not tied to any specific machine, the district court did not need to address the machine prong of the test.⁷⁵ Addressing the transformation prong, the court found that a claim to “analyzing” DNA merely covered interpreting DNA sequence data; an analytic claim did not include the transformative physical isolation and processing of DNA molecules.⁷⁶ Thus, the data gathering step did not claim transformation.⁷⁷ Further, the court reasoned that even if physical transformation did occur in the data gathering step, it was merely “insignificant extra-solution activity.”⁷⁸

The court may also have considered whether the claims covered any transformation of the patient.⁷⁹ Although a medical procedure—tissue collection—must have occurred prior to the “analyzing” step, this procedure was not included in the claims.⁸⁰ Furthermore, the test was not claimed in the context of any treatment, such as mastectomy, though a treatment step would seemingly involve transformation of the patient.⁸¹

72. See *id.* at 234. Some claims cover similar methods, for example, analyzing the BRCA DNA sequence to determine whether BRCA mutation was involved in creating a tumor that has already grown. *Id.* at 235.

73. See *In re Bilski*, 545 F.3d 943, 959–60 (Fed. Cir. 2008) (constructing the machine or transformation test). But see *Bilski v. Kappos*, 130 S. Ct. 3218, 3227 (2010) (holding that the machine or transformation test is useful but not dispositive).

74. *Ass’n for Molecular Pathology*, 702 F. Supp. 2d at 234–35.

75. See *id.* at 232–37 (discussing Myriad’s argument that the patented methods transform DNA, but not analyzing the machine prong of the test).

76. *Id.* at 234–36. This transformation is logically required for “analyzing”, but not literally recited in the disputed claims. *Id.* at 235–36.

77. *Id.* at 234–36.

78. *Id.* at 236–37.

79. See *id.* at 235. The district court states:

Similarly, the inclusion of the phrases “from a human subject” or “from a nontumor sample” in the claims serve only to specify the identity of the DNA or RNA sequence to be “analyzed” or “compared,” i.e., from a human sample as opposed to an animal sample or cell culture, and do not, as Myriad argues, establish that the claims should be read to include the physical transformations associated with obtaining DNA from those sources.

Id. (emphasis added).

80. *Id.*

81. See, e.g., U.S. Patent No. 5,709,999 col. 161 l. 17 (filed June 7, 1999). The ’999 patent claims:

The court also analyzed a claim for identifying anti-cancer drugs by growing human cells with a high-risk *BRCA* DNA sequence and “comparing” the cells’ growth with and without potential drugs.⁸² The court reasoned that the claim recited “the scientific method itself,”⁸³ analogous to the *Classen* describing controlled experiments in anti-vaccine reactions.⁸⁴

Although the court conducted its analysis under the machine-or-transformation standard, its holding that the diagnostic method claims covered unpatentable mental processes may stand, pending appeal to the Federal Circuit.⁸⁵ Given the high probability that the DNA composition claims will eventually come before the Supreme Court,⁸⁶ the related method claims make a likely test case for the patentability of diagnostic correlations post-*Bilski*.

4. Prometheus Labs., Inc. v. Mayo Collaborative Services

Prometheus Laboratories, Inc. patented methods for dosing drugs from a class of chemicals termed thiopurines, which treat autoimmune disorders.⁸⁷ These drugs do not have a direct effect on the immune system.⁸⁸ Instead, the patient’s body breaks the drugs down into new chemicals, including 6-methyl-mercaptopurine and 6-thioguanine.⁸⁹ These new chemicals, or

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1. 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 20 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.

Id.

82. See *Ass’n for Molecular Pathology*, 702 F. Supp. 2d at 237 (analyzing claim 20 of U.S. Patent No. 5,747,282).

83. *Id.*

84. See *Classen Immunotherapies, Inc. v. Biogen IDEC*, No. WDQ-04-2607, 2006 WL 6161856, at *5 (D. Md. 2006).

85. *Ass’n for Molecular Pathology v. U.S. PTO*, 702 F. Supp. 2d 181 (S.D.N.Y. 2010), *appeal docketed*, No. 2010-1406 (Fed. Cir. June 16, 2010).

86. Harold C. Wegner, *Myriad DNA Case: ACLU Declares Victory, Wins SG Support*, IP FRONTLINE (Feb. 22, 2011), <http://www.ipfrontline.com/depts/article.aspx?id=24955&deptid=7> (noting that “discussions about the Myriad case have suggested an inevitability of a Supreme Court review,” but also noting that the case could turn “on the procedural basis of a lack of justiciable controversy”).

87. Prometheus Labs., Inc. v. Mayo Collaborative Servs. (*Prometheus II*), 581 F.3d 1336, 1339 (Fed. Cir. 2009).

88. *Id.*

89. *Id.*

“metabolites,” can treat the patient but may have dangerous side effects.⁹⁰ The patents at issue, 6,355,623 (“the ’623 patent”) and 6,680,302 (“the ’302 patent”), claim methods for optimizing thiopurine dosage by measuring the levels of the pharmacologically active metabolites.⁹¹ The claims specify levels of metabolites.⁹² If the metabolite levels are too high, it “indicates a need” to decrease dosage.⁹³ If the levels are too low, it “indicates a need” to increase dosage.⁹⁴ The claims cover a three step process: (1) the thiopurine is administered (“administering” step), (2) the levels of metabolites are determined (“determining” step), and (3) a need to adjust dosage is indicated (“inference” step).⁹⁵

Prometheus manufactured a testing kit, previously used by Defendants Mayo Collaborative Services and the Mayo Clinic Rochester.⁹⁶ Mayo planned to begin using its own kit, testing for the same metabolites but using different levels to determine toxicity.⁹⁷ Prometheus then sued Mayo for patent infringement, prompting Mayo to suspend its plans pending resolution of the case.⁹⁸ The District Court held the patents invalid under § 101.⁹⁹ The Federal

90. *Id.*

91. *Id.* at 1340.

92. *Id.* at 1339–40.

93. *Id.*

94. *Id.*; see also U.S. Patent No. 6,355,623 col. 20 l. 10 (filed April 8, 1999) (claim 1). The inventors of the ’623 patent claimed:

1) 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 8×10^8 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 8×10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Id.

95. Prometheus Labs., Inc. v. Mayo Collaborative Servs. (*Prometheus I*), No. 04-CV-1200 JAH (RBB), 2008 WL 878910, at *6 (S.D. Cal. Mar. 28, 2008). Note that the “administering” and “determining” steps are so named by the Court using the actual claim language, while the “inferring” step is purely this author’s own appellation for convenience. The *Prometheus I* court refers to the “inferring” step as the “warning” step, another appellation not found in the claim language. *Id.*

96. *Prometheus II*, 581 F.3d at 1340.

97. *Id.*

98. *Id.*

99. *Prometheus I*, 2008 WL 878910, at *14.

Circuit then reversed and remanded.¹⁰⁰ Mayo appealed to the Supreme Court, which granted certiorari, reversed, and remanded for reconsideration post-*Bilski*.¹⁰¹ The Federal Circuit again held the claims valid.¹⁰²

Back in 2008, the Southern District of California held the patents invalid under § 101 because they claimed unpatentable subject matter.¹⁰³ First, the court reasoned that the patents primarily claimed the correlation between metabolite levels and drug efficacy.¹⁰⁴ The court adopted Mayo's proposed construction of "indicates a need," interpreting the phrase to mean that "when the identified metabolites reach the specified level, the doctor is warned or notified that a dosage adjustment may be required," if the doctor believes that is the proper procedure.¹⁰⁵ Thus, the court rejected the view that the patent recited correlation in the context of a method of treatment, because under the adopted construction of "indicates a need," no actual treatment is required.¹⁰⁶ The court also determined that "administering" and "determining" steps were "merely necessary data-gathering steps for any use of the correlations"¹⁰⁷ and that these steps were merely grafted onto the core claim of the correlation.¹⁰⁸

The district court then held that the correlation recited was an unpatentable natural phenomenon, relying heavily on the *LabCorp* dissent's reasoning and language.¹⁰⁹ The court reasoned that because the bodily processes converting the thiopurines occur naturally, the correlation was *discovered* rather than *invented*.¹¹⁰

100. *Prometheus II*, 581 F.3d at 1350.

101. Mayo Collaborative Servs. v. Prometheus Labs., Inc. (*Prometheus III*), 130 S. Ct. 3543 (2010).

102. Prometheus Labs., Inc. v. Mayo Collaborative Servs. (*Prometheus IV*), 628 F.3d 1347 (Fed. Cir. 2010).

103. *Prometheus I*, 2008 WL 878910, at *14.

104. *Prometheus I*, 2008 WL 878910, at *6.

105. *Id.* ("[T]he 'warning' step does not require that dosage be adjusted, or any other action. Indeed, contrary to Plaintiff's assertion, the 'warning step' does not require that the doctor (or any person) 'provide' a warning.").

106. *See id.*

107. *Id.*

108. *Id.* ("[T]he claims recite the correlations themselves.").

109. *Id.* at *6–8 (citing *Lab. Corp. of Am. Holdings v. Metabolite Laboratories, Inc.*, 548 U.S. 124 (2006) (Breyer, J., dissenting from dismissal of certiorari)). The District Court also referenced *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948), in which the Supreme Court held that a naturally occurring mixture of bacteria was not patentable. *Id.* at *7. In relying on *Funk Bros.*, the District Court glossed over the distinction between method and product claims. *Id.* at *9 (citing *Funk Bros.*, 333 U.S. at 130, 132).

110. *Id.* at *7.

According to the district court, recitation of a natural phenomenon invalidates a claim if the claim wholly preempts use of the natural phenomenon.¹¹¹ In this case, the court held that the patents claimed a general correlation between drug administration, metabolite levels, drug efficacy, and toxicity, without limitation to a specific disease, and without requiring any actual treatment action after the diagnostic test.¹¹² Because the correlation can only be observed after “administering” treatment and “determining” metabolite levels, and because the “inferring” step requires no action, it is impossible to observe the correlation without performing all three steps. Thus, the District Court held that the claims wholly preempt the natural correlation.¹¹³

The district court issued its decision prior to the Federal Circuit’s *In re Bilski* decision, but *Prometheus*’s appeal was post-*In re Bilski*.¹¹⁴ The Federal Circuit thus applied its “machine or transformation” test to find the claims patentable under § 101.¹¹⁵ The Federal Circuit held that the “administering” and “determining” steps are transformative, reasoning that “administering” the drug transforms the patient and that “determining” metabolite levels transforms patient samples.¹¹⁶ Yet these findings were merely a threshold analysis; the Federal Circuit recognized that patentability also requires that the transformative steps be more than ancillary to an unpatentable core process.¹¹⁷

The core process in the *Prometheus* patents is a medical treatment.¹¹⁸ Unlike the District Court, the Federal Circuit held that even though the patents do not require post-diagnostic action, the diagnostic correlation is still linked to a medical treatment.¹¹⁹ Thus, even if the “inferring” step is a purely mental step, the “administering” and “determining” steps are “not

111. *Id.* at *10.

112. *Id.* at *6, 11.

113. *Id.* at *10–12.

114. Prometheus Labs., Inc. v. Mayo Collaborative Servs. (*Prometheus II*), 581 F.3d 1336, 1345 n.2 (Fed. Cir. 2009).

115. *Id.* at 1342–43, 1345–46.

116. *Id.* at 1345–47. The Federal Circuit declined to analyze the machine prong because it was moot. *Id.* at 1346.

117. *Id.* at 1347 (citing *In re Bilski*, 545 F.3d 943, 962 (Fed. Cir. 2008)).

118. See *Prometheus II*, 581 F.3d at 1348.

119. *Id.*, 581 F.3d at 1348. This connection to a specific treatment distinguishes *Prometheus* from the prior *Grams* case, in which the Federal Circuit invalidated a diagnostic algorithm that existed independent of any specific disease or treatment regimen. *Id.* (citing *In re Grams*, 888 F.2d 835, 840 (Fed. Cir. 1989)).

merely data-gathering steps or insignificant extra-solution activity.”¹²⁰ Instead, these steps connect the final “inferring” step to a specific medical treatment process—i.e., to the “transformation” of a patient.¹²¹ Indeed, the patents claim not only a maximum level of metabolite to avoid inherent toxicity, but also a minimum level required for effective treatment.¹²²

Following its decision in *Bilski*, the Supreme Court granted certiorari, vacated without comment, and remanded *Prometheus* to the Federal Circuit for reconsideration consistent with *Bilski*.¹²³ In *Prometheus IV*, the Federal Circuit again held the patents valid.¹²⁴ The Federal Circuit accepted the Supreme Court’s holding that the machine-or-transformation test was merely a “useful and important clue, an investigative tool,” and found that this “clue” was dispositive for the *Prometheus* patents.¹²⁵ The three-judge panel unanimously restated the court’s earlier conclusion that the patents fulfilled the transformation prong because the human body was transformed by thiopurine treatment and the measurement process transformed patient samples.¹²⁶ The Federal Circuit held that the patents claimed a specific treatment method,¹²⁷ and therefore rejected the argument that the transformative steps were merely ancillary data-gathering steps appended to a natural process claim.¹²⁸ Interestingly, the Federal Circuit specifically declined to discuss or apply Justice Breyer’s influential *LabCorp* dissent, stating “it is not controlling law.”¹²⁹

On remand, the Federal Circuit again reasoned that the final step is an extension of medical drug treatment, just as the *Diehr* algorithm was an extension of a rubber curing machine.¹³⁰ Thus, the court held that the presence of a mental step is not sufficient to invalidate a claim if the mental

120. *Id.* at 1348 (internal quotations omitted).

121. *Id.*

122. See U.S. Patent No. 6,355,623 col. 20 l. 17 (filed April 8, 1999).

123. Mayo Collaborative Servs. v. Prometheus Labs., Inc. (*Prometheus III*), 130 S. Ct. 3543 (2010).

124. Prometheus Labs., Inc. v. Mayo Collaborative Servs. (*Prometheus IV*), 628 F.3d 1347 (Fed. Cir. 2010).

125. *Id.* at 1355.

126. *Id.* at 1356–58.

127. *Id.* at 1356–57.

128. *Id.* at 1357.

129. *Id.* at 1356 n.2.

130. See *Diamond v. Diehr*, 450 U.S. 175, 188 (1981); *Prometheus IV*, 628 F.3d at 1357–59 (finding that the correlation between metabolite levels and physiological effect is applied as part of a claimed treatment). This is also analogous to *In re Abele*, 684 F.2d 902 (C.C.P.A. 1982), in which an image processing algorithm was an extension of an imaging machine. *Prometheus IV*, 628 F.3d at 1358 (citing *Abele*, 684 F.2d at 908).

step can be attached to steps that *do* concern patentable subject matter.¹³¹ In cases where the tangible steps might be unpatentable for lack of novelty or obviousness, this is analogous to permitting an improvement patent in which the improvement is a purely mental step.

Because of the direct tie between the mental step and the specific, transformative medical treatment, there is little danger that the *Prometheus* patents will preempt the underlying biological processes responsible for breaking the drug down into metabolites or even the correlation between the metabolite and treatment efficacy. Indeed, the core purpose of the machine-or-transformation test may have been to construct an easily applicable proxy for preemption—as the Federal Circuit stated in *Prometheus II*, the machine-or-transformation test subsumed the preemption test.¹³² Although in *Bilski v. Kappos* the Supreme Court held that the machine or transformation test was not necessarily dispositive,¹³³ *Prometheus IV* reasserted the utility of the machine-or-transformation test as sufficient to ensure a patent does not preempt a law of nature.¹³⁴

Additional evidence suggests the *Prometheus* patents are not preclusive: they can potentially be invented around. A patient's ability to break down the toxic metabolite is determined in large part by whether the patient has two, one, or zero working copies of the *TPMT* gene.¹³⁵ Indeed, the correlation between the gene and the gene's medically relevant activity is much tighter than for *BRCA*, in which only some *BRCA*-positive patients develop breast cancer.¹³⁶ The *TPMT* correlation is in the prior art of the *Prometheus* patents.¹³⁷ Testing for the *TPMT* gene or the gene's product, *TPMT* enzyme, can single out the patients most endangered by treatment with the thiopurine drug.¹³⁸

131. *Prometheus IV*, 628 F.3d at 1358–59.

132. Prometheus Labs., Inc. v. Mayo Collaborative Servs. (*Prometheus II*), 581 F.3d 1336, 1349 (Fed. Cir. 2009) (citing *In re Bilski*, 545 F.3d 943, 954 (Fed. Cir. 2008)).

133. *Bilski v. Kappos*, 130 S. Ct. 3218, 3227 (2010).

134. *Prometheus IV*, 628 F.3d at 1355, 1359.

135. Liewei Wang, *Pharmacogenomics: A Systems Approach*, 2 WIRES SYSTEMS BIOLOGY AND MEDICINE 1, 6 (Jan/Feb 2010). A person with two working copies of the thiopurine methyltransferase gene (*TPMT*) makes metabolite at normal levels, a person with one working copy makes reduced levels, and a person with no working copies makes no metabolite. *Id.* at 6.

136. *Id.* at 6; Ass'n for Molecular Pathology v. U.S. PTO, 702 F. Supp. 2d 181, 202 (S.D.N.Y. 2010) (stating that breast cancer incidence may reach 85%, among women with certain *BRCA* DNA sequences).

137. U.S. Patent No. 6,355,623 at [56], col. 14 l. 13, col. 19 l. 26 (filed April 8, 1999).

138. See E. A. Fargher et al., *Current Use of Pharmacogenetic Testing: A National Survey of Thiopurine Methyltransferase Testing Prior to Azathioprine Prescription*, 32 J. CLINICAL PHARMACY &

Although this testing cannot fully predict patients' precise metabolite levels,¹³⁹ further research into determinants of thiopurine metabolism might enable accurate predictions of toxic metabolite levels and avoid the need to use patients as guinea pigs for their own medical treatment.

D. UNCERTAINTY ABOUT MEDICAL DIAGNOSTIC PATENTS

The patentability of medical diagnostic claims remains uncertain. The Supreme Court may grant certiorari to *Prometheus*, particularly given the Federal Circuit's dismissive language declining to discuss the *LabCorp* dissent.¹⁴⁰ The Federal Circuit still faces *Classen* on remand from the Supreme Court and *Ass'n for Molecular Pathology* on appeal from the Southern District of New York.

The Federal Circuit, evidenced by its opinion in *Prometheus IV*, seems committed to the machine-or-transformation test, but the Supreme Court may weigh in again, and might choose to apply any of several alternative standards. These alternatives include: (1) invalidating all patents on diagnostic correlations, (2) allowing all diagnostic correlations as patentable subject matter, and (3) allowing diagnostic correlation patents only in some cases—for example, only when the diagnostic relates to a medical intervention. Under the current Federal Circuit analysis, a specific medical therapy necessarily transforms the body and an associated diagnostic is patentable.¹⁴¹ In contrast, the Federal Circuit could adopt the Southern District of New York reasoning from *Ass'n of Molecular Pathology* to find that a diagnostic dissociated from any known medical intervention fails the machine-or-transformation test, unless the diagnostic is connected to a specific machine.¹⁴²

1. No Patents for Diagnostic Correlations

One possible standard would be to broadly interpret and apply Justice Breyer's *LabCorp* dissent and prohibit patenting all diagnostic correlations.¹⁴³

THERAPEUTICS 187, 188 (2007) (referencing the "tight correlation between absent TPMT activity and severe neutropaenia").

139. *See id.* (referencing "the less than 100% predictive value of TPMT testing").

140. *See Prometheus Labs., Inc. v. Mayo Collaborative Servs. (Prometheus IV)*, 628 F.3d 1347, 1356 n.2 (Fed. Cir. 2010).

141. *See id.* at 1356, 1359.

142. *See Ass'n for Molecular Pathology v. U.S. PTO*, 702 F. Supp. 2d 181, 234–35 (S.D.N.Y. 2010).

143. *See Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 135 (2006) (Breyer, J., dissenting) (arguing that the correlationn between vitamin B and homocysteine is a natural phenomenon, but noting that "this case is not at the boundary").

Justice Breyer argued that correlations between data and medical prognoses are natural processes or products of nature, and therefore unpatentable.¹⁴⁴ A broad application of this rule might invalidate all diagnostic correlations patents, including not only the *LabCorp* patent, but also the *Prometheus*, *Classen*, and *Ass'n of Molecular Pathology* patents—all of which center around gathering data on one aspect of human biology and correlating those data with another aspect of human health.¹⁴⁵

As the Federal Circuit has observed, a broad application of Justice Breyer's standard could be problematic, because all inventions operate via natural laws and processes.¹⁴⁶ If courts were to presume that claims preclude all applications of the natural processes involved in an invention's operation, it would be impossible to draft any valid patent. Such a high barrier to patentability would seemingly invalidate both an improved combustion engine whose operation presumes the laws of thermodynamics and a new music playing device whose operation requires human hearing for utility. Despite the potential for doctrinal inconsistency, § 101 does not require perfect congruity across fields of discovery. Indeed, § 101's vague implication that some inventions are not appropriate subject matter for patents serves fundamentally as a tool for enabling such inconsistencies, when other patentability requirements fail to operate in accord with the broad policy goals of the patent system. Thus, concerns over inhibited research and limited patient access might lead some to support invalidating all medical correlation patents via § 101 or rendering such patents irrelevant via an infringement liability exemption.¹⁴⁷

144. *Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc.*, 548 U.S. 124, 137–38 (2006) (Breyer, J., dissenting) (“[Metabolite] cannot avoid the fact that the process is no more than an instruction to read some numbers in light of medical knowledge.”).

145. See, e.g., *Prometheus IV*, 628 F.3d at 1356 (quoting the '623 specification: “[t]he present invention provides a method of optimizing therapeutic efficacy of 6-mercaptopurine drug treatment of an immune-mediated gastrointestinal disorder”); *Classen Immunotherapies, Inc. v. Biogen IDEC*, No. WDQ-04-2607, 2006 WL 6161856, at *5 (D. Md. Aug. 16, 2006) (“[T]he 139 and 739 patents are an indirect attempt to patent the idea that there is a relationship between vaccine schedules and chronic immune mediated disorders.”); U.S. Patent No. 5,709,999, at [57], col. 161 l. 17 (filed June 7, 1995) (the abstract states, “the invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer,” and claim 1 accomplishes this by “analyzing a sequence of a BRCA1 gene.”).

146. *Prometheus IV*, 628 F.3d at 1356 (“[Q]uite literally every transformation of physical matter can be described as occurring according to natural processes and natural law.”)

147. See, e.g., Rochelle C. Dreyfuss, *The Patentability of Genetic Diagnostics in U.S. Law and Policy*, N.Y.U. SCH. OF LAW, LAW & ECONOMICS RESEARCH PAPER SERIES, No. 10-44 at 17, 29 (2010), available at <http://ssrn.com/abstract=1678123> (discussing, without endorsing,

2. Allow All Patents on Diagnostic Correlations

Diagnostic correlations might be generally permissible as patentable subject matter. Courts can view the law of nature standard as a tool for implementing the constitutional mandate to advance science and the useful arts. If the standard is simply intended to avoid preclusion that hinders advancement of the useful arts, perhaps it should be inapplicable to laws of nature so narrow that there is little danger of precluding further research and development. Alternatively, courts may not view diagnostic correlations as laws of nature at all, because the patented processes begin with a necessary data-gathering step and involve interactions with patients.

3. The Human Intervention Standard and the Anti-Preclusion Standard

A variety of intermediate positions are possible in addition to the machine-or-transformation standard applied by the Federal Circuit. One might, for example, distinguish patentable from unpatentable diagnostic methods by considering whether human intervention creates the observed correlation¹⁴⁸ or whether the claims actually preclude subject matter outside the scope of the actual invention.¹⁴⁹

The human intervention standard would permit patents in cases where human intervention creates the phenomenon being correlated to human health, on the theory that the correlation is not “natural.”¹⁵⁰ Thus, the *Prometheus* patents would be valid because they correlate the results of pharmacological treatment with thiopurine drugs. A broader version of this

the possibility of a ban on diagnostic methods and discussing a liability exemption for diagnostic testing recommended in the SEC’Y’S ADVISORY COMM. ON GENETICS, REVISED DRAFT REPORT ON GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS, HEALTH, AND SOC’Y 90 (2010), available at <http://oba.od.nih.gov/oba/SACGHS/SACGHS%20Patents%20Report%20Approved%202-5-2010.pdf>.

148. See Chris Holman, *The Impact of Bilski on Biotechnology*, Holman’s Biotech IP Blog (July 3, 2010, 11:22 AM), <http://holmansbiotechipblog.blogspot.com/2010/07/impact-of-bilski-on-biotechnology.html>.

149. Cf. Brian P. Murphy & Daniel P. Murphy, *Bilski’s ‘Machine-or-Transformation’ Test: Uncertain Prognosis for Diagnostic Methods and Personalized Medicine Patents*, 20 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 755, 763–67 (2010) (discussing the older and more permissive test prohibiting patents that wholly preclude all applications of a fundamental principle).

150. See Holman, *supra* note 148 (“By drawing a line between biological phenomena that occurs absent human intervention and phenomena that occurs as a result of human intervention, one could have a principled basis for finding the [LabCorp] claim patent ineligible while upholding the eligibility of the *Prometheus* claims, and drug patents in general.”). As discussed above, all processes are natural in the broad sense. *Prometheus IV*, 628 F.3d at 1356.

standard would also permit patents on detection of a pre-intervention state that correlates with efficacy of a subsequent intervention. Such a standard would not necessarily require a subsequent intervention step, but might allow the claims to merely reference the possibility—analogous to the *Prometheus* patents whose “inference” steps suggest, but do not require, altering thiopurine dosage.¹⁵¹ The human intervention standard recognizes that all inventions operate in conjunction with the laws of nature and does not require diagnostic correlations to be treated any differently than combustion engines, which are also (and obviously) the product of human intervention in the natural world.

Although human intervention might seem to set a reasonably bright line, there is potential ambiguity. If unintentional contact with human-generated pollutants causes a disease, would it qualify as human intervention? Would treating Vitamin B deficiencies qualify as a human intervention to validate the *LabCorp* patent, or would the *LabCorp* patent be invalid because Vitamin B remains a natural product, even when given as a megadose in purified pill form? Would the *Ass’n of Molecular Pathology* patents be valid under this standard if Myriad had claimed bilateral prophylactic mastectomy as the final step?

Another approach would ask whether a specific diagnostic correlation claim actually precludes other uses of the natural processes involved, such that the bar against preclusive claiming is not fatal in fact, but instead leads to a fact-specific analysis rooted in claim construction. This approach could be applied instead of, or in addition to, the human intervention standard. Permitting only non-preclusive diagnostic method patents would give inventors an incentive to draft their claims narrowly, and to argue for narrow constructions during litigation. Permitting only narrow claims to pass the § 101 threshold test would be consistent with traditional written description and reduction to practice principles. Such a standard might function similarly to the machine or transformation test, limiting patents to specific contexts to prevent patent holders from blocking or extracting rents from later inventions, practices which might inhibit discovery.

II. THE SCIENCE BEHIND THE LAW

Modern diagnostic correlations tend to fall into one of several broad classes, depending on the type of data analyzed. Genetic diagnostics analyze

^{151.} See *Prometheus Labs., Inc. v. Mayo Collaborative Servs. (Prometheus I)*, No. 04-CV-1200 JAH (RBB), 2008 WL 878910, at *6 (S.D. Cal. Mar. 28, 2008).

the sequence of a specific piece of DNA, like the Myriad Genetics patents in *Ass'n for Molecular Pathology*.¹⁵² Other diagnostics use antibodies to detect the presence of specific proteins or large sugar complexes.¹⁵³ Diagnostics can also detect some proteins or sugars via chemical reactions in which a new, easier to detect chemical is produced.¹⁵⁴ Chemical reaction diagnostics can also sometimes detect smaller molecules produced by the body—metabolites—but more direct methods can also detect metabolites, including the mass spectrometry used in the *LabCorp* patent and the high-pressure liquid chromatography (HPLC) used in the *Prometheus* patents.¹⁵⁵ A unifying theme in the development of these diagnostics is the increasing standardization of collecting data from medical samples.¹⁵⁶ As a result, it will become increasingly difficult to obtain patent protection for diagnostic advances by claiming novel, non-obvious data-gathering techniques.

Genetic diagnostics represent a limiting case within the field of diagnostic medicine. While the mechanisms for gathering genetic data are among the most standardized, the ability to gather vast quantities of data has only increased the complexity of data analysis.¹⁵⁷ Furthermore, genetic diagnostics

152. See, e.g., U.S. Patent No. 5,709,999 (filed June 7, 1999) (claiming analyzing the *BRCA* gene to detect inherited mutations, termed “germline” mutations).

153. See, e.g., A. Kappel et al., *Fully Automated Immunoassay for Quantitative Determination of FXIII*, 31 HÄMOSTASEOLOGIE 1, 1–6 (2011) (describing invention of an antibody diagnostic for a blood clotting disorder by scientists at Siemens Healthcare Diagnostics Products GmbH).

154. See, e.g., Nestor Chamois et al., *Hurler-Like Phenotype: Enzymatic Diagnosis in Dried Blood Spots on Filter Paper*, 47 CLINICAL CHEMISTRY 2098 (2001) (describing a new variation on methods for detecting of defects in lysosome proteins by measuring the proteins’ alteration of small chemicals).

155. The *LabCorp* ’658 patent claims detection by mass spectrometry (independent claim 1); high-pressure liquid chromatography (HPLC) (e.g., derivative claim 16); and chemical reaction with a radioactive label (e.g., derivative claim 17). U.S. Patent No. 4,940,658 col. 41 l. 2, col. 42 l. 11, col. 42 l. 19 (filed July 10, 1990). The *Prometheus* ’623 patent claims HPLC detection (e.g., derivative claim 6) but explains several other techniques in the prior art and specification, included under the broader claims which do not limit the detection method. U.S. Patent No. 6,355,623 col. 20 l. 38, col. 9 l. 12 (filed Apr. 8, 1999). Mass spectrometry identifies molecules by determining the ratio of their weight to their electrical charge. HARVEY LODISH ET AL., MOLECULAR CELL BIOLOGY 94–95 (5th ed. 2003). HPLC identifies molecules by how quickly they pass through a material that lets molecules through at different speeds. DONALD VOET ET AL., FUNDAMENTALS OF BIOCHEMISTRY 99–100 (Upgrade ed. 2002); see also LODISH ET AL. *supra*, at 90–93 (describing methods of liquid chromatography).

156. See Hans V. Westerhoff & Bernhard O. Palsson, *The Evolution of Molecular Biology into Systems Biology*, 22 NATURE BIOTECHNOLOGY 1249, 1249 (2004) (describing the “scaling up” of molecular biology).

157. See *id.* at 1249–52.

can implicate potentially basic elements of human biology or unchanging attributes of individuals.

A. DNA-BASED DIAGNOSTICS

Genes are discrete, physical units of heritability. When genes were first discovered by Gregor Mendel, the physical basis for genes was not understood.¹⁵⁸ During the mid-twentieth century, scientists first realized that genes were encoded by strands of deoxyribonucleic acid (DNA), composed of four chemical units, termed nucleotides (abbreviated A, T, C, and G¹⁵⁹) and arranged in ordered sequence.¹⁶⁰ The sequence of nucleotides in a gene specifies the sequence of an intermediate molecule, RNA, whose sequence in turn specifies the sequence of amino acids in the protein produced by the gene.¹⁶¹ The sequence of amino acids determines the chemical properties which enable a protein to function biologically within the human body.¹⁶² The protein made from the DNA gene actually performs the “work” of the gene, conferring traits on a person which are referred to as the person’s “phenotype.”¹⁶³

DNA sequencing technology has made it possible to sequence genes and whole genomes.¹⁶⁴ The advancing ability to obtain massive quantities of raw

158. VOET ET AL., *supra* note 155, at 53.

159. Adenine, thymine, guanine, and cytosine. *Id.* at 42–47.

160. *Id.* at 53–55.

161. *Id.* at 54–55.

162. *Id.* at 94.

163. LODISH ET AL., *supra* note 155, at 22.

164. The DNA genomes of all living creatures are bonded strands of the individual A, T, C, and G DNA nucleotides. VOET ET AL., *supra* note 155, at 48–52. Each genome has two strands which stick together like a zipper. LODISH ET AL., *supra* note 155, at 103–04. These strands are complementary and form strongly associated nucleotide pairs, known as base pairs—with rare exceptions, A always pairs with an opposite strand T, and C with an opposite strand G. *Id.* at 104. Each strand has one end that is chemically reactive, termed the three-prime (3') end. *See id.* at 102. When DNA replicates each strand is left naked and used as a template to build a new complementary strand. *Id.* at 131. The new strand starts from a short DNA or RNA stub called a primer. *Id.* at 133. The primer sticks to the original strand using A-T, C-G matching, and the 3' end of primer “attacks” complementary DNA nucleotides, reacting chemically to bond them to the growing complementary strand. *See id.* DNA sequencing techniques mimic natural replication. These techniques initiate replication of a DNA strand using an artificial primer and then track which complementary nucleotides are added first, second, third, and onwards, relative to the primer. *Id.* at 372–75. Thus, the sequencing process requires beginning with some knowledge of the DNA sequence. This bit of primer sequence is the only unique aspect of a method for sequencing a specific gene. *See id.* As sequencing costs have been driven down by next generation sequencing techniques, random (also termed “shotgun”) sequencing of pieces of DNA has become more affordable, making it possible to sequence entire genomes rather than merely specific genes of interest.

DNA sequence was essential for whole-genome sequencing in particular.¹⁶⁵ In 1995, scientists sequenced the genome of a bacterium, *Haemophilis influenzae*.¹⁶⁶ A race between a private company and government coalition to sequence the human genome ensued, and the field of “genomics” continues to accelerate.¹⁶⁷ By 2003, the whole human genome had been sequenced—an achievement that took thirteen years and almost three billion dollars.¹⁶⁸ Advances in technology have driven down sequencing costs,¹⁶⁹ making sequencing fast and relatively inexpensive. For example, it is now possible to sequence more nucleotides than the entire human genome’s length for around \$1000.¹⁷⁰ Because whole-genome sequencing is now possible, future

See Pauline Ng & Ewen Kirkness, *Whole Genome Sequencing*, in 628 METHODS IN MOLECULAR BIOLOGY 215, 217–18 (Michael Barnes & Gerome Breen eds., 2010). It follows that a genetic diagnostic can only receive meaningful patent protection if the claims cover the correlation itself.

165. See Westerhoff, *supra* note 156, at 1250 tbl. 1 (diagramming the development of genomics).

166. See *id.*

167. See, Julia Karow, *The Human Genome Race: A Tale of the Tortoise and the Hare . . . and the Fly and the Worm and the Mouse*, SCIENTIFIC AMERICAN (Apr. 24, 2000), <http://www.scientificamerican.com/article.cfm?id=the-human-genome-race>.

168. See National Human Genome Research Institute, National Institutes of Health, *The Human Genome Project Completion: Frequently Asked Questions*, <http://www.genome.gov/11006943> (last visited Feb. 18, 2011).

169. See Paola Benaglio & Carlo Rivolta, *Ultra High Throughput Sequencing in Human DNA Variation Detection: A Comparative Study on the NDUFA3-PRPF31 Region*, 5 PLOS ONE e13071 (2010), <http://www.plosone.org/article/fetchObjectAttachment.action?jsessionid=C66991AA62E3EA7E86E9843CABA46165.ambra02?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0013071&representation=PDF> (reviewing and comparing next generation sequencing techniques including 454 and Illumina).

170. For example, the Duke core sequencing facility can use Illumina technology to sequence more nucleotides than the entire human genome length for \$1050. *Duke IGSP Genome Sequencing & Analysis Core Facility Price List*, <http://www.genome.duke.edu/cores/sequencing/illumina/documents/DukeIGSPSeq.CorePricelist.pdf> [hereinafter *Duke Price List*]. The need to oversequence to ensure full genome coverage and computationally reassemble the disjointed sequence fragments requires multiple sequencing runs, raising the price for whole genome sequencing at least ten-fold. See *id.* Scientists predict the \$1000 genome to be just around the corner. See, e.g., Howard Wolinsky, *The Thousand-Dollar Genome*, 8 EMBO REPORTS 900, 900–03 (2007) (speculating that a \$1000 genome will soon exist); *Question of the Year*, NATURE GENETICS, <http://www.nature.com/ng/qoty/index.html> (last visited Feb. 18, 2011) (posing the Nature Genetics question of the year for 2007: “What would you do if it became possible to sequence the equivalent of a full human genome for only \$1000?” Scientists’ answers to the question are posted on the website.). As mentioned *supra*, such sequencing now exists. See *Duke Price List*, *supra*. Further, doctors or scientists can specifically sequence the human “exome,” a portion of the genome that includes all protein-coding sequences. See Jamie Teer & James Mullikin, *Exome Sequencing: The Sweet Spot Before Whole Genomes*, 19 HUMAN MOLECULAR GENETICS R145, R145 (2010).

genetic diagnostics are unlikely to receive meaningful patent protection unless the diagnostic correlation itself is patentable. Although a \$1000 of random “shotgun” sequencing is unlikely to reveal every nucleotide in a given patient’s genome, the cost of whole genome sequencing is becoming competitive with the over \$3000 charged by Myriad for their patented *BRCA* diagnostic.¹⁷¹

The human genome projects sequenced DNA only from select individuals,¹⁷² but every person has a unique DNA sequence. Each individual version of a gene is called an allele, and certain alleles can cause disease.¹⁷³ This recognition, coupled with the ability to sequence DNA, has lead to an explosion of genetic diagnostics.¹⁷⁴

One of the first genetic tests was for Huntington’s disease, a neurodegenerative disease which famously killed folk singer Woody Guthrie.¹⁷⁵ Doctors observed that a child of a Huntington’s disease sufferer had a fifty percent chance of inheriting the disease, indicating that the disease was caused by a dominant mutation.¹⁷⁶ Because the inheritance pattern was simple and the disease was caused by a defect in a single gene, scientists could identify the genetic basis of Huntington’s disease relatively easily.¹⁷⁷

Huntington’s disease does not manifest symptoms until middle age.¹⁷⁸ Thus, although there is no cure for Huntington’s disease, some children of sufferers choose to sequence their own Huntington’s gene and determine

171. See Ass’n for Molecular Pathology v. U.S. PTO, 702 F. Supp. 2d 181, 203 (S.D.N.Y. 2010) (*BRCA* tests priced at over \$3000 each).

172. See Emily Singer, *Craig Venter’s Genome: The Genomic Pioneer Bares His Genetic Code to the World*, TEC. REV. (Sept. 4, 2007), <http://www.technologyreview.com/biomedicine/19328/?a=f;>; National Human Genome Research Institute, *supra* note 168.

173. LODISH ET AL., *supra* note 155, at 22.

174. See GENE TESTS, <http://www.genetests.org> (last visited Feb. 18, 2011). The website, run by the University of Washington, provides a comprehensive list of tests and providers in the United States. *Id.*

175. See Heidi Chial, *Huntington’s Disease: The Discovery of the Huntington Gene*, NATURE EDUCATION (2008), http://www.nature.com/scitable/topicpage/huntington-s-disease-the-discovery-of-the-851;_Hereditary-Disease-Foundation-Supports-and-Catalyzes-Critical-Achievements-Toward-the-Cure, HEREDITARY DISEASE FOUNDATION, <http://www.hdfoundation.org/achievements.php> (describing the Hereditary Disease Foundation’s role in discovering the gene); J.M. Ringman, *The Huntington Disease of Woody Guthrie: Another Man Done Gone*, 20 COGNITIVE BEHAVIORAL NEUROLOGY 238 (2007).

176. See Chial, *supra* note 175.

177. This relative ease does not reflect absolute ease. The research program took over a decade. See *id.*; Hereditary Disease Foundation, *supra* note 175.

178. Chial, *supra* note 175.

whether they have inherited the disease allele.¹⁷⁹ This information can guide their life choices.

The Huntington's diagnostic is only one of many tests for genetic diseases caused by mutation in a single gene. Few single gene mutation tests enable individuals to take specific actions to prevent their own disease, although *BRCA* positive patients, for example, can elect prophylactic double mastectomy.¹⁸⁰ Actual cures are even less common, but the diagnoses can help guide medical research and life planning decisions. For example, some Ashkenazi Jews base family planning decisions in part on the results of genetic tests for disease alleles that often lie dormant in that population.¹⁸¹

B. OBTAINING NON-GENETIC MEDICAL DATA FROM PATIENT SAMPLES

After the advantages of large scale acquisition of raw genetic data were revealed, interest grew in obtaining other large medical data sets. The various approaches for analyzing comprehensive data sets are denoted with the suffixes “ome” and “omics.”¹⁸² For example, the entirety of proteins in a given sample is the “proteome” and research on the proteome is “proteomics.”¹⁸³

The unifying feature of the “omics” is that they involve large investments of money and expertise in building tools that make data gathering cheaper, easier, and more uniform.¹⁸⁴ Transcriptomics was one of the earliest “omics”, enabled by the Affymetrix-developed technology of chip microarray hybridization, which allowed simultaneous analysis of all the RNA transcripts

179. *Id.*

180. L. Lustumbo, et al., *Prophylactic Mastectomy for the Prevention of Breast Cancer*, 11 COCHRANE DATABASE SYSTEMATIC REVIEWS at 54–55 (2010) (reviewing and synthesizing studies of women receiving bi-lateral prophylactic mastectomy).

181. See, e.g., V.R. Sutton, *Tay-Sachs Disease Screening and Counseling Families at Risk for Metabolic Disease*, 29 OBSTETRICS & GYNECOLOGY CLINICS OF N. AM. 287, 287 (2002) (reviewing testing procedures and family planning options and noting that for non-Ashkenazi individuals, potential Tay-Sachs carriers should be screened “enzymatically” for protein activity, rather than genetically for presence of the particular mutation common among Ashkenazi).

182. See Joshua Lederberg & Alexa T. McCray, ‘Ome Sweet ‘Omics—A Genealogical Treasury of Words, 15 THE SCIENTIST 8, 8 (2001).

183. Barbara Marte, *Proteomics*, 422 NATURE 191, 191 (2003). The proteome alternately refers to the entire set of proteins potentially made from the genome of a given organism, or to the set of proteins actually made at a given time, given tissue, or given cell. *Id.*

184. See Westerhoff, *supra* note 156, at 1249.

in a cell or tissue (the “transcriptome”).¹⁸⁵ Proteomics developed next.¹⁸⁶ Proteins are more chemically diverse than DNA and RNA molecules and therefore relatively challenging to apply the “omics” model to.¹⁸⁷ One particular approach is analogous to the blind process of genomic “shotgun” sequencing: LC/MS, in which a collection of proteins are chopped into pieces, separated, and analyzed by mass spectrometry to determine each fragment’s charge to mass ratio and deduce which amino acids compose it.¹⁸⁸ By comparison to other protein fragments or to genomic data, it is then possible to deduce the order of these amino acids and obtain the protein sequence.¹⁸⁹ Another approach—2D gel electrophoresis—involves taking two samples, separating all the proteins in each sample, and then identifying the protein differences between the samples, possibly by mass spectrometry.¹⁹⁰ Yet another approach is to test pairs of proteins for their ability to stick together inside cells, thereby mapping all the potential physical interactions between pairs of proteins.¹⁹¹

The sugars, fats, hormones, and other small molecules that comprise the metabolites are even more chemically diverse than proteins.¹⁹² It follows that whole-metabolome analysis remains at best extremely challenging.¹⁹³ Metabolomics requires first the separation of small molecules—for example, by gas chromatography, HPLC, or capillary electrophoresis.¹⁹⁴ Each of these

185. See Mark Schena et al., *Quantitative Monitoring of Gene Expression Patterns with a Complementary DNA Microarray*, 270 SCIENCE 467, 467–70 (1995) (reporting the first use of a microarray for global transcript profiling).

186. See Akhilesh Pandey & Matthias Mann, *Proteomics to Study Genes and Genomes*, 405 NATURE 387, 387 (2000) (reviewing early post-genomic advances in proteomics).

187. VOET ET AL., *supra* note 155, at 80–81, 94–95. Proteins are made up of strings of amino acids. *Id.* at 94–95. Twenty different amino acids are used and these twenty vary widely in chemical properties—literally ranging from “like oil” to “like water” and from positive to negative electrical charge. *Id.*

188. Ruedi Aebersold & Matthias Mann, *Mass Spectrometry-Based Proteomics*, 422 NATURE 198, 198 (2003).

189. *Id.* at 202.

190. *Id.* at 200.

191. Eric Phizicky et al., *Protein Analysis on a Proteomic Scale*, 422 NATURE 208, 208 (2003).

192. See Haleem Issaq et al., *Analytical and Statistical Approaches to Metabolomics Research*, 32 J. SEPARATION SCI. 2183, 2183–84 (2009) (describing diverse metabolites, of which amino acids are one subset).

193. See *id.*

194. *Id.* at 2186–89. Table 1 tallies the occurrences of each approach using keyword searches of PubMed, a database of scientific publications. *Id.* at 2189 tbl. 1. The higher values in the right-hand “metabolite” column suggest that each separation technique is used most frequently to study metabolites one or two at a time, outside the metabolomics context.

techniques works well on some types of metabolites and poorly or not at all on other types.¹⁹⁵ Furthermore, the precise settings used in a separation procedure also affect which metabolites can be isolated best.¹⁹⁶ The separated metabolites are then analyzed, often by mass spectrometry.¹⁹⁷ Nuclear magnetic resonance (NMR) can analyze either separated or unseparated samples.¹⁹⁸

The development of uniform techniques for gathering data on any given DNA, protein, or metabolite makes it increasingly difficult to protect a diagnostic technique by patenting a specific data-gathering method. The techniques used in metabolomics are generally the same basic techniques that would be used to analyze a single metabolite.¹⁹⁹ The '623 *Prometheus* diagnostic patent, for example, claims HPLC detection.²⁰⁰ Of course, a tailored version of detection is cheaper and easier. It remains cheaper to sequence a single gene than the entire genome.²⁰¹ Similarly, it is easier to detect and measure a protein of interest with a single specific antibody than by simultaneously analyzing the thousands of proteins in a sample.²⁰² Still, the continuing advance of “omics” techniques makes data-gathering patents

Id. It is worth noting that metabonomics is largely synonymous with metabolomics. *Id.* at 2183.

195. *See id.* at 2186.

196. *See, e.g., id.* at 2187 (“HPLC separations are not limited to one mode (mechanism) of separation, which is an advantage when a global metabolome analysis is required. It can be tailored to the separation of a specific class of compounds using RP, normal phase, ion exchange, chiral, size exclusion, hydrophilic interaction chromatography (HILIC), and mixed modes.”).

197. *See id.* at 2189–90.

198. *Id.* at 2189–90.

199. *See id.* at 2189; *supra* note 124 and accompanying text.

200. *See U.S. Patent No. 6,355,623 col. 20 l. 38 (filed Apr. 8, 1999) (dependent claim 6).*

201. Cf. *Duke Price List*, *supra* note 170. Compare the \$1.75 cost of “traditional” Sanger sequencing, providing 800–900 contiguous bases, with the cost of Illumina sequencing, which can sequence 200 million 36–72 nucleotide patches in a single run. *Id.*

202. Antibodies themselves are proteins, produced the immune systems of humans and other vertebrates to stick or “bind” to foreign molecules, thereby tagging the foreign molecules for destruction by other immune system effectors. LODISH ET AL., *supra* note 155, at 73. Over an animal’s life, it encounters new foreign molecules, and develops new antibodies to tag these new molecules for destruction. *Id.* at 73, 237. By harnessing this process, scientists can produce an antibody against “your favorite protein.” *Id.* at 237–39. Antibody patents are granted not on a specific antibody, but on the collection of all antibodies that tag a specific molecular motif, or epitope—for example, a specific fragment of protein. *See Deborah Lu et al., The Patentability of Antibodies in the United States*, 23 NATURE BIOTECHNOLOGY 1079, 1079 (2005) (citing *Noelle v. Lederman*, 355 F.3d 1343, 1350 (Fed. Cir. 2004)). Most proteins will have many different epitopes susceptible to antibody detection. LODISH ET AL., *supra* note 155, at 73, 237.

increasingly easy to invent around. If in fact granting patent exclusivity on new medical diagnostics represents good policy, permitting direct patenting of diagnostic correlations could soon be the only option.

III. THE POLICY BASIS FOR DIAGNOSTIC METHOD PATENTS

Four related trends support granting patents on diagnostics. First, scientists are attempting to tackle complex diseases in which multiple genes interact with environmental factors. The challenges these diseases present belie the notion that diagnostic medical research has become intellectually or financially trivial. Second, genetic diagnostics are increasingly connected with the development of new therapies. Third, genetic diagnostics—specifically in the field of personalized medicine—now let doctors avoid unnecessary and potentially harmful therapies. Fourth, it will become increasingly difficult to enforce diagnostic method patents against individual patients and their doctors.

A. COMPLEX DISEASES ARE HARD TO STUDY

One justification for patents is that they provide an incentive for expensive research, development, and commercialization by providing assurance that inventors or their licensees will have exclusive rights to market inventions.²⁰³ If research and development becomes trivial, this justification is undermined. Complex genetic diseases caused by defects in more than one gene (“polygenic diseases”) belie the notion that discovering diagnostic correlations is now cheap or routine. Even though genomics is the most advanced of the “omics” disciplines, the sequencing and data processing necessary to discover such correlations remain expensive, and the sample collection and organization are also likely to be extremely costly. The more genes and alleles that contribute to a disease, the more patient samples required to discover its cause. It is entirely possible as a matter of mathematics that some complex genetic diseases would remain underdetermined even when working with samples from the entire world population.²⁰⁴

203. See Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265, 266, 276–78 (1977); Peter S. Menell & Suzanne Scotchmer, *Intellectual Property Law*, in 2 HANDBOOK OF LAW AND ECONOMICS 1474, 1525 (A. Mitchell Poninsky & Steven Shavell eds., 2007); Ted Sichelman, *Commercializing Patents*, 62 STAN. L. REV. 341, 373–76 (2010).

204. See generally Teri A. Manolio et al., *Finding the Missing Heritability in Complex Diseases*, 461 NATURE 747, 449 (2009) (“Sample size is even more strongly affected by small odds

The current best mode for studying gene correlations with diseases is genome-wide association (GWA).²⁰⁵ Researchers using this method first detect differences between the genomes of donor samples.²⁰⁶ Most commonly, researchers analyze single nucleotide differences (“single nucleotide polymorphisms,” or “SNPs”), though other differences gene copy-number variants (CNVs) can be used.²⁰⁷ The researchers then look for statistical correlations between specific SNPs and a phenotype.²⁰⁸ Because adjacent DNA segments are usually inherited together, researchers often observe that a cluster of adjacent SNPs all correlate with a phenotype.²⁰⁹ The researchers must then conduct a more targeted analysis to determine which alleles of which gene in the SNP neighborhood actually cause the phenotype.²¹⁰ One study, funded by Schering-Plough,²¹¹ analyzed over 1,600 genomes from patients in treatment for Hepatitis C.²¹² In their attempt to identify alleles that made some of these patients resistant to treatment-induced anemia, the researchers analyzed over 500,000 SNPs per study volunteer.²¹³ They discovered a cluster of SNPs in a region of chromosome 20, and through several rounds of further analysis, discovered that variants of one gene, inositol triphosphatase (*ITPA*), protected patients from therapy-induced anemia.²¹⁴ There also were hints that the study might have discovered even more genes if they had tested more patient samples. Several SNPs showed weak, statistically insignificant association with the anemia phenotype.²¹⁵ Some of these SNPs were near a gene already known to be involved in some forms of anemia, suggesting that their weak association was

ratios than by small [minor allele frequency], so low frequency and rare variants will need to have higher odds ratios to be detected.”).

205. See generally Mark I. McCarthy et al., *Genome-Wide Association Studies for Complex Traits: Consensus, Uncertainty, and Challenges*, 9 NATURE REVIEWS GENETICS 356 (2008) (reviewing the value and challenges of GWA studies).

206. See *id.* at 359–60.

207. See *id.* at 359–60, 365 (“GWA scans have focused almost exclusively on the detection of effects that are attributable to common SNPs.”).

208. See *id.* at 360–62.

209. See *id.* at 362.

210. See *id.* at 364 (“Because genome-wide association (GWA) studies directly genotype only a small proportion of the variants that segregate within the population examined, it is unlikely that the causal variant(s) will be among those for which genotype data are available.”).

211. Jacques Fellay et al., *ITPA Gene Variants Protect Against Anemia in Patients Treated for Chronic Hepatitis C*, 464 NATURE 405, 408 (2010).

212. *Id.* at 405.

213. *Id.*

214. *Id.* at 405, 407.

215. *Id.* at 405.

real and that 1,600 patient samples were simply not powerful enough to reveal all the genes involved in the phenotype.²¹⁶

A particularly striking example of the difficulty of studying polygenic phenotypes comes from research on height. 80% of height variation is attributable to inheritance.²¹⁷ Teams of researchers conducting smaller studies of other phenotypes also collected data on patient height and combined all their data into one large study.²¹⁸ They analyzed 63,000 patient samples for approximately 500,000 SNPs each at a cost of roughly \$30,000,000.²¹⁹ The researchers discovered 54 genes involved in determining height, including 40 new genes.²²⁰ Collectively, these genes accounted for only 5% of height variation—only around 1/16 of the total genetically determined height variation.²²¹

As the \$30,000,000 cost of the height study indicates, analyzing data is not the only difficulty when studying complex diseases. Gathering massive quantities of raw data on the chemical composition of a medical sample remains expensive, although it grows easier by the year.²²² Furthermore, collecting medical samples is not trivial. Only licensed medical professionals, whose time is expensive, can collect samples. Researchers must identify or screen sample donors, and may often need to compensate them. Researchers must also take safety precautions to avoid possible infection via blood or other means. Finally, donors must give informed consent to the sample collection and the research.²²³

216. *Id.* at 405. Fellay et al state that

[f]urther association signals were detected in the hexokinase 1 gene (HK1) This result is not genome-wide significant, but supported by other lines of evidence: rare HK1 mutations cause severe haemolytic anaemia in both humans and mice; in a recent GWAS, HK1 SNPs associated with differences in Hb concentration and haematocrit in Europeans.

Id.

217. See Peter M. Visscher, *Sizing Up Human Height Variation*, 40 NATURE GENETICS 489, 489 (2008).

218. See *id.* at 489–90 (2008) (reviewing three different studies on height genetics, each of which analyzed the aggregated data acquired during multiple smaller studies).

219. *See id.*

220. *See id.* at 490 (2008).

221. See Teri A. Manolio et al., *supra* note 204, at 747–48 tbl.1 (summarizing the percentage of heritability explained for a variety of physiologic attributes and diseases).

222. See, e.g., Benaglio & Rivolta, *supra* note 169, at 1; *Duke Price List*, *supra* note 170.

223. See generally Dean Troyer, *Biorepository Standards and Protocols for Collecting, Processing, and Storing Human Tissues*, 441 METHODS IN MOLECULAR BIOLOGY 193 (B.C.S. Liu ed.) (describing the technical, administrative, personnel, and ethics requirements for banking medical samples for research).

New research studies often require collecting new samples, rather than reusing old ones. Medical histories of the sample donors must exist to draw correlations with the sample data, but a given collection of donors may not be rich in every syndrome.²²⁴ Although collecting detailed medical histories of donors would increase the potential for sample reuse, ethical limitations apply, because acquiring excessive information can compromise donor anonymity.²²⁵ Sample reuse is also complicated by informed consent. Many research groups and institutions believe it impossible for a donor to grant generic informed consent to all research projects.²²⁶ In one recent scandal, Native Americans who had donated genetic material for diabetes research withdrew their samples from an Arizona research group after discovering that the samples had been used for other research projects, including one that revealed historical inbreeding.²²⁷

The private sector may be better equipped than the public sector to handle studies on complex diseases, because academia favors smaller-scale projects with more scope for innovation by individual investigators and because industry is more easily incentivized to undertake the organizational and funding challenges.²²⁸ Although the human genome project represents a partial counter-example in that the publicly funded project was promoted and completed, organizing political support for large scale science projects can be challenging.²²⁹

224. See *id.* at 204–05, 214 n.5.

225. Indeed, even pure genomic data may be impossible to anonymize. See Jennifer Couzin, *Whole-Genome Data Not Anonymous, Challenging Assumptions*, 321 SCIENCE 1278 (2008).

226. But see generally David Wendler, *One-Time General Consent for Research on Biological Samples: Is It Compatible With the Health Insurance Portability and Accountability Act?*, 166 ARCHIVES INTERNAL MED. 1449 (2006) (discussing mechanisms by which generalized consent to research could be made compatible with the HIPAA medical privacy statute).

227. Amy Harmon, *Indian Tribe Wins Fight to Limit Research of Its DNA*, N.Y. TIMES, Apr. 21, 2010, at A1, available at https://www.nytimes.com/2010/04/22/us/22dna.html?_r=1.

228. See, e.g., Karow, *supra* note 167. Karow states:

The race to sequence the human genome—now in its final laps—is speeding up. Some three weeks ago, the Maryland company Celera Genomics—a relative newcomer to the track, headed by Craig Venter—appeared to lurch ahead of the favored contestant, the publicly funded Human Genome Project. On April 6, Celera announced that after only seven months of work, they had deciphered close to all 3,000,000,000-odd base pairs, or letters of the genetic alphabet, in the human genome.

Id.

229. See, e.g., Paul Berger, *For Sale: \$20 Million Particle Accelerator, Never Used*, WIRED (Sept. 9, 2009, 7:54 PM), at 2, <http://www.wired.com/wiredscience/2009/09/super-collider-gallery/2/> (describing the Superconducting Supercollider, abandoned half-finished in Texas).

Private sector research on complex genetic diseases would be disincentivized by the inability to obtain patents. Diagnostic testing and analysis is regulated lightly by the FDA and, absent any regulatory link to a drug, there is little barrier to entry into the diagnostic market by free riders.²³⁰ Indeed, in 2009 the average post-discovery cost to develop a single-gene diagnostic testing kit was only \$10,000.²³¹ Assuring potential inventors that they can recoup their research costs without competition from free riders is one traditional policy rationale underlying the U.S. patent system.

There is some concern that research on polygenic diseases could be inhibited by thickets of gene patents claiming DNA sequences. Patents on genetic diagnostics are more limited in scope than traditional DNA product patents.²³² Even under the broadest interpretation, modeled on Justice Breyer's *LabCorp* dissent, genetic diagnostics would only confer exclusivity in relation to a specific function of a gene. Newly discovered functions would not be covered, and thus genetic diagnostic patents present less of a concern for this developing field. Furthermore, there is little empirical evidence that such thickets pose a significant problem.²³³

230. See James T. O'Reilly, "Personalized Medicine" Diagnostic Issues, 1 FOOD & DRUG ADMIN. § 18:114.50 (3d ed. 2010) (noting that if tests are performed at a central lab, the facility is overseen by the Center for Medicare and Medicaid, but FDA clinical testing is required to distribute testing kits to doctors or pharmacies). When a diagnostic test is coupled to an FDA regulated drug, full pharmaceutical regulations apply. See Jeanene Swanson, *Companion Diagnostics Take Off*, GENOMEWEB (Oct. 2009), <http://www.genomeweb.com/dxpgx/companion-diagnostics-take> (describing the recent surge of "companion" diagnostics approved in connection with drug prescribing, usage, or labelling).

231. SEC'Y'S ADVISORY COMM. ON GENETICS, REVISED DRAFT REPORT ON GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS, HEALTH, AND SOC'Y, *supra* note 147, at 31.

232. Compare U.S. Patent No. 5,747,282 col. 153 l. 57 (filed June 7, 1995) (claim 1) ("An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2."), with U.S. Patent No. 6,033,857 col. 169 l. 47 (filed Mar. 20, 1998) (claim 2) ("A method for diagnosing a predisposition for breast cancer in a human subject which comprises comparing the germline sequence of the BRCA2 gene or the sequence of its mRNA in a tissue sample from said subject with the germline sequence of the wild-type BRCA2 gene or the sequence of its mRNA, wherein an alteration in the germline sequence of the BRCA2 gene or the sequence of its mRNA of the subject indicates a predisposition to said cancer."). See also Tina Saladino, Note, *Seeing the Forest Through the Trees: Gene Patents and the Reality of the Commons*, 26 BERKELEY TECH. L.J. 301, 318 (2011).

233. See Lisa Larrimore Ouellette, *Access to Bio-Knowledge: From Gene Patents to Biomedical Materials*, 2010 STAN. TECH. L. REV. N1, N11–13 (2010).

B. DIAGNOSTIC METHOD PATENTS CAN INCENTIVIZE THERAPY DEVELOPMENT

One traditional rationale for patents is that they provide an incentive for risky or expensive research and development.²³⁴ Patents on diagnostic methods can not only incentivize discovery and development of complex diagnostics,²³⁵ but they can also incentivize the discovery and development of new medical therapies. A diagnostic method patent can act as a drug target patent for therapy development.²³⁶ Furthermore, the FDA has approved some therapies that can only be prescribed after performing a companion diagnostic test.²³⁷ Patents on such companion diagnostics increase the chances that the inventor's exclusive right to provide the treatment will survive litigation by generic drug manufacturers.²³⁸ If a companion diagnostic patent is filed after the physical drug patent, the diagnostic patent will extend the functional term of patent protection.²³⁹

As biomedical science develops, it is increasingly possible to understand the causes and consequences of diseases at a molecular level. This understanding enables highly specific diagnostics based on the presence of particular alleles, proteins, or metabolites. At the same time, detailed molecular understanding of a disease lets researchers design therapies that directly target the molecular mechanism causing a disease. These parallel

234. See Kitch, *supra* note 203, at 266, 276–78; Menell & Scotchmer, *supra* note 203, at 1525; Sichelman, *supra* note 203, at 373–76.

235. See *supra* Section III.A.

236. Cf. Marvin M. Goldberg, *Trastuzumab, a Recombinant DNA-Derived Humanized Monoclonal Antibody, a Novel Agent for the Treatment of Metastatic Breast Cancer*, 21 CLINICAL THERAPEUTICS 309, 309 (1999) (stating that the HER2 protein acts as a diagnostic biomarker for a class of breast cancers, because HER2 has carcinogenic activity. Genentech developed a therapy that specifically disrupts that carcinogenic activity.).

237. See Swanson, *supra* note 230 (“The Personalized Medicine Coalition, a nonprofit advocacy group, reports that there are currently about 40 drugs in the US that have companion diagnostic tests associated with them—whether that means as a requirement to their being prescribed, a recommendation for use, or label information that lists genetic susceptibility relating to efficacy or dose.”).

238. See Gregory J. Glover, *Securing Exclusivity for Your Product Throughout Its Life Cycle*, 878 PLI/PAT 609, 614, 616–19 (2006) (stating that the FDA allows generic manufacturers to submit generic drugs for approval only if the relevant “Orange Book” patents covering the original drug are expired or invalid, therefore if a “method of using such drug” is patented, a generic manufacturer must invalidate two patents to enter the market).

239. See 35 U.S.C. § 154 (2006) (providing that patent terms in the United States run for fixed periods from the date of filing—presumptively twenty years, but subject to patent term modifications).

applications of basic medical discoveries interact in important ways, illustrated by the following example from the genetics of cancer biology.

Cancers are polygenic diseases. For cancer to arise, cells must collect a series of mutations in their DNA, with each mutation conferring new traits.²⁴⁰ For example, the “parent” cell which grows into a prostate tumor might first acquire a mutation that makes it likely to acquire mutations quickly.²⁴¹ The cell might then need to acquire mutations allowing it to grow more quickly, to avoid natural cell death pathways that would limit its lifespan, to avoid the immune system’s cancer monitoring processes, and to obtain adequate blood supply.²⁴² This list of functional shifts en route to becoming full blown cancer is non-exhaustive, and each functional shift could be enabled by mutations to different single genes or combinations of genes.²⁴³

Even though two cancers of the same general type might appear similar, the different mutations they acquire might mean that they are different at the cellular and molecular level.²⁴⁴ For example, a subset of cancers might express a molecule that confers resistance to chemotherapy, while expression of another molecule might make another subset of cancers a promising target for developing a new chemotherapy. One prominent example is the *HER2*-type breast cancer.²⁴⁵ The *HER2* gene is mutated in a subset of breast cancers.²⁴⁶ Unlike *BRCA*, *HER2* mutations are not generally inherited and therefore are not easily tested for as an indicator of increased risk of developing breast cancer.²⁴⁷ Instead, *HER2* can become mutated in a single cell so that the *HER2* gene makes elevated levels of *HER2* protein, which can lead to cancer.²⁴⁸ Genentech recognized that *HER2* mutations were implicated in a subset of breast cancers and developed a therapy that

240. LODISH, *supra* note 155, at 940–41.

241. *Id.* at 964.

242. *Id.* at 951–61.

243. *Id.*

244. See, e.g., William D. Foulkes et al., *Triple-Negative Breast Cancer*, 363 NEW ENG. J. MED. 1938 (2010) (reviewing the varied properties of breast cancers that have no known cancer gene).

245. See Goldenberg, *supra* note 236, at 309.

246. See Foulkes et al., *supra* note 244, at 1939 (stating that 15–20% of breast cancers have extra copies of *HER2*).

247. See P. Kenemans et al., *Oncogenic Pathways in Hereditary and Sporadic Breast Cancer*, 49 MATERITAS 34, 37 tbl. 1 (2004).

248. Frédérique Penault-Llorca et al., Emerging Technologies for Assessing *HER2* Amplification, 132 Am J Clin Pathol 539, 539 (2009).

inhibited HER2 protein activity and turned it partially “off.”²⁴⁹ Based on the mechanism of the treatment, the HER2 inhibition therapy is effective only against breast cancers expressing the HER2 protein.²⁵⁰

Because cancers are so varied and respond to different therapies, matching potential therapies to specific cancer subtypes can be essential for proving efficacy in FDA clinical trials. Indeed, Genentech’s current goal is to always have a matching diagnostic test when they initiate clinical trials.²⁵¹ Some doctors believe that the FDA’s recent withdrawal of provisional approval for the cancer drug Avastin could have been avoided if a diagnostic test existed that could specifically identify the small fraction of patients for whom the drug is effective.²⁵²

While increasing the odds of FDA approval is a powerful incentive to discover diagnostics that help target therapies, granting patents on such diagnostics can also be a valuable means of incentivizing therapy development. Additionally, granting patents on diagnostics with therapeutic tie-ins can discourage a particularly unproductive form of drug development gamesmanship which has been rising in the pharmaceutical industry—the creation of marginally distinctive “mimic” or “me too” drugs which, unlike true generics, can win patent protection and require full FDA testing prior to approval.²⁵³

249. See Goldenberg, *supra* note 236, at 309. The treatment’s precise mechanism of action is uncertain. See Rebecca A. Burrell, *Targeting Chromosomal Instability and Tumour Heterogeneity in HER2-Positive Breast Cancer*, 111 J. CELLULAR BIOCHEMISTRY 782, 783 (2010) (“Trastuzumab has multiple potential mechanisms of action”).

250. Frédérique Penault-Llorca et al., *supra* note 248, at 540.

251. *Personalized Medicine Could Shake Up Drug Industry*, EUROPEAN AIDS TREATMENT GROUP (Apr. 3, 2010), <http://www.eatg.org/eatg/Global-HIV-News/Pharma-Industry/Personalized-medicine-could-shake-up-drug-industry>. A Genentech spokeswoman stated that “Genentech is always looking for biomarkers to help identify patients for its new drugs and builds biomarkers into all of its pipeline products.” *Id.*

252. Andrew Pollack, *F.D.A. Rejects Use of Drug in Cases of Breast Cancer*, N.Y. TIMES, Dec. 16, 2010, at A1, available at <https://www.nytimes.com/2010/12/17/health/policy/17drug.html> (“Many experts said Avastin appeared to help some patients live longer. But right now, it is impossible to predict in advance which patients. If Genentech could figure out how to predict this—such as by a genetic test—it would clear the way for the drug to retain approval for a subset of patients.”).

253. Robert A Bohrer, *Reach-Through Claims for Drug Target Patents: Rx for Pharmaceutical Policy*, 26 NATURE BIOTECHNOLOGY 55, 55–56 (2008); Ron A. Bouchard et al., *The Pas de Deux of Pharmaceutical Regulation and Innovation: Who’s Leading Whom?*, 24 BERKELEY TECH. L.J. 1461, 1482 (2009) (“Specifically, we argue that the global pharmaceutical industry is leaning away from the development of new drugs and towards incremental changes in existing drugs as a result of firms locking in to discrete IPR rights targets provided for by law.”).

Patents currently play a major role in incentivizing therapy development. Therapy development comprises two stages: first, initial discovery and pre-clinical development, and second, clinical trials mandated by the FDA.²⁵⁴ In the biotechnology industry, initial discovery and development costs an average of \$615 million, including capital costs and accounting for failures, while FDA mandated clinical testing adds another \$626 million.²⁵⁵

Although exclusive rights conferred by patents play a role in incentivizing companies to move forward with FDA trials, the clinical testing itself represents a significant barrier to entry—both as an expense and as a regulatory hurdle. In some instances, generic drug manufacturers can avoid having to repeat clinical trials, but only if the original drug maker has no valid patents covering the drug.²⁵⁶ As a result, certain companion diagnostics might reduce risk for a company considering entering clinical trials, and thereby increase drug development incentives. Yet, in the case of biologic medicines like purified proteins, the clinical trial barrier often provides insurmountable exclusivity.²⁵⁷ Thus, FDA approval can itself confer first movers with benefits that parallel the exclusive right granted by patent. Yet even in these cases, patents can still confer beneficial exclusivity, because nearly half the cost of therapy development occurs before the FDA approval process has begun.²⁵⁸

Patents are most important for biologic medicines at the discovery and development stage. At this stage a company may try a wide array of formulations as a potential therapy. A company developing a traditional small-molecule pharmaceutical might test hundreds or thousands of potential drugs to determine whether they have promising affects in a relatively affordable system, possibly cells grown on a lab bench or laboratory mice.²⁵⁹ A drug company then generally synthesizes a collection of potential drugs similar to the best initial candidates and repeats the testing, at some point moving to more expensive preclinical and clinical testing of the most

254. Joseph A. DiMasi & Henry B. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 477 (2007).

255. *Id.*

256. Glover, *supra* note 256, at 618–19.

257. See DiMasi & Grabowski, *supra* note 254, at 477; Linfong Tzeng, Note, *Follow-on Biologics, Data Exclusivity, and the FDA*, 25 BERKELEY TECH. L.J. 135, 141 (2010).

258. Cf. DiMasi & Grabowski, *supra* note 254, at 477 (discovering that, in the biotechnology industry, \$615 million of the \$1.241 billion cost of drug development is incurred before clinical trials begin).

259. See, e.g., Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356–63 (Fed. Cir. 2007) (describing discovery of diabetes drug in the context of obviousness analysis); *In re Brana*, 51 F.3d 1560, 1562–63 (Fed. Cir. 1995) (describing discovery of a cancer chemotherapy agent in the context of utility analysis).

promising candidates.²⁶⁰ Similarly, a biotechnology company attempting to turn off a protein like HER2 using an antibody may test many monoclonal antibodies, each of which attaches to the target protein in a different way or at a different epitope location on the protein.²⁶¹

While the physical products tested are patentable, they are all targeted to a single market. Like patients with high cholesterol who take only a single statin (such as Lipitor), patients will generally receive little benefit from taking two drugs with the same mode of action.²⁶² This means that the exclusivity benefit of a product patent is severely compromised, because a competitor need not replicate any specific therapy to enter the market. This potential for competition might have little effect on incentives to develop potential “blockbuster” drugs, but it could harm incentives to develop more economically marginal therapies.

Lack of economic incentives to develop drugs for small markets—termed “orphan” drugs—is a long standing problem in the pharmaceutical industry. The Orphan Drug Act somewhat addresses this problem by granting seven years of exclusivity post-FDA approval.²⁶³ This problem is increasingly significant because the parallel growth of new diagnostics and targeted therapeutics actually creates smaller potential markets as it

260. See, e.g., *Takeda* 492 F.3d at 1356–63.

261. See Davinder S. Gill, *Protein Pharmaceuticals: Discovery and Preclinical Development*, in PHARMACEUTICAL BIOTECHNOLOGY 28, 29 (Carlos Alberto Guzman & Giora Z. Feuerstein eds., 2009) (describing wide scope of the initial screening process and stating “[i]ncreasingly however, the trend has been to carry out functional assays upfront where possible”).

262. See Robert J. Herman, *Drug Interactions and the Statins*, 161 CAN. MED. ASS'N J. 1281, 1285 (1999) (“Drug interactions commonly occur in patients taking multiple medications. Although there may be some differences in the potential for statin preparations to be involved in serious adverse drug reactions, in general, they have a proven record of safety and efficacy in large clinical studies.”). Although mimic drugs often provide little benefit over the first drug in a family, one important exception occurs in anti-retroviral combination therapy against H.I.V. Although many of the best combination therapies rely on drugs with different modes of action (e.g., a nucleoside analog inhibitor (NAI) and a protease inhibitor), combinations of NAIs are more effective than treatment with a single NAI. See Stefano Alcaro, *Molecular and Structural Aspects of Clinically Relevant Mutations Related to the Approved Non-Nucleoside Inhibitors of HIV-1 Reverse Transcriptase*, DRUG RESISTANCE UPDATES at 1 (Feb. 3, 2011) (electronic publication ahead of print, available online at [Id.](http://www.sciencedirect.com/science?_ob=MImg&_imagekey=B6WDK-523DFN2-1-1&_cdi=6769&_user=4420&_pii=S1368764611000033&_origin=search&_coverDate=02%2F03%2F2011&_sk=99999999&zview=c&wchp=dGLzVzz-zSkzS&md5=a50b32d956fb9d85562538fd623d25d&ie=/sdarticle.pdf)

263. See 21 U.S.C. § 360cc (2006). Orphan drug development also receives tax incentives. See Small Business Job Protection Act of 1996, Pub. L. No. 104-188 § 1205.

subdivides diseases. For example, not every breast cancer is a *HER2* breast cancer.²⁶⁴ Even if the subdivision does not create a true orphan disease, it may create markets so small that they can only support a single drug with any given mode of action. Thus, after the first drug with a given mode of action is approved, it may not make sense for another firm to develop a mimic with the same mode of action. A firm might even decline to continue development if another drug of the same class has already entered the FDA process, reasoning that if the first drug succeeds, the market will be too small to justify development costs, while if the first drug fails, the odds that the second fails will increase too much to justify development costs. Such behavior would not greatly harm the public interest, because one drug would already exist. Indeed, creation of non-identical mimic therapies is a wasteful expenditure of scientific resources incentivized by the current patent and FDA approval system.²⁶⁵ Furthermore, it should be easy for firms to determine which among them has won the race at each stage of FDA testing.

In contrast, initial discovery and development is more opaque. Even when firms choose to publicize their early progress, the lack of clear benchmarks and presence of undiscovered hurdles make it difficult to determine if any firm has an insurmountable lead. The risk of coming in second can of course create an incentive to rush forward with development, but the limited term of patent protection and the costs of research capital already provide incentives for speed. More significantly, the risk of finishing second can discourage early stage development entirely.

Patents on molecular diagnostics required for therapy can act as patents on particular modes of drug action.²⁶⁶ Such patents encourage companies to invest in discovery and initial development by removing uncertainty regarding potential competition.²⁶⁷ The patents simultaneously deter pharmaceutical companies from socially wasteful investments in mimic therapeutics.²⁶⁸ DNA product patents have served a similar role in the biotechnology industry.²⁶⁹ The therapy incentivizing role of genetic diagnostics would be particularly valuable if DNA product patents are

264. See Foulkes, *supra* note 244.

265. See Bouchard, *supra* note 253, at 1482.

266. See Bohrer, *supra* note 253, at 55.

267. This is a traditional “prospect” rationale for the patent system. See Kitch, *supra* note 203, at 266, 276–78; Menell & Scotchmer, *supra* note 203, at 1525.

268. See Bohrer, *supra* note 253, at 55.

269. See Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1676–77 (2003).

invalidated.²⁷⁰ Indeed, diagnostic correlation patents represent a less preclusive alternative to traditional DNA purified product patents.²⁷¹ Unlike a product patent, which precludes all use of a particular gene, a genetic diagnostic patent is limited to the context of a specific disease. Thus, a genetic diagnostic patent cannot preclude undiscovered roles for the gene. It follows that diagnostic method patents can function as narrow “target” patents, providing exclusivity to incentivize therapy development targeting a specific gene or gene-product as it functions to cause a specific disease.

C. DIAGNOSTIC METHOD PATENTS CAN INCENTIVIZE BENEFICIAL INACTION

Medical therapies do not always cure. As discussed in Section III.B., cancers are varied and often a therapy will only work against a specific subtype. Not every breast cancer makes HER2, so not every breast cancer is treatable with Genentech’s anti-HER2 drug, Avastin.²⁷² Similarly, certain patients cannot metabolize particular drugs into medically active forms. The *Prometheus* thiopurines serve as just one example.²⁷³

These therapies can be expensive and have dangerous side effects. Chemotherapy agents for cancer treatment are famously harsh.²⁷⁴ The *Prometheus* diagnostic is useful in part because it helps doctors protect their patients from toxic concentrations of thiopurine metabolites.²⁷⁵ Knowing under what circumstances a drug will work can be extremely valuable in obtaining FDA approval.²⁷⁶ After full FDA approval, although patients would benefit from knowledge of what subsets of disease a drug will treat, that same knowledge might financially harm drug companies and medical

270. *See Ass’n for Molecular Pathology v. U.S. PTO*, 702 F. Supp. 2d 181, 232 (S.D.N.Y. 2010) (holding DNA product patents invalid under 35 U.S.C. § 101); *Saladino*, *supra* note 232, at 318.

271. *See supra* note 232.

272. *Foulkes*, *supra* note 244.

273. *See generally* *Wang*, *supra* note 135, at 6–9 (discussing thiopurine metabolism and other genetic pathways that influence drug efficacy).

274. *See Chemotherapy Side Effects Fact Sheets*, NATIONAL CANCER INSTITUTE, <http://www.cancer.gov/cancertopics/coping/chemo-side-effects> (last visited Feb. 16, 2011); *Chemotherapy Effects*, AMERICAN CANCER SOCIETY, <http://www.cancer.org/Treatment/TreatmentsandSideEffects/PhysicalSideEffects/ChemotherapyEffects/index> (last visited Feb. 16, 2011).

275. *Prometheus Labs., Inc. v. Mayo Collaborative Servs. (Prometheus II)*, 581 F.3d 1336, 1339 (Fed. Cir. 2009).

276. *See European AIDS Treatment Group*, *supra* note 251; *Pollack*, *supra* note 252.

service providers because it would limit the market for the drug.²⁷⁷ Diagnostic method patents can provide a financial incentive to develop diagnostics in these situations where incentives for overtreatment might otherwise suppress continued efficacy research.

If drug pricing were based entirely on medical value, the price of drugs needed to cure five patients of a given disease might always be the same. It would make little difference if doctors had to give the drug to one hundred patients to cure five, or whether they had to give the drug to only five patients. Indeed, if the pricing accounted for negative side effects, the cost to cure five out of five patients might actually be higher than the cost to cure five out of one hundred. In fact, the market-based pricing currently dominant in the United States can have the opposite result. Marketing—both to physicians and direct to consumers (DTC)—can increase demand beyond what a drug's effectiveness would dictate, as the patients pay a premium for hope.²⁷⁸ Arguably, a modest “hope premium” could actually reflect real benefits of the placebo effect.

A company holding the patent on an FDA approved drug could capture this lost hope premium by charging for the diagnostic test itself. This capture might be difficult absent patent protection that enables a price premium. Importantly, the drug owner could best recapture its lost hope premium if it discovered the diagnostic. If another company such as Prometheus, Metabolite, or Myriad Genetics discovered the diagnostic, it could market and sell the test itself, or charge the drug-maker for a license. This creates an incentive for pharmaceutical and biotechnology firms to research market-limiting diagnostics for their own drugs. Such an incentive benefits the public, because the firm that develops a drug has inherent advantages that make its continuing research more efficient. The original innovator has an advantage in aggregating data related to its own sales and may employ or have partnerships with medical researchers who acquired expertise on the drug during the development process. Granting patents on market-limiting discoveries discourages pharmaceutical companies from letting these natural advantages go to waste and instead encourages their use for the private and public benefit.

^{277.} See Paula Tironi, *Pharmaceutical Pricing: A Review of Proposals to Improve Access and Affordability of Prescription Drugs*, 19 ANNALS HEALTH L. 311, 340 (2010).

^{278.} See Eileen M. Kane, *Patent-Mediated Standards in Genetic Testing*, 2008 UTAH L. REV. 835, 841–42 (2008); Tironi, *supra* note 277, at 343. See generally CONG. BUDGET OFFICE, PRESCRIPTION DRUG PRICING IN THE PRIVATE SECTOR (2007), available at www.cbo.gov/doc.cfm?index=7715 (describing factors other than “hope” that influence drug prices).

Granting diagnostic method patents also provides an incentive for firms to promote their tests. Exclusivity prevents generic competitors from free-riding on marketing expenses.²⁷⁹ This pattern of increased marketing of patented products is widespread in the pharmaceutical industry, as marketing is an extremely effective means of affecting physician and patient behavior.²⁸⁰ This influence is often characterized as pernicious, but it can be harnessed for positive ends. Physicians are notoriously bad at adopting best practices as they are discovered.²⁸¹ Incentivizing the aggressive marketing of diagnostics tests for which physicians can charge and that bring patient care more in line with best practices can help improve public health while living within the suboptimal overtreatment incentives of the American healthcare system.²⁸²

D. DIAGNOSTIC METHOD PATENTS WILL BECOME DIFFICULT TO ENFORCE AGAINST PATIENTS AND THEIR DOCTORS

A major policy argument against granting diagnostic method patents is that patents increase testing costs, thereby burdening patients. The Association of Molecular Pathology argued this in the Southern District of New York and the court noted that Myriad Genetics' *BRCA* test costs \$3000 in the United States, while similar tests retail for one-third of that cost just over the Canadian border, where the patent is not enforced.²⁸³ The basis for this concern is fading, however, as it becomes possible for patients to analyze their own genome, proteome, or metabolome.²⁸⁴ This option will both save

279. See Kitch, *supra* note 203, at 266, 277.

280. See Ashley Wazana, *Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift?*, 283 JAMA 373, 378–79 (2000); NO FREE LUNCH, <http://www.nofreelunch.org> (last visited Feb. 16, 2011).

281. See Ford Fessenden, *Quick, What Do You Give a Heart Attack Patient?*, N.Y. TIMES, Aug. 28, 2005, at 14NJ, available at <https://www.nytimes.com/2005/08/28/nyregion/nyregionspecial2/28njHEART.html#> (discussing low conformity with best practices in heart attack and pneumonia care, revealed in a national survey of hospitals, and stating “[d]octors can be stubborn . . . [you need] physician buy-in”).

282. Cf. Atul Gawande, *The Cost Conundrum: What a Texas Town Can Teach Us About Health Care*, NEW YORKER (June 1, 2009), http://www.newyorker.com/reporting/2009/06/01/090601fa_fact_gawande#ixzz1GXmxhRZV (describing how reimbursement practices incentivize doctors to over-treat patients, resulting in high Medicare costs in McAllen, TX).

283. Ass'n for Molecular Pathology v. U.S. PTO, 702 F. Supp. 2d 181, 203 (S.D.N.Y. 2010).

284. See, e.g., Steven L. Salzberg & Mihaela Peretea, *Do-It-Yourself Genetic Testing*, 11 GENOME BIOLOGY at 1 (2010) (announcing the successful design of software for home analysis of *BRCA* phenotype using only files with raw data from Illumina sequencing, and announcing that the authors were sharing this free, open source software with the public); see also Kevin E. Noonan, “*At-Home*” Testing for *BRCA* Gene Mutations, PAT. DOCS: BIOTECH & PHARMA PAT. & NEWS BLOG (Oct. 13, 2010, 11:46 PM), <http://www.patentdocs.org/>

money for patients who avail themselves of the opportunity and likely create some downward pressure on prices for patented diagnostics, in a manner analogous to purchases of prescription drugs from Canada.²⁸⁵

The “omics” revolution has lead to increasing automation of data-collection, enabling large amounts of raw data to be collected semi-randomly. Data collection companies and core research facilities specialize in gathering this raw data and delivering it for analysis.²⁸⁶ A patient receiving this raw data may be able to analyze it independently. For example, a patient whose entire genome has been sequenced might be able to search for *BRCA* mutations.²⁸⁷ Such self-diagnosis would be particularly achievable if patients had access to software that can perform the data analysis for them. While creators and distributors of such software might be liable for patent infringement, the software could be designed with relative ease by patient or public domain activists and spread via the same distribution channels that currently bedevil record companies and the RIAA. Alternatively, a patient might email the raw data overseas for analysis, or send a tissue sample to Canada or India. Overseas processing and re-importation of test results could potentially violate 35 U.S.C. § 271(f) or § 271(g). This result is far from clear and infringement by individuals within the United States may be more likely than off-shoring.²⁸⁸

Given that an entire genome sequence will have non-infringing uses, holders of patents on pure genetic diagnostics like the *BRCA* patents will have little ability to enforce their patent rights against providers of whole genome sequencing. The remaining enforcement options are unenviable. Tracking down and suing individuals for single acts of infringement is expensive and inefficient. Faced with a similar dynamic as internet music

2010/10/at-home-testing-for-brca-gene-mutations.html (summarizing Salzberg & Pertea, and discussing the significance of their work). Noonan notes that at-home testing lacks the support and educational capability of medical settings, potentially creating emotional and other hardships for self-diagnosers. *Id.*

285. See Michael J. Rosenquist, U.S. v. Rxdepot: *The Battle Between Canadian Store-Front Companies, the FDA and Brand-Name Companies*, 9 MARQ. INTELL. PROP. L. REV. 423, 430–31 (2005); Luke W. Cleland, *Modern Bootlegging and the Prohibition on Fair Prices: Last Call for the “Repeal” of Pharmaceutical Price Gouging*, 15 ALB. L.J. SCI. & TECH. 183, 185–86 (2004).

286. See, e.g., DUKE INSTITUTE FOR GENOME SCIENCES AND POLICY: TECHNOLOGIES AND CORE FACILITIES, <http://www.genome.duke.edu/cores/index.php> (last visited February 28, 2011).

287. See Salzberg & Pertea, *supra* note 284.

288. Amy E. Hayden, Note, *Cardiac Pacemakers v. St. Jude Medical: The Federal Circuit Has Re-opened the Deepsouth Loophole for Method Claims*, 26 BERKELEY TECH. L.J. 197, 215 (2011).

sharing grew widespread, the Recording Industry Association of America (RIAA) pursued a strategy of deterrent “show trials” with only modest success.²⁸⁹ A woman seeking a double mastectomy after discovering a *BRCA* mutation in her genome sequence would likely make a more sympathetic defendant than a college student sharing music. Any deterrent “show trial” following the RIAA model would have uncertain results at trial and would invite Congressional action in the form of a liability exemption like § 287(c).²⁹⁰

Alternatively, Myriad Genetics might bring suit against doctors or insurance companies for contributory infringement under 35 U.S.C. § 271(b) if they perform a prophylactic mastectomy on a *BRCA* gene carrier.²⁹¹ Even if courts were willing to find contributory infringement after the patient had already performed the infringing act, it would be hard to prove that the treatment decision was based on the diagnostic. Again, such suits might even invite Congressional action in the form of another liability exemption. Finally, personal analysis of one’s own genome could easily be construed as falling under the “idle curiosity” experimental use exemption.²⁹²

Diagnostic tests closely tied to specific treatments, like the *Prometheus* test, are less susceptible to at-home infringement. The *Prometheus* test can only be performed using patient samples collected during a course drug treatment.²⁹³ Thus, it is unlikely that patient whose blood was drawn in the necessary window and analyzed for a broad collection of metabolites would have a non-infringing purpose, and such testing would likely create a strong inference of contributory infringement by the hospital or testing center.

In sum, it will be difficult to enforce diagnostic method patents against individuals empowered to analyze their own medical data. The exceptions to this difficulty occur with the very diagnostics that are least controversial—those that necessarily involve unique testing procedures or that are coupled to a prior medical treatment. Given that the burden of diagnostic method

289. See Ken Nicholds, *The Free Jammie Movement: Is Making A File Available to Other Users over A Peer-to-Peer Computer Network Sufficient to Infringe the Copyright Owner's 17 U.S.C. § 106(3) Distribution Right?*, 78 FORDHAM L. REV. 983, 990–91 (2009).

290. 35 U.S.C. § 287(c) (2006); see also Pallin v. Singer, 36 U.S.P.Q.2d (BNA) 1050 (D. Vt. 1995) (the proximal cause of Congressional action).

291. See 35 U.S.C. § 271(b) (2006) (“Whoever actively induces infringement of a patent shall be liable as an infringer.”).

292. See *Madey v. Duke Univ.*, 307 F.3d 1351, 1362 (Fed. Cir. 2002) (discussing and restricting the scope of the research exemption).

293. See U.S. Patent No. 6,355,623 col. 20 l. 13 (filed April 8, 1999) (claiming as the methods first step “administering a drug”).

patents on individual patients will weaken substantially, weight should be placed on the value of these patents as incentives for research and development.

IV. CONCLUSION—THE POSSIBLE STANDARDS FOR MEDICAL DIAGNOSTICS

Section 101 is sometimes framed as a space to hash out competing policy arguments, and medical diagnostics are no exception. A rational standard must balance the goals of broad medical access and unfettered research against the goal of preserving incentives for therapy development, complex disease diagnostics, and beneficial inaction. A variety of standards might suffice, including the Federal Circuit's continued application of the machine-or-transformation test.

The importance of diagnostic patents in therapy development and as incentives for inaction weighs in favor of some form of patentability. Similarly, although discovery grows easier, significant hurdles remain, particularly for more complex diagnostics. Given that the potential of diagnostic patents to harm patients is likely to decrease substantially, the fact that some less complex diagnostics might still be discovered without patent incentives should not be a dispositive argument against the patentability of the entire class of discoveries. Indeed, to the extent that a diagnostic correlation is trivial to discover, obviousness doctrine should be applied to prohibit patentability.

Some important policy goals facilitated by diagnostic method patents are unrelated to actual therapies. For example, the discovery of complex diagnostics might enable valuable life-planning by patients, without connection to medical therapy. Thus, the human intervention standard—narrowly construed—would not be an ideal compromise for preserving the ability to patent diagnostic correlations.

The potential of diagnostic method patents to restrict further research is particularly dangerous. This possibility could be limited by a standard under which diagnostic correlation patents are read narrowly. Alternatively, forceful application of the written description standard might help to limit broad preclusive effects of these patents.

The courts already have doctrinal tools that favor socially valuable patents. A blanket prohibition on diagnostic method patents under § 101 would needlessly undermine the positive effects of these patents. Regardless of the ultimate result, wise judicial decision-making will require a nuanced understanding of biomedical science and industry dynamics.

