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Ethan M. Weiner

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DEFINING A NATURAL PHENOMENON AFTER *PROMETHEUS*

Ethan M. Weiner[†]

The Supreme Court's historical jurisprudence on patentable subject matter is wrought with confusion, confounding academics and practitioners alike.[1] The *Benson-Flook-Diehr* trilogy[2] left those in the field uncertain as to how much needed to be added to a natural phenomenon to make it a patentable process rather than an attempt to monopolize a decidedly unpatentable law of nature. After *Diehr*, the Supreme Court was silent on the issue of patentable subject matter for nearly thirty years. In 2010, the Supreme Court reentered the field with a whimper with the *Bilski* decision.[3] Many in the field hoped that the *Bilski* decision would finally provide clear guidance to determine what is patentable subject matter.[4] *Bilski* was ultimately a disappointment, and instead of providing a test for patentable subject matter, the Court's narrow holding simply stated that the machine-or-transformation test could not be the exclusive test for the patent eligibility of process claims.[5] Perhaps recognizing the need to put forward an affirmative test of patentable subject matter, the Supreme Court granted certiorari in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*[6]

As framed by the *Prometheus* Court, patent eligibility for claims that depend on natural laws centers on the issue of whether or not "the patent

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† J.D. Candidate, 2014, University of California, Berkeley School of Law.

1. *See* Peter S. Menell, *Forty Years of Wondering in the Wilderness and No Closer to the Promised Land: Bilski's Superficial Textualism and the Missed Opportunity to Return Patent Law to Its Technology Mooring*, 63 STAN. L. REV. 1289 (2011).

2. Diamond v. Diehr, 450 U.S. 175 (1981); Parker v. Flook, 437 U.S. 584 (1978); Gottschalk v. Benson, 409 U.S. 63 (1972).

3. Bilski v. Kappos, 130 S. Ct. 3218 (2010).

4. *See* Menell, *supra* note 1, at 1291.

5. *Bilski*, 130 S. Ct. at 3226–27.

6. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 131 S. Ct. 3027 (2011) (granting certiorari). Justice Breyer had earlier recognized the need to establish clear rules of patentable subject matter to guide the balance between incentive and overprotection. *See* Lab. Corp. of Am. Hlds. v. Metabolite Labs., Inc., 548 U.S. 124 (2006) (Breyer, J., dissenting from dismissal of certiorari as improvidently granted) ("One way in which patent law seeks to sail between these opposing and risky shoals [of overprotection and incentive to invent] is through rules that bring certain types of invention and discovery within the scope of patentability while excluding others.").

claims add *enough*" to a natural law to make them an application of the natural law rather than an attempt to claim the natural law itself.[7] Clarity on this issue could provide stability to the emerging field of medical diagnostics, which frequently relies on physiological responses to personalize treatment plans or diagnose diseases.[8] Unfortunately, the *Prometheus* decision was not the guiding beacon for patentable subject matter that the PTO, the Federal Circuit, and inventors anxiously awaited. Instead, the granting of certiorari was nothing more than the song of Sirens, leaving inventors shipwrecked on an island of patentable subject matter confusion. The *Prometheus* Court failed to deliver any clear rule controlling patentable subject matter for process claims.

This Note argues that the Supreme Court's poorly crafted *Prometheus* decision obfuscated not only the methodology of examining a process claim relying on a natural phenomenon, but also the very understanding of a natural phenomenon itself. If not carefully applied by the Federal Circuit, the *Prometheus* decision risks destabilizing the patent system and industries that rely on applications of the natural laws, particularly computer software, medical diagnostics, and biotechnology. Part I traces the history of the natural phenomenon doctrine and explores the difficulties courts have had in distinguishing natural phenomena and abstract ideas from their applications. It also sets forth the preemption and inventive concept standards that courts use to determine whether a claim involving a natural phenomenon is patent-eligible. Part II closely examines the recent *Prometheus* decision and demonstrates how the Supreme Court's misunderstanding of a natural phenomenon makes it difficult to appreciate the inventive contribution embodied in claims related to medical diagnostics. Part III attempts to distinguish natural correlations from man-made correlations and argues how a poor definition of a natural phenomenon makes the natural phenomenon doctrine impracticable to apply.

I. THE NATURAL PHENOMENON DOCTRINE

While the basic premise of the patent system is to "promote the Progress of . . . the useful Arts,"[9] some commentators disagree as to the scope of patentable subject matter that best achieves this goal.[10] An overly broad allowance of patent monopolies may ultimately inhibit downstream

7. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1297 (2012).

8. *See* Allen K. Yu, *Within Subject Matter Eligibility—A Disease and a Cure*, 84 S. CAL. L. REV. 387, 401 (2011).

9. U.S. CONST. art I, § 8.

10. *See, e.g.*, Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839 (1990).

innovation, as inventors are unable to make technological progress without approval from other patent holders.[11] On the other hand, the right to a patent may encourage inventors, allowing them to hedge failure through the promise of a limited market monopoly if they are successful.[12] The scope of patentable subject matter can therefore be thought of as controlling the balance between the two theories of downstream obstruction and inventor incentive.[13] Allowing an overly broad scope for patentable subject matter will generate too many blocking patents, hindering downstream technological development, while too narrow scope risks nullifying the incentive effects. The scope of patentable subject matter can be controlled through § 101 by putting limits on what types of inventions can be patented.[14]

Section 101 of the Patent Act provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[15] This text is largely unchanged from its original drafting by Thomas Jefferson in 1793.[16] A strict textualist reading of the statute suggests that both discoveries and inventions are included in patentable subject matter. Yet over 150 years of judicial common law has restricted the breadth of this section. Specifically, the Supreme Court has declared "laws of nature, physical phenomena, and abstract ideas" to be non-patentable subject matter.[17] The discovery of a natural phenomenon is not sufficient to earn a patent on that natural phenomenon. An application of a natural law, however, can be patentable subject matter.[18]

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11. *See* Maureen A. O'Rourke, *Toward a Doctrine of Fair Use in Patent Law*, 100 COLUM. L. REV. 1177, 1194 (2000) (describing how "blocking patents" generate negotiating leverage over a future inventors improving on a patented invention); Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698 (1998) (arguing that an overabundance of patents will inhibit an inventor's ability to further progress the technological art).

12. *See* Peter Menell & Suzanne Scotchmer, *Intellectual Property Law*, *in* 2 HANDBOOK OF LAW & ECONOMICS 1473, 1478 (A. Mitchell Polinsky & Steven Shavell eds., 2007).

13. *See* Mark A. Lemley, et al., *Life After* Bilski, 63 STAN. L. REV. 1315, 1328–29 (2011).

14. *See id.* at 1329–32 (distinguishing scope limitations in § 101 and § 112).

15. 35 U.S.C. § 101 (2006).

16. *See* Patent Act of 1793, ch. 11, 1 Stat. 318, 319–320 (1793) (patents were available for "any new and useful art, machine, manufacture or composition of matter" or improvements thereof). The term "art" was changed to "process" in the 1952 Patent Act without any substantive change to its meaning. *See* Menell, *supra* note 1, at 1296.

17. Bilski v. Kappos, 130 S. Ct. 3218, 3225 (2010) (quoting Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980)).

18. *See* Diamond v. Diehr, 450 U.S. 175, 187–88 (1981).

Several justifications for the exclusion of natural laws from patentable subject matter have been suggested including altruistic motives of the discoverers of natural laws, natural rights of others, lack of novelty, claim overbreadth, and preserving research tools in the public domain.[19] Underlying each of these concerns is the idea that using a patent as an incentive for discovering natural laws would slow the progress of technology rather than encourage its development.[20] Courts have generally employed two different but overlapping tests to determine if the scope of a method claim has become so broad that it should be unpatentable. The first is the preemption standard.[21] This approach directly confronts when a claim is so broad that it prevents others from using a natural phenomenon.[22] The second is the inventiveness standard, which assesses when an inventor has done enough to apply the natural law to warrant a patent.[23] The Court of Customs and Patent Appeals ("C.C.P.A.") and, subsequently, the Federal Circuit struggled to integrate these two standards into a single coherent test. The C.C.P.A. developed the *Freeman-Walter-Abele* test, which the Federal Circuit replaced with the machine-or-transformation test.[24] The Supreme Court, however, dismissed the machine-or-transformation test, without articulating the proper test for patentable subject matter.[25]

A. PREEMPTION STANDARD

Courts frequently express concern that allowing patents on natural phenomena would hinder downstream scientific progress.[26] If a discoverer of a law of nature lays claim to the natural law, then no later inventor or

19. *See* Alan L. Durham, *Natural Laws and Inevitable Infringement*, 93 MINN. L. REV. 933, 952–60 (2009) (giving a critical assessment of each of these justifications); *see also* Joshua D. Sarnoff, *Patent-Eligible Inventions After* Bilski*: History and Theory*, 63 HASTINGS L.J. 53, 84–90 (2011) (describing how Lockean moral principles of "God-given commons" contributed to the ban on patentability of laws of nature).

20. *See* Durham, *supra* note 19, at 951–52.

21. *See* Gottschalk v. Benson, 409 U.S. 63, 72 (1972) (holding that a claim that wholly preempts a mathematical algorithm is not patentable subject matter).

22. *See Bilski*, 130 S. Ct. at 3231 (holding that a patent on hedging was not patentable subject matter because it would pre-empt all use of an abstract idea).

23. Parker v. Flook, 437 U.S. 584, 594 (1978) (holding that a mathematical algorithm cannot be patented unless there is an inventive concept).

24. *See In re* Bilski, 545 F.3d 943, 958–59 (Fed. Cir. 2008).

25. *See Bilski*, 130 S. Ct. at 3226–27.

26. *See, e.g.*, Classen Immunotherapies, Inc. v. Biogen IDEC, 659 F.3d 1057, 1080 (Fed. Cir. 2011) (Rader, J., concurring) (arguing that claims that "so clearly offend the constitutional imperative to promote the useful arts, where they preempt all application of a principle idea" are unpatentable subject matter); *Bilski*, 130 S. Ct. at 3253 (Stevens, J., concurring) (arguing that patents on laws of nature, natural phenomena, and abstract ideas "would stifle the very progress that Congress is authorized to promote").

discoverer could exploit that natural law without permission from the patent owner during the term of the patent.[27] The downstream inventor would be preempted from utilizing the natural law because of the power bestowed onto the upstream patent holder. Of course, all patents preempt later inventors to some extent, as many inventions are made through incremental improvements of previously patented inventions. For example, a patent on a new microprocessor chip would preempt any new computer using that chip. In these circumstances, licensing agreements are frequently made between inventors to avoid an absolute bar to downstream innovations. Nevertheless, the Supreme Court has found patents on natural phenomena to be overly preemptive.[28]

To what extent a patent preempts later inventions depends on the scope of its claims. The broader the scope of the claim, the more preemption affects downstream innovations. If the goal of the patent system is to incentivize the most technological innovation in the shortest period of time, then patent scope should be broad enough to encourage the development of a technology but not so broad as to preclude others from entering that technological field and making their own inventive contributions.[29] Put another way, if a patent claim is so broad that no inventions could be made in that field without ensnaring the prior art, other inventors may be unwilling to continue exploring the field.[30] Historically, the courts drew a line finding natural law patents as overly preemptive, while patents applying natural law as reasonably preemptive.[31]

The origins of the preemption doctrine can be traced back more than 150 years to *O'Reilly v. Morse*, although the focus of the Court's concern was the written description requirement rather than patentable subject matter.[32]

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27. *See* Zenith Radio Corp. v. Hazeltine Research, Inc., 395 U.S. 100, 135 (1969) ("A patentee has the exclusive right to manufacture, use, and sell his invention.").

28. *See* Gottschalk v. Benson, 409 U.S. 63, 67 (1972) (explaining that natural phenomena are the "basic tools of scientific and technological work," and cannot be patented).

29. *See* Merges & Nelson, *supra* note 10, at 875–76.

30. *See also* Christina Bohannan & Herbert Hovenkamp, *IP and Antitrust: Reformation and Harm*, 51 B.C.L. REV. 905, 955 (2010) ("Overly broad claims eliminate rivalry because the patent covers not only the technology that the patentee actually invented, but other potentially competing technologies that might have entered the market had the patent not squelched them.").

31. *See* Diamond v. Diehr, 450 U.S. 175, 187 (1981) (reasoning that the inventors of a process applying an equation "do not seek to pre-empt the use of that equation" but "seek only to foreclose from others the use of that equation in conjunction with all of the other steps in their claimed process").

32. O'Reilly v. Morse, 56 U.S. 62, 113 (1853) (Morse claimed "an exclusive right to use a manner and process which he has not described and indeed had not invented").

The PTO granted Morse a patent on the electromagnetic telegraph in 1840.[33] The *Morse* Court invalidated claim 8, which claimed "electro-magnetism, however developed for making or printing intelligible characters, signs or letters, at any distances."[34] Of significant concern for the Court was preemption.

> If this claim can be maintained, it matters not by what process or machinery the result is accomplished. For aught that we now know some future inventor, in the onward march of science, may discover a mode of writing or printing at a distance by means of the electric or galvanic current, without using any part of the process or combination set forth in the [Morse] specification. His invention may be less complicated—less liable to get out of order—less expensive in construction, and in its operation. But yet if it is covered by this patent the inventor could not use it, nor the public have the benefit of it without the permission of [Morse].[35]

The concept of electro-magnetism is, presumably, a natural phenomenon. It is not something created by Morse, but something that existed in nature whether or not Morse had discovered it. But claim 8 was directed to "making or printing intelligible characters" by way of electro-magnetism.[36] The Court appeared to be more concerned with the scope of the invention, and that it claimed more than Morse actually had invented.

Morse attempted to claim more than he actually described (claiming any electro-magnetism for making letters and signs at a distance rather than the use of electro-magnetism confined to his telegraph machine), raising the concern of preemption.[37] The written description requirement in a patent application can be traced back to the Patent Act of 1793.[38] The purpose of this requirement was to instruct other inventors of the scope of the patent and to enable them to make further innovations.[39] But *Morse* expanded the purpose of the requirement to ensure the patentee's claims were not overly broad, thereby ensuring the inventor actually invented the claimed invention

33. U.S. Patent No. 1,647 (issued June 20, 1840) [hereinafter '647 Patent].

34. *See Morse*, 56 U.S. at 113; '647 Patent.

35. *Id.*

36. *See* '647 Patent.

37. *See Morse*, 56 U.S. at 113. *But see* Jur Strobos, *Stalking the Elusive Patentable Software: Are There Still Diehr or Was it Just a Flook?*, 6 HARV. J.L. & TECH. 363, 365 n.8 (1993) (distinguishing preemption from claim overbreadth).

38. *See* Jacob Adam Schroeder, *Written Description: Protecting the Quid Pro Quo Since 1793*, 21 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 63 (2010) (describing the history of the written description requirement).

39. *See* Evans v. Eaton, 20 U.S. 356, 366–67 (1822).

and preventing the preemption of downstream inventions.[40] This concern that overly broad claims might cause inventors to claim more than they actually invented ultimately led to a judicially created ban on claims covering natural phenomena.[41]

With the rise of software patents in the 1960s and 1970s, the Supreme Court began to implement this preemption doctrine to justify patent invalidity for Information Age technologies.[42] This was not done through the written description requirement, however, but by using the preemption standard to justify excluding natural phenomena as patentable subject matter under § 101.[43] The *Benson* Court held that a computer program designed to convert signals from binary-coded decimal form into pure binary form was not patentable because the "patent would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself."[44] Under the Court's reasoning, the algorithm has no "substantial practical application" outside of a computer, and therefore a patent of the algorithm, even when strictly tied to the computer, should not be patent eligible.[45] The Court acknowledged that the algorithm could be used without a computer,[46] but a patent on the algorithm when used with a computer was not sufficient to move the claim from an unpatentable abstract idea to patentable subject matter.[47]

The preemption concern in *Benson* was centered on the position that a patent should not prevent others from using "the basic tools of scientific and technological work."[48] As with the *Morse* claim, the scope of this claim was too broad to be allowed by the Supreme Court. Unlike *Morse*, however, there was no issue with the written description of the claims. Instead the *Benson* Court was concerned that the Patent Act was not intended to grant monopolies on the type of thing the inventors were attempting to claim.

40. *See* Schroeder, *supra* note 38, at 74.

41. *See* Funk Bros. Seed Co. v. Kalo Inoculat Co., 333 U.S. 127, 130 (1948) (explaining that the only patentable invention arising from a natural phenomenon would be in its application); *see also* Le Roy v. Tatham, 55 U.S. 156, 175 (1852).

42. Information Age technologies, such as computer software and medical diagnostics, can be distinguished from Industrial Age technologies, such as mechanical machines or a new metal alloy. *See* Bilski v. Kappos, 130 S. Ct. 3218, 3227 (2010).

43. *See* Gottschalk v. Benson, 409 U.S. 63, 72 (1972) (stating a claim that wholly preempts a mathematical formula is "in practical effect" a claim over the mathematical formula itself and thus not patentable subject matter).

44. *Id.* at 71–72.

45. *Id.* at 71.

46. *See id.* at 67.

47. *Id.* at 71–72.

48. *Id.* at 67.

Benson held that claims over "[p]henomena of nature, though just discovered, mental processes, and abstract intellectual concepts," such as mathematical algorithms, were too preemptive and thus unpatentable.[49]

Following *Benson*, lower courts understood the wholly preemptive standard to be an applicable test for patentable subject matter.[50] The C.C.P.A. significantly limited this preemption standard test, as well as the *Benson* holding, as applicable only to "algorithms."[51] The two-step test established by *In re Freeman* required first, a determination that the claim recites an algorithm, and second, a determination if the claim "in its entirety . . . wholly preempts that algorithm."[52]

The Supreme Court stepped away from its "wholly preempts" language when it considered the claims at issue in *Parker v. Flook*.[53] The *Flook* claims were directed to a method of calculating an alarm limit by employing a mathematical formula.[54] But the claims were also limited to the field of "chemical conversion of hydrocarbons" and not to all uses of the algorithm.[55] The Court acknowledged that the claim does not "wholly preempt the mathematical formula" since the claim covered the use only in a specific field, leaving the formula available to the public for use outside of that field.[56] Nevertheless, the Court found the claims to be unpatentable because they did not adequately apply the formula.[57] The C.C.P.A. reformulated its *Freeman* test in response to *Flook* in *In re Walter* such that a claim need not wholly preempt the mathematical formula to be declared

49. *Id.*

50. *See In re* Chatfield, 545 F.2d 152, 155–56 (C.C.P.A. 1976) ("[T]he fundamental rationale we glean from *Benson* is that a patent containing Benson's claims would have preempted all practical use of both the underlying mathematical formula and the involved algorithm."). The preemption standard remained in contention with the "point of novelty" test, discussed *infra* Section I.B. *Compare In re* Christensen, 478 F.2d 1392, 1394 (C.C.P.A. 1973) (Lane, J.) (holding a process is unpatentable when the only "point of novelty" is a mathematical formula), *with id.* at 1396 (Rich, J., concurring) (arguing that, in accordance with *Benson*, a claim is not patentable subject matter when it preempts a formula with no application outside of the claim). The C.C.P.A. overruled *Christensen* in *In re* Taner, 681 F.2d 787 (C.C.P.A. 1982) (reasoning *Diehr* negated any point of novelty test). *See also In re* Walter, 618 F.2d 758 (C.C.P.A. 1980) ("We do not read *Flook* as adopting a 'point of novelty' test; as we have shown, such a test flies in the fact of Supreme Court precedent reaffirmed in *Flook* and does violence to the statute.").

51. *See In re* Freeman, 573 F.2d 1237, 1245 (C.C.P.A. 1978).

52. *Id.*

53. Parker v. Flook, 437 U.S. 584 (1978).

54. *Id.* at 585.

55. *Id.* at 586.

56. *Id.* at 589–90.

57. *See id.* at 590 (holding "post-solution activity" cannot transform an unpatentable mathematical algorithm into a patentable process); *see also infra* Section I.B.

unpatentable. Rather, a claim may be found unpatentable if it is directed only to solving the mathematical formula but not to applying the result of the calculation.[58]

The preemption standard for determining patentable subject matter was implemented to ensure the "basic tools of scientific and technological work" were available for later inventors to innovate.[59] In *Morse*, the Court was concerned that a patent on electro-magnetism would prevent later inventors from utilizing that natural phenomenon.[60] In *Benson*, the Court was concerned that a patent would wholly preempt a mathematical formula.[61] However the Supreme Court also recognized that a "wholly" preemptive standard was insufficient in *Flook*, as a claim might not be wholly preemptive but still not sufficiently apply a natural law to warrant a patent.[62] The question remains as to how preemptive is too preemptive.[63]

B. INVENTIVE CONTRIBUTION STANDARD

In addition to preemption concerns, courts frequently express concern that an applicant should not be granted a patent if she does not make a sufficiently inventive contribution.[64] When the invention relates to a natural phenomenon, it can be difficult to determine whether a claim is something inventive or "new" rather than a claim on the natural phenomenon itself. While the preemption standard inquires whether a claim is so broad it prevents other uses of a natural phenomenon, the inventive contribution standard inquires whether or not a natural phenomenon has been adequately applied.[65] The finding that a claim is "new" under § 101 is presumably different from the novelty requirement of § 102, which requires an element-by-element approach to determine what is new in the invention.[66] Instead,

58. *See In re* Walter, 618 F.2d 758, 767 (C.C.P.A. 1980).

59. Gottschalk v. Benson, 409 U.S. 63, 67 (1972).

60. *See* O'Reilly v. Morse, 56 U.S. 62, 113 (1853).

61. *See* Gottschalk v. Benson, 409 U.S. 63, 71–72 (1972).

62. *See* Parker v. Flook, 437 U.S. 584, 589–90 (1978).

63. *See* Samantak Ghosh, *Prometheus and the Natural Phenomenon Doctrine: Let's not Lose Sight of the Forest for the Trees*, 90 J. PAT. & TRADEMARK OFF. SOC'Y 330, 349–50 (2012).

64. Cuno Eng'g Corp. v. Automatic Device Corp., 314 U.S. 84, 90 (1941) (explaining that to be patentable, a claim must be more than "new or useful" but must actually be an "invention").

65. *See Flook*, 437 U.S. at 594.

66. *See In re* Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999) (explaining that each element must be found, either expressly or inherently, in the prior art to anticipate an invention).

inventiveness under § 101 should, in theory, be determined considering the claim as a whole.[67]

Conceptually, the discovery of a natural phenomenon is neither inventive nor new. The natural phenomenon existed prior to its discovery, and remains unchanged after its discovery.[68] The Supreme Court reaffirmed this principle in *Funk Bros.*, declaring laws of nature are "free to all men and reserved exclusively to none."[69] The *Funk Bros.* claim was directed to a combination of several strains of nitrogen-fixing bacteria, which, to the surprise of the industry, did not inhibit one another.[70] Without dismissing the importance of the discovery, the Court held that the applicants could not patent the claims because there was nothing inventive.[71] The *Funk Bros.* Court reasoned that the inventor did "not create state of inhibition or of non-inhibition in the bacteria. Their qualities are the work of nature."[72] Since the discovery was a natural phenomenon rather than an invention, it was not patentable subject matter.[73] The *Funk Bros.* discovery can be compared to the claims in *Chakrabarty*, which were patentable because the genetically engineered bacteria at issue had been modified by the inventors and were not simply found in nature.[74] This concept of "inventiveness" and the determination of when a process adequately *applies* a natural law have plagued the patent field for decades.[75]

1. Point of Novelty Test Before Flook

Even before *Benson*, the C.C.P.A. employed the "point of novelty" test to determine when a natural phenomenon was applied rather than an attempt to claim the natural phenomenon itself.[76] Often used in connection with the

67. *See In re* Chatfield, 545 F.2d 152, 158 (C.C.P.A. 1976) (rejecting the notion that if a portion of a claim is non-statutory then the claim as a whole is non-statutory, since under § 101 the claim should be considered as a whole).

68. *See* Le Roy v. Tatham, 55 U.S. 156, 175 (1852) ("The elements of the power exist; the invention is not in discovering them, but in applying them to useful objects.").

69. Funk Bros. Seed Co. v. Kilo Inoculant Co., 333 U.S. 127, 130 (1948).

70. *See id.* at 128–29.

71. *See id.* at 132.

72. *Id.* at 130.

73. *See Id.*

74. *See* Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (holding that under § 101, "anything under the sun that is made by man" is patentable subject matter).

75. *See generally* Irah H. Donner, *Two Decades of Gottschalk v. Benson: Putting the "Rithm" Back Into the Patenting of Mathematical Algorithms*, 5 SOFTWARE L.J. 419, 426–27 (1992) (describing the many tests for patentable subject matter used and discarded by courts).

76. *See id.* at 426–27.

mental steps doctrine,[77] the "point of novelty" test rejected any claim as unpatentable under § 101 if the only novel element of a process was a mental step or other unpatentable element, such as a natural phenomenon.[78] Thus, adding an unpatentable element to a known process would not generate a new patentable process.

The C.C.P.A. was inconsistent with its adoption of the "point of novelty" test, however, first accepting it under *In re Abrams*,[79] rejecting it under *In re Musgrave*,[80] resurrecting it in *In re Christensen*,[81] and finally rejecting it again in *In re Chatfield*.[82] *Chatfield* put particular emphasis on the need to examine the claim as a whole, rather than dissecting the claim and searching for the novel element.[83] Furthermore, the "point of novelty" test fails to allow an inventive combination of known elements to be patentable subject matter, contrary to the provisions of § 103.[84]

2. Inventive Contribution and the Point of Novelty Test After Flook

Much of the C.C.P.A.'s confusion over the "point of novelty" test was centered on the inconsistent approaches taken by the Supreme Court in *Flook* and *Diehr*. The Board of Appeals of the PTO originally rejected the *Flook* claims because the mathematical algorithm was the only "point of novelty."[85] The C.C.P.A., having rejected the "point of novelty" test in *Christensen*,

77. Similar to the natural phenomenon doctrine, the mental steps doctrine holds that mental steps of a process are generally unpatentable. It is to be noted that this doctrine has been highly scrutinized by both courts and commentators. *See* Kevin Emerson Collins, *Propertizing Thought*, 60 S.M.U. L. REV. 317, 355–56 (2007).

78. *See* Diamond v. Diehr, 450 U.S. 175, 200 n.15 (1981).

79. *See In re* Abrams, 188 F.2d 165 (C.C.P.A. 1951) (holding that when the novel element of a patent claim is a mental step, the claim is unpatentable). *Abrams* clarified the growing mental steps doctrine, a parallel to the point of novelty test. *See* Julie E. Cohen, *Reverse Engineering and the Rise of Electronic Vigilantism: Intellectual Property implications of "Lock-Out" Programs*, 68 S. Cal. L. Rev. 1091, 1170–71 (1995); Pamela Samuelson, *Benson Revisited: The Case Against Patent Protection for Algorithms and Other Computer Program-Related Inventions*, 39 EMORY L.J. 1025, 1034–38 (1990).

80. *See In re Musgrave*, 431 F.2d 882, 889–90 (C.C.P.A. 1970) (reasoning that difficulty interpreting the term "mental steps" could lead to an unsound rule).

81. *In re* Christensen, 478 F.2d 1392, 1394 (C.C.P.A. 1973) (holding a claim to be unpatentable where the point of novelty is a mathematical equation).

82. *See In re* Chatfield, 545 F.2d 152, 158 (C.C.P.A. 1976) (rejecting the idea of dissecting the claim to determine a point of novelty).

83. *See id.*; *see also In re* Taner, 681 F.2d 787, 790–91 (C.C.P.A. 1982) (arguing *Diehr* rejected the "point of novelty" analysis).

84. 35 U.S.C. § 103 (2006); *see Chatfield*, 545 F.2d at 158; Graham v. John Deere Co., 383 U.S. 1 (1966).

85. Parker v. Flook, 437 U.S. 584, 587 (1978).

reversed the PTO.[86] In doing so, the C.C.P.A. indicated the claims were patentable because they did not "wholly pre-empt" the mathematical algorithm.[87] In overturning the C.C.P.A. and rejecting the claims, the Supreme Court stated that the mathematical algorithm ought to be considered to be in the prior art, leaving nothing "inventive" in the claim, while at the same time rejecting the notion they were dissecting the claim.[88] *Flook* required an inventor to make some inventive contribution in addition to the mathematical formula to render a claim patentable subject matter.[89]

It is difficult to accept that the *Flook* Court's analysis was internally consistent when it claimed to evaluate the claims as a whole while at the same time it isolated the mathematical algorithm and determined that nothing, in addition to the algorithm, was inventive.[90] The latter approach by the Court necessarily dissects the claims in search of a novel element. Just as in the "point of novelty" test of the lower courts, the Supreme Court indicated that the mathematical formula was to be considered in the prior art while the remainder of the claim was examined for inventiveness.[91] The C.C.P.A. refused to believe *Flook* was endorsing any "point of novelty" approach, stating such an approach "would immeasurably debilitate the patent system," and it did not believe the Supreme Court "acted in a manner so potentially destructive."[92] Other commentators, however, suggest that *Flook* did indeed resurrect the point of novelty test with a more destructive tone, as such a method would question the patent eligibility of any drugs or computer software because both rely on some natural phenomenon.[93] The C.C.P.A. interpreted *Flook* narrowly to avoid the result that would arise under a point of novelty approach and held as patentable subject matter a process where the only novel element was a computer program.[94]

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86. *See In re* Flook, 559 F.2d 21 (C.C.P.A. 1977).

87. *Id.* at 23. *See supra* Section I.A.

88. *See Flook*, 437 U.S. at 594 ("Our approach . . . is, however, not at all inconsistent with the view that a patent claim must be considered as a whole.").

89. *Id.*

90. *See* Samuelson, *supra* note 79, at 1080–82.

91. *See Flook*, 437 U.S. at 591–92.

92. *In re* Walter, 618 F.2d 758, 766 (C.C.P.A. 1980). *But see* Mark Nusbaum, *35 U.S.C. 101 Claim Analysis—The Point of Novelty Approach*, 62 J. PAT. OFF. SOC'Y 521, 522–23 (1980) (arguing that the only way to meaningfully approach claims after *Flook* is through a "point of novelty" approach).

93. *See* Mark A. Lemley, *Point of Novelty*, 105 NW. U.L. REV. 1253, 1278 (2011). Lemley suggested that under *Flook*, a natural substance effective as a drug might not be patentable because the only point of novelty in the claim would be the physiological response of the body to the drug. Such a physiological response could be considered a natural phenomenon. *Id.*

94. *See* Diamond v. Diehr, 450 U.S. 175, 200, 205 (1981).

The dissent in *Flook* did not explicitly accuse the majority of re-establishing the point of novelty test, however it still harshly criticized the majority for doing precisely what it claimed to not be doing: dissecting the claims and looking for a novel element.[95] Such issues of novelty, the dissent argued, should be decided under § 102 and § 103, and not under § 101.[96] The divergent view between the majority and dissent was centered on how the claim was viewed. The majority viewed the claim as an unpatentable mathematical formula, and a "competent draftsman" simply added "post-solution activity" in an attempt to patent the mathematical formula itself.[97] The dissent, however, viewed the claim as a patentable process (although perhaps not novel or nonobvious under § 102 or § 103), which the applicant limited by adding a mathematical formula.[98]

The *Flook* dissent waited only three years before Justice Renquist, of the *Flook* dissent, authored the majority opinion in *Diehr*, illustrating his point.[99] *Diehr* re-emphasized that the claims should not be dissected but considered as a whole and that adding a non-patentable element to an otherwise patent eligible process does not necessarily render the entire process unpatentable under § 101 due to a lack of inventiveness.[100] But *Deihr* would not go so far as to overturn *Flook* and instead attempted to distinguish the *Deihr* claims from the *Flook* claims.[101] The Court drew a tenuous distinction between the claims, determining the *Flook* claim was not patentable because it simply calculated an alarm limit whereas the *Deihr* claim used a mathematical formula integrated in the process.[102]

But Justice Stevens, author of the *Diehr* dissent and the *Flook* majority, was not convinced that the majority was preserving the *Flook* decision.[103] Instead, the dissent accused the majority of misunderstanding what the actual claimed invention was.[104] According to Justice Stevens, if the invention was a new process that utilized a mathematical algorithm, then it should be considered patentable subject matter. But if, as the dissent argued, the

95. *See Flook*, 437 U.S. at 599 (Stewart, J., dissenting) (indicating that the issue is if the claim becomes unpatentable "simply because *one step* in the process would not patentable subject matter if considered in isolation").

96. *Id.* at 600.

97. *Id.* at 590.

98. *Id.* at 599 (Stewart, J., dissenting).

99. *See Diehr*, 450 U.S. at 175.

100. *Id.* at 188–89.

101. *Id.* at 186–87.

102. *Id.*

103. *Id.* at 211 (Stevens, J., dissenting) (arguing that the majority and the C.C.P.A. both misapplied *Flook*).

104. *Id.* at 194.

invention was simply a method of calculating how long a step of the process should take, then it is too close to an algorithm to be patentable.[105]

The *Diehr* dissent's methodology of determining what was the claimed invention was no clearer than the majority's and again appears to reiterate the point of novelty approach. Justice Stevens highlighted that the only difference between the conventional methods in the art and the claimed invention was the calculation of the mathematical formula.[106] But Justice Stevens also carefully explained the history of the point of novelty approach and how it had been dismissed by the C.C.P.A.[107]

The *Diehr* and *Flook* opinions illustrate diverging approaches to patentable subject matter. Under *Flook*, if the only novel element is unpatentable subject matter while the remainder is "conventional," then the entire claim is unpatentable. Under *Diehr*, however, if the claim is patentable subject matter without the unpatentable element, then the claim, taken as a whole, might still be patentable. Thus, under *Diehr*, a claim may still be patentable subject matter even if each element is known because the combination of the elements is inventive. The combination of *Flook* and *Diehr* has resulted in significant confusion over what is patentable subject matter. *Flook* is certainly not dead law, with courts increasingly relying on it in recent cases under the pretense that it is somehow consistent with *Diehr*.[108]

C. DEFINING A TEST FOR PATENTABLE SUBJECT MATTER

The inconsistencies of the *Benson-Flook-Diehr* trilogy left those in the field struggling to find a workable test for patentable subject matter.[109] While *Benson* made clear that an algorithm wholly preempted by a patent claim is not patentable subject matter,[110] it was unclear how much preemption would be allowed under *Flook* and *Diehr*. The conflicting approaches of *Flook* and *Diehr* also made it difficult to determine when a patent claim was adequately applied. Furthermore, each of these Supreme Court cases evaluated the patent eligibility of a claim related to a mathematical algorithm or computer

105. *Id.* at 206–07.

106. *Id.* at 208.

107. *Id.* at 200–02.

108. *See* Bilski v. Kappos, 130 S. Ct. 3218, 3227 (2010) (holding a business method to be unpatentable because it amounted to no more than an abstract idea, in view of *Benson*, *Flook*, and *Diehr*); Dennis Crouch and Jason Rantanen, *The Revival of* Parker v. Flook, PATENTLYO.COM (Oct. 5, 2012, 3:13 PM), http://www.patentlyo.com/patent/2012/10/the-revival-of-parker-v-flook.html (indicating that after a short hiatus, *Flook* has been cited with increased frequency since 2005).

109. *See* Menell, *supra* note 1.

110. *See* Gottschalk v. Benson, 409 U.S. 63, 72 (1972).

program, and the tests developed by the C.C.P.A. were formulated accordingly.[111] It was not clear if these tests were equally applicable to the other judicially created exceptions to patentable subject matter: laws of nature, natural phenomena, or abstract ideas.[112]

The C.C.P.A. developed the *Freeman-Walter-Abele* test after *Diehr* to more clearly define the limitations of the inventive contribution standard and move away from a direct application of the wholly preemptive standard used in *Benson*.[113] The applicability of this test, however, continued to be limited. First, the test was directed only to algorithms and not other natural processes. Second, the test left generally vague how to determine whether or not a process claim adequately applied the algorithm.[114] The Federal Circuit ultimately discarded the *Freeman-Walter-Abele* test in favor of the machine-or-transformation test, which held a process claim to be patentable if it was tied to a particular machine or transformed some tangible article.[115] *In re Bilski* addressed process claims covering a business method for hedging risk in a commodities market.[116] The Federal Circuit determined that the business method was not patentable subject matter because it was neither tied to a machine nor did it transform a tangible object.[117] The Federal Circuit rationalized the machine-or-transformation test on the basis of preemption, stating:

> A claimed process involving a fundamental principle that uses a particular machine or apparatus would not pre-empt uses of the principle that do not also use the specified machine or apparatus in the manner claimed. And a claimed process that transforms a particular article to a specified different state or thing by applying a fundamental principle would not pre-empt the use of the principle to transform any other article, to transform the same article but in a

111. The *Walter* test attempted to determine patentable subject matter based on whether or not the mathematical result of an algorithm was applied. *See In re* Walter, 618 F.2d 758, 767 (C.C.P.A. 1980).

112. *See* Andrei Iancu & Peter Gratzinger, *Machines and Transformations: The Past, Present, and Future Patentability of Software*, 8 NW. J. TECH. & INTELL. PROP. 247, 267–69 (2010) (describing the difficulty courts have had defining a mathematical algorithm).

113. *See In re* Abele, 684 F.2d 902, 905–06 (C.C.P.A. 1982). The *Freeman-Walter-Abele* test "had two steps: (1) determining whether the claim recites an 'algorithm' within the meaning of *Benson*, then (2) determining whether that algorithm is 'applied in any manner to physical elements or process steps.' " *In re* Bilski, 545 F.3d 943, 959 (Fed. Cir. 2008).

114. *See In re* Bilski, 545 F.3d at 959.

115. *Id.* at 956.

116. *Id.* at 949.

117. *See id.* at 966.

> manner not covered by the claim, or to do anything other than transform the specified article.[118]

The machine-or-transformation test, unlike the *Freeman-Walter-Abele* test, had broader applicability to all process claims "involving a fundamental principle" rather than only mathematical formulae.[119]

The Supreme Court rejected the machine-or-transformation test as the "sole test" for patentable subject matter but recognized it as an "important clue."[120] The Court acknowledged the machine-or-transformation test may have been more useful in the Industrial Age, but it recognized it might not be an appropriate test in the Information Age where the patent system is more frequently confronted with new technologies, such as medical diagnostics.[121] A claim could therefore be directed towards patentable subject matter but still fail the machine-or-transformation test. *Bilski* reinforced the wholly preemptive standard, but failed to provide a new test to determine when a claim is preemptive. The Supreme Court simply stated that the claims at issue in *Bilski* could not be patented because they were drawn to an "abstract idea" and thus preempted the use of hedging in all fields.[122] By abandoning the machine-or-transformation test, *Bilski* abandoned the only available test to determine when a patent claim preempts a natural law in recognition of the rising Information Age. In doing so, however, the Supreme Court failed to provide any alternative guidance beyond the non-harmonious *Benson-Flook-Diehr* trilogy.

II. BIOTECHNOLGOY PATENTS IN THE INFORMATION AGE

The most recent tests for patentable subject matter have been developed largely by considering the software patents at issue in the *Benson-Flook-Diehr* trilogy. Each of the claims at issue questioned whether or not a mathematical algorithm utilized by computer in the form of software could be within the realm of patentable subject matter.[123] To aid the patentable subject matter

118. *Id.* at 954.
119. *See id.*
120. Bilski v. Kappos, 130 S. Ct. 3218, 3227 (2010).
121. *See id.*
122. *See id.*
123. *See* Diamond v. Diehr, 450 U.S. 175, 177–78 (1981) (upholding a patent claiming a process to cure rubber even though one step of the process relies on a mathematical formula, the Arrhenius equation, to calculate a temperature); Parker v. Flook, 437 U.S. 584, 585 (1978) (invalidating a patent claiming a mathematical algorithm useful for calculating an alarm limit); Gottschalk v. Benson, 409 U.S. 63, 65 (1972) (invalidating a patent claiming a

analysis, the Federal Circuit established the machine-or-transformation test as the appropriate test to analyze a process claim for patentable subject matter.[124] The Supreme Court narrowed the applicability of this test, noting that while it may have been useful during the Industrial Age, it may not be as useful in the Information Age of software and biotechnology.[125]

Initial rumblings questioning the patentability of diagnostics tests in the biotech industry arose in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*, where the patentee claimed a method of diagnosing a vitamin deficiency by measuring homocysteine levels in a subject and correlating elevated homocysteine levels with a vitamin deficiency.[126] The patentee conceded that the correlation between homocysteine and vitamin levels is a natural phenomenon but nonetheless argued that the use of the natural phenomenon should be patentable subject matter because it is integrated into a process.[127] But Justice Breyer disagreed in his dissent from the dismissal of certiorari, stating that the claim was nothing more than a natural phenomenon with "an instruction to read some numbers in light of medical knowledge."[128] *Metabolite* is not binding law, although it did bring a dark cloud on the medical diagnostics industry. With *Metabolite* being dismissed, it was only a matter of time before the medical diagnostics industry would confront subject matter eligibility again. That opportunity arose with the filing of *Prometheus*.

A. *PROMETHEUS* IN THE LOWER COURTS

Prometheus Laboratories ("Prometheus") was the exclusive licensee of a method patent directed towards determining the appropriate dosage regime of thiopurine drugs when treating autoimmune diseases such as Crohn's disease and ulcerative colitis.[129] After administering a thiopurine drug, such as 6-mercaptopurine or azathioprine, a patient's blood could be measured for

computer program designed to convert signals from binary-coded decimal form into pure binary form).

124. *In re* Bilski, 545 F.3d 943 (Fed. Cir. 2008).

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

126. Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., 548 U.S. 124, 125 (2006) (Breyer, J. dissenting). This case was dismissed as improvidently granted after a determination that the appellants had not argued invalidity for lack of patentable subject matter under § 101. *See id.* at 132–33.

127. *Id.* at 135–36 (respondents argue the process requires a transformation of the blood sample and produces a "useful, concrete, and tangible result" in detecting the vitamin deficiency).

128. *Id.* at 137.

129. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1293–94 (2012).

certain metabolites, such as 6-thioguanine ("6-TG") and 6-methyl-mercaptopurine ("6-MMP"), and these concentrations could be correlated to a harmful overdose or ineffective underdose of the drug.[130] The exemplar claim evaluated by the courts, claim 1, was as follows:

> 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 $8x10^8$ 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 $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.[131]

Mayo Collaborative Services ("Mayo") bought and used tests manufactured by Prometheus, but soon announced its intention to develop its own test.[132] Prometheus brought an infringement suit against Mayo, who responded that the patent was invalid under § 101.[133] Drawing from Justice Breyer's dissenting opinion in *Metabolite*, the district court determined that while the patent was infringed, it was also invalid because the claim was an attempt to monopolize a natural phenomenon.[134] The district court construed the claim to comprise three steps: an "administering" step, a "determining" step, and a "warning" step.[135] The "administering" and "determining" steps were categorized by the district court as "conventional" "data-gathering steps" insufficient to improve a natural phenomenon into the realm of patentable subject matter under *Flook*.[136] The "warning" step, according to the district court, was only a "mental step" employing a natural

130. *Id.* at 1294.

131. U.S. Patent No. 6,355,623 col. 20 l. 10–25 (filed Apr. 8, 1999).

132. *See Prometheus*, 132 S. Ct. at 1295–96.

133. *See* Prometheus Labs., Inc. v. Mayo Collaborative Servs., No. 04CV1200 JAH (RBB), 2008 WL 878910 (S.D. Cal. Mar. 28, 2008).

134. *Id.* at *7–8.

135. *Id.* at *6.

136. *Id.*

phenomenon.[137] Finally, the district court concluded that the claim " 'wholly pre-empts' all practical use" of the natural phenomenon.[138]

The Federal Circuit reversed, originally stating in its pre-*Bilski* decision that the "definitive test" for a process claim is the machine-or-transformation test.[139] The Federal Circuit rejected the categorization of the administering and determining steps as "data-gathering" and instead explained them to be "transformative."[140] Further, the Federal Circuit stated that the administering and determining steps were an integral part of the method of treatment, and therefore went beyond "insignificant extra-solution activity."[141] Once the Federal Circuit established the first two steps were patent eligible, the court noted that further limiting the claim by including a natural phenomenon did not render the claim non-statutory.[142] Under the Federal Circuit's reasoning, these "methods of treatment" were patentable subject matter.[143]

The Federal Circuit decision did not stand long, as the Supreme Court issued a GVR order after limiting the scope of the machine-or-transformation test in *Bilski v. Kappos*.[144] The Federal Circuit interpreted *Bilski* as holding the machine-or-transformation test could no longer be used to definitively exclude patentable subject matter but did not prevent its use as a test of sufficiency.[145] Maintaining the logic of its previous decision, the Federal Circuit again held the *Prometheus* claims to be patentable subject matter.[146]

B. THE SUPREME COURT DECISION

The Supreme Court again granted certiorari and reversed the Federal Circuit in a unanimous opinion authored by Justice Breyer.[147] Rejecting the Federal Circuit's post-*Bilski* application of the machine-or-transformation test, the Court emphasized that "one must do more than simply state the law

137. *Id.*

138. *Id.* at *10.

139. *See* Prometheus Labs., Inc. v. Mayo Collaborative Servs., 581 F.3d 1336, 1342 (Fed. Cir. 2009).

140. *See id.* at 1346–47.

141. *Id.* at 1348.

142. *See id.* at 1348–49.

143. *Id.* at 1346 (reasoning that methods of treatment "are always transformative when a defined group of drugs is administered to the body to ameliorate the effects of an undesired condition").

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

145. Prometheus Labs., Inc. v. Mayo Collaborative Servs., 628 F.3d 1347, 1355 (Fed. Cir. 2010).

146. *Id.* at 1359.

147. *See* Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289 (2012).

of nature while adding the words 'apply it.' "[148] According to the Court, the claims did not "add *enough*" to the natural law to make them patentable applications.[149] In reaching its conclusion, the Court claimed to rely on the precedential requirements that the claims contain "an 'inventive concept' sufficient to ensure the patent in practice amounts to significantly more than a patent upon the natural law itself" and that the claims do not "too broadly preempt the use of a natural law."[150]

The Court viewed the claim as simply reciting a natural law and including an "administering" step, a "determining" step, and a "wherein" or informing step.[151] The Court identified the natural law as the correlation between the metabolite levels and the need to increase or decrease the drug dosage.[152] The "administering" step, according to the Court, provided a reference to those who would be interested in the natural law (doctors treating patients with the drug), the "determining" step only informed the relevant audience to do something that was "well known in the art," and the "wherein" step did nothing more than inform a doctor about the natural law.[153] The Court concluded that the claims simply informed doctors about the natural law and added "routine, conventional activity."[154] The steps were therefore not "enough," taken either independently or as a whole, to contain the requisite "inventive concept."[155] Without an inventive contribution applying the natural phenomenon, the *Prometheus* Court held that the claims were not patentable subject matter.[156]

As an alternative justification for excluding the *Prometheus* claim as unpatentable subject matter, the Supreme Court engaged in a preemption analysis. After defining the natural law as the correlation between an artificial drug metabolite and effective drug dosage, the Court reasoned that the claims "broadly preempt[ed]" this natural law.[157] Consistent with previous Courts and commentators, the *Prometheus* Court was concerned that patent protection over natural laws would "inhibit further discovery by improperly

148. *Id.* at 1294; *see also* USPTO, 2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature, USPTO.GOV (July 3, 2012), *available at* http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf.

149. *See Prometheus*, 132 S. Ct. at 1297, 1302–03.

150. *Id.* at 1294.

151. *Id.* at 1297.

152. *See id.*

153. *See id.* at 1297–98.

154. *See id.*

155. *See id.* at 1299.

156. *See id.*

157. *Id.* at 1294, 1302.

tying up the future use of the laws of nature."[158] The Court feared that validating the patent would "tie up the doctor's subsequent treatment decision," prevent the development of "more refined treatment recommendations" that might be combined with later discovered natural laws, or preempt later developed forms of the "determining" step.[159] While the Court acknowledged this natural law is narrowly defined, it refused to allow this to factor into its decision to avoid "depart[ing] from case law precedent."[160]

In a surprisingly noncommittal corollary to the preemption analysis, the *Prometheus* Court noted that it was not deciding the case on the preemptive features of the claims but on the lack of inventive contribution of the claims.[161] The Court stated, "We need not, and do not, now decide whether were the steps at issue here les conventional, these features of the claims would prove sufficient to invalidate them."[162] The opinion is unclear as to whether or not an inventive concept would allow an application of a natural law to be patentable subject matter if that application preempts any future use of the natural law.

C. DIAGNOSING THE *PROMETHEUS* DECISION

Despite the need for clarity on the issue of patentable subject matter, the *Prometheus* decision ultimately can only be described as judicial sausage.[163] As a preliminary matter, the *Prometheus* Court failed to adequately justify its

158. *Id.* at 1301.

159. *Id.* at 1302.

160. *See id.* at 1302.

161. *See id.* (noting in dicta that the preemption analysis "simply reinforces our conclusion that the process described in the patents are not patent eligible").

162. *Id.*

163. Otto von Bismarck is frequently credited with describing the legislative process as grotesque as making sausage. *See* Charles W. Wolfram, *Bismarck's Sausages and the ALI's Restatements*, 26 HOFSTRA L. REV. 817, 817 (1998). Similarly, the judicial process can be described as making sausage when inconsistent opinions are joined together to form a potentially unjust result. *See* Roscoe Pound, *Enforcement of Law*, 20 GREEN BAG 401 (1908). As described by Pound:

> The process and the result are conceived of as something purely logical and scientific. If the result chances to be just, so much the better. But justice in the cause in hand is not the chief end. The facts of concrete causes are to be thrown into the judicial sausage-mill and are to be ground into uniformity; and the resulting sausage is to be labeled justice. Absolute uniformity of decision of cases logically alike and entire certainty in advance as to the outcome on any given state of facts are the ends it seeks.

Id. at 404.

determination that the correlation between an artificial drug metabolite level and drug efficacy should be considered a natural law. Even if the correlation is a natural law, *Prometheus* did not provide clear guidance as to what, precisely, would be "enough" to render a claimed invention a claim over an application of a natural law rather than a claim over the natural law itself. The Court reiterated the *Flook* holding that adding insignificant, post-solution activity to a natural law was not "enough"[164] but failed to specify why the claims in *Diehr* were "enough." Once the Court determined that the *Prometheus* claims were unpatentable subject matter, it rationalized this decision through a superficial preemption analysis that misapprehended the purpose underlying the preemption standard.

1. The Imprecise Natural Law

The Supreme Court previously justified excluding natural laws from patentable subject matter because it considered the natural laws to be "basic tools of science and technological work" and reserved for all of mankind.[165] It is a reasonable assertion that if a patent is so broad that future inventors are unable to conduct research or develop technologies, then the constitutional mandate to promote innovation will not be met. For this reason, it is well established that laws of nature and natural phenomena, such as electro-magnetism or $E=mc^2$, cannot be patentable subject matter.[166] In order to determine if a patent claim broadly preempts a natural law, however, it is important to fully understand the natural law at issue.

The natural law at issue in the *Prometheus* claims can be better appreciated with an understanding of the biochemical context (Figure 1). The thiopurine drug 6-mercaptopurine ("6-MP") is commonly used to treat inflammatory bowel disease.[167] Once administered, the enzyme hypoxanthine-guanine phosphribosyltransferase ("HGPRT") converts 6-MP into 6-thioinosine 5'-monophosphate ("6-TIMP").[168] Other enzymes metabolize 6-TIMP into pharmacologically active 6-TG metabolites referred to by the *Prometheus* claims.[169] HGPRT is not able to convert all available 6-MP, however, as the competing enzyme thiopurine methyltransferase ("TPMT") simultaneously

164. *Prometheus*, 132 S. Ct. at 1297.

165. *See* Gottschalk v. Benson, 409 U.S. 63, 67 (1972).

166. *See* Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).

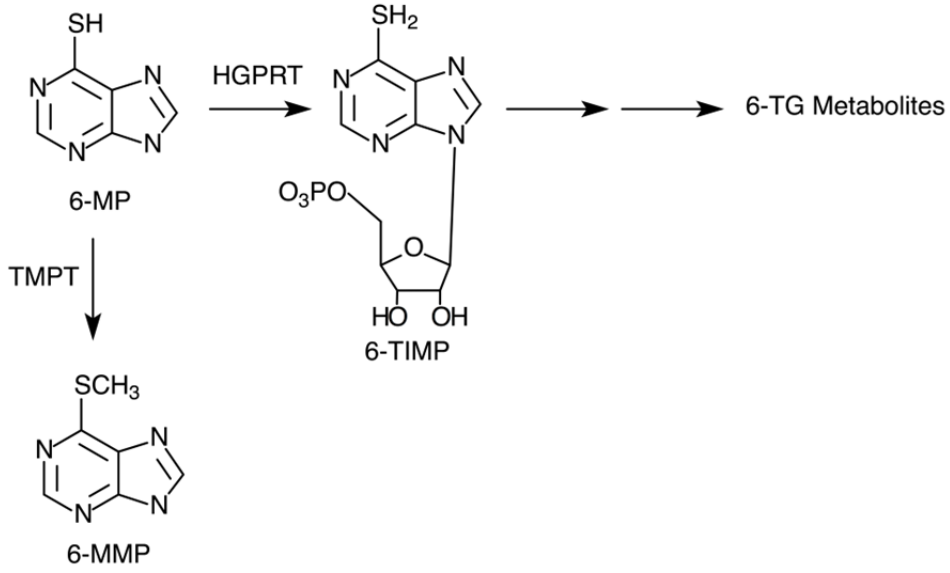
167. Marla C. Dubinsky, et al., *Pharmacogenomics and Metabolite Measurements for 6-Mercaptopurine Therapy in Inflammatory Bowel Disease*, 118 GASTROENTEROLOGY 705, 705 (2000).

168. Elise Petit, *Differential Toxic Effects of Azathioprine, 6-Mercaptopurine and 6-Thioguanine on Human Hepatocytes*, 22 TOXICOLOGY IN VITRO 632, 633 (2008).

169. *See id.*

metabolizes some of the administered drug into 6-methyl-mercaptopurine ("6-MMP").[170] Different patients may have differing levels of TPMT activity, making it difficult for doctors to know precisely how much of the administered 6-MP drug is metabolized into the desired 6-TG metabolite and how much is metabolized into the undesired 6-MMP metabolite.[171] Additionally, very high levels of 6-TG can result in undesired side effects.[172] The inventors of the *Prometheus* claims discovered precise levels of 6-TG that are necessary for drug efficacy and those that result in the undesired side effects.[173]

Figure 1: Metabolic pathway of the synthetic drug 6-mercaptopurine.

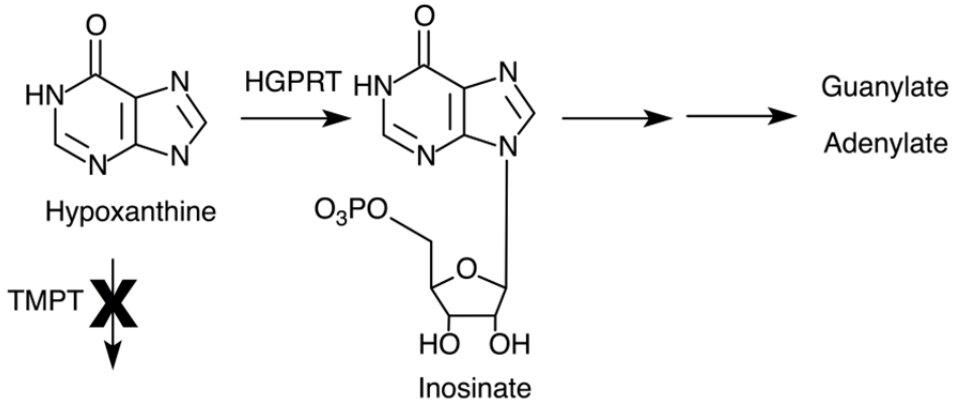


Of course, as recognized by the *Prometheus* Court, 6-TG is an artificial metabolite that would not exist without the "human action (the administration of a thiopurine drug) to trigger a manifestation" of the correlation.[174] Under natural conditions (i.e., without human action), HGPRT acts upon naturally occurring hypoxanthine or guanine to generate inosinate or guanylate (Figure 2).[175] This metabolizing reaction could certainly be considered a natural law. Drug activation, however, frequently relies on an enzyme's ability to recognize and metabolize *artificial* substrate analogs, such

170. *See* Dubinsky, *supra* note 167, at 705.
171. *Id.*
172. *Id.* at 711 (explaining how excessively high 6-TG levels can result in leukopenia).
173. U.S. Patent No. 6,355,623 (Filed April 8, 1999).
174. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1297 (2012).
175. JEREMY M. BERG, ET AL., BIOCHEMISTRY 698 (5th ed. 2002).

as 6-MP. The Court suggested that even though human action is required to supply the artificial substrate analog, an enzyme's ability to metabolize the artificial substrate analog is itself an "entirely natural process."[176]

Figure 2: Metabolism of Natural Substrates



The rationale provided by the Court is weak. The Court assumed that the process whereby HGPRT metabolizes hypoxanthine into inosinate is identical to the process whereby HGPRT metabolizes 6-MP into 6-TIMP.[177] The Court provided no basis for this assumption. While the same enzyme may be used in both processes, enzymatic binding affinities and kinetic parameters likely vary between substrates. While differences between the processes may be subtle, they cannot be described as identical. The metabolism of the artificial substrate, 6-MP, to the pharmacologically active product, 6-TG, should not be considered a natural law but an exploitation of HGPRT's ability to metabolize its natural substrate. The inventive contribution of the patent claim can therefore be seen as the application of the enzyme's natural abilities to an artificial substrate.

The correlation described by the *Prometheus* claim was further removed from this already artificial reaction of the substrate analog. The maximum and minimum 6-TG levels indicated by the claimed process are parameters for controlling the artificial reaction correlated with drug efficacy and harmful side effects. The *Prometheus* Court stated that this correlation was itself a law of nature.[178] But there is nothing natural about drug efficacy or drug induced toxicity. There is no justification for the presumption that an

176. *Prometheus*, 132 S. Ct. at 1297.

177. *See id.* ("The relation [between drug metabolite concentration and drug toxicity] is a consequence of the ways in which thiopurine compounds are metabolized by the body—entirely natural processes.").

178. *Id.* at 1296.

artificial substance can cause a natural effect. Similarly, a correlation between an artificial metabolite blood level and an artificially induced effect should not be deemed a natural law.

2. Preemption of an Imprecise Natural Law

The vague "broadly preempts" standard implemented by *Prometheus* Court destabilizes the historic "wholly preempts" standard established by *Benson* and affirmed in *Bilski*.[179] The Court is unclear if the term "broadly preempts" is intended to capture the wholly preemptive standard articulated in *Benson* or if it suggests that a process claim might also be invalid when it preempts some subset of natural law applications but not the natural law in its entirety. Additionally, it is unclear if a process claim is invalid for lack of patentable subject matter if it includes nonconventional activity, and therefore contains an inventive concept, but is still broadly preemptive.

Benson applied the "wholly preempted" standard independent of any inventive concept analysis.[180] By relegating a claim that allows no "substantial practical application" of a natural law as unpatentable subject matter, future inventors can continue to discover novel applications without the hurdle of a patent over the natural law itself.[181] The *Flook* Court implemented the inventive concept requirement after acknowledging a claimed process did not wholly preempt the algorithm but should nonetheless be unpatentable subject matter.[182] The *Prometheus* Court may have attempted to capture the *Flook* criteria in formulating the "broadly preempt[s]" standard to indicate the claim need not wholly preempt the natural law when there is no inventive concept.[183] Alternatively, the *Prometheus* Court may have intended the broad preemption standard to be a separate analytical prong from the requirement of an inventive concept, rendering an applied natural phenomenon unpatentable subject matter because the application itself preempts any other future application of the natural law.

The *Prometheus* Court found the claims to be unpatentable because the "determining" step was conventional, as "scientists routinely measured metabolites as part of their investigations into the relationship between metabolite levels and efficacy and toxicity of thiopurine compounds."[184] It is,

179. *See* Gottschalk v. Benson, 409 U.S. 63, 72 (1972); Bilski v. Kappos, 130 S. Ct. 3218, 3231 (2010) (reasoning that a patent on "risk hedging would pre-empt use of this approach in all fields"); *see also* Ghosh, *supra* note 63, at 349–50.

180. *Benson*, 409 U.S. at 63.

181. *See Benson*, 409 U.S. at 71–72.

182. *See* Parker v. Flook, 437 U.S. 584, 589–90 (1978).

183. *Prometheus*, 132 S. Ct. at 1294.

184. *Id.* at 1298.

however, imaginable that in a similar claim, an applicant develops a diagnostic test where determining the concentration of a particular drug metabolite is as novel and nonconventional as the application of the results. This would pass the inventive concept test even if a natural law were included, as the "determining" step would be nonconventional. But the preemptive weight of the claim would not be any different. If the nonconventional elements of the claim render the claim patentable subject matter, then the preemption standard becomes meaningless. If, on the other hand, the broadly preemptive nature of the claim alone renders the claim unpatentable, the nonconventional aspect of the claim becomes meaningless.

The *Prometheus* Court did not indicate an answer to whether or not a nonconventional step may sustain a claim even if it is preemptive of a natural law.[185] The Court did, however, suggest that new drugs and new methods of using an existing drug would remain patentable.[186] Given the Court's willingness to broadly define a natural law, a method of using a drug surely preempts some natural law.[187] Presumably it's the nonconventional nature of the drug that allows it to be patentable subject matter rather than its non-preemptive aspects.

3. The Inventive Concept and the False Harmonization of Flook and Diehr

Even if the *Prometheus* Court's formulation of the natural law within the claims at issue are correct, the Court failed to set forth a clear test to indicate enough has been added to the natural law to make it a patentable application. *Prometheus* emphasized the need for an "inventive concept" by attempting to harmonize *Flook* and *Diehr*.[188] The Court concluded that the "case for patentability . . . [of the *Prometheus* claim] is weaker than the (patent-eligible) claim in *Diehr* and no stronger than the (unpatentable) claim in *Flook*."[189] To reach this conclusion, the *Prometheus* Court separately examined each of the process steps and determined that none consisted of anything more than "well-understood, routine, conventional activity" and that "those steps, when

185. *Id.* at 1302 ("We need not, and do not, now decide whether were the steps as issue here less conventional, these [preemptive] features of the claims would prove sufficient to invalidate them.").

186. *See id.* at 1302 (stating that new drugs or methods of using an existing drug are not a claim over the natural laws).

187. The fact that a drug molecule of a particular size, shape, and electrostatics inhibits a particular enzyme active site could be construed as a natural law. Once the drug is ingested, the laws of physics allow the particular drug to inhibit the particular enzyme through no human activity. Any patent on a particular inhibitor of a particular enzyme preempts a very narrow physical law. This result is, of course, absurd.

188. *Prometheus*, 132 S. Ct. at 1294.

189. *Id.* at 1299.

viewed as a whole, add nothing significant beyond the sum of their parts taken separately."[190] The *Prometheus* Court reiterated the requirement in *Diehr* that the claim should be analyzed as a whole, and even emphasized that a novel combination of known steps may still be patentable.[191] But in application, the Court dissected the claims and examined each step for something more than conventional activity, precisely the methodology used in *Flook*.

As discussed in Section I.B, *supra*, there is significant tension between analyzing a claim as a whole, as emphasized in *Diehr*, and the point of novelty approach, utilized in *Flook*. Ignoring this conflict, the Court laid *Diehr* and *Flook* on a patentability spectrum, where the rubber curing process in *Diehr* is an application and therefore patentable subject matter, while the alarm-limit calculation in *Flook* is a non-patentable law of nature with non-inventive conventional activity. Attempting to rationalize the inconsistency between *Flook* and *Diehr*, the *Prometheus* Court seemed to revise the *Diehr* opinion thirty years after it was decided. In referring to the *Diehr* claims *Prometheus* stated, "[the *Diehr* Court] nowhere suggested that all these steps, or at least the combination of those steps, were in context obvious, already in use, or purely conventional."[192] Of course the reason *Diehr* did not make a determination as to the novelty or obviousness of the added steps was because *Diehr* flatly rejected the point of novelty approach of *Flook*.[193]

The vastly different approaches taken by *Flook* and *Diehr* render the *Prometheus* analysis internally inconsistent. An analysis under *Diehr* would not require an inquiry as to whether or not the "administering" and "determining" steps were conventional or novel but would require an inquiry into what was being claimed as a whole. At no point was there an evaluation of the *Prometheus* claim as a whole. The Court examined the "administering" and "determining" steps individually and found them to be "conventional." The only novel element, according to the Court, was a law of nature, which was insufficient to render the conventional steps patentable. This was the methodology used in *Flook*.

Another way to consider the misapplication of *Flook* and *Diehr* by the *Prometheus* Court is to consider the starting points of each claim. In *Flook*, the

190. *Id.* at 1298.

191. *Id.* ("[A] new combination of steps in a process may be patentable even though all of the constituents of the combination were well known and in common use before the combination was made." (quoting Diamond v. Diehr, 450 U.S. 175, 188 (1981))).

192. *Id.* at 1299.

193. *See Diehr*, 450 U.S. at 188–89 (rejecting the use of "novelty" in making a determination of patentable subject matter).

Court noted the use of a mathematical formula within the claim and asked if the other steps in the process brought the claim into the realm of patentable subject matter. That is, did the additional steps narrow the scope of the claim enough to make it patentable subject matter, or was it "insignificant post-solution activity?" In *Diehr*, the focus was directed towards the process as a whole. The question for the Court then became whether or not the mathematical formula brought the rest of the process out of the scope of patentable subject matter. The other steps of the rubber curing process were undoubtedly patentable subject matter without the mathematical formula, even if the steps were conventional (and thus unpatentable under § 102 and § 103). Since an accepted doctrine of patent law is that additional elements narrow the scope of the claim, the addition of a mathematical formula should not move an otherwise patentable process into the sphere of non-patentable subject matter.[194] However this is precisely the conclusion reached by the *Prometheus* Court. It appears the *Prometheus* Court represents a shift back towards the *Flook* approach under the false pretext of uniform jurisprudence.

III. BIOLOGICAL CORRELATIONS AS NATURAL LAWS

Any test for patentable subject matter should be viewed in the context of the constitutional mandate to promote the progress of science and technology. Ideally, each circumstance would be viewed with an eye towards determining how much patent incentive is required to promote innovation, and to what degree patents cause more harm to technological development than help it. It is therefore important not to grant patents on the "basic tools of scientific and technological innovation,"[195] as overly broad claims may inhibit innovation more than encourage it. But it does not logically follow that a patent over any correlation will inhibit innovation more than a patent incentive would help spur it.

The judicially created natural law doctrine is an often-used approach to balancing the scope of patentable subject matter and inventor incentive, although it is not without critics.[196] Professor Risch, for example, argues that inconsistent and unclear jurisprudence guiding the doctrine generates a destabilizing effect that outweighs any benefit of a bright-line rule.[197] Instead,

194. *See* Robert A. Armitage, *A Prometheus, Playing With Fire, Gets Burned*, 4 LANDSLIDE 1, 11 (2012).

195. *See* Gottschalk v. Benson, 409 U.S. 63, 267(1972).

196. *See* Michael Risch, *Everything is Patentable*, 75 TENN. L. REV. 591, 624–28 (2008) (arguing patent scope is better contained through strict enforcement of patentability restrictions rather than patent eligible subject matter restrictions).

197. *See id.* at 645–50.

Risch argues that cases questioning patentable subject matter are more appropriately decided through rigorous application of the other patentability requirements of novelty (§ 102), nonobviousness (§ 103), and written description and enablement (§112).[198] Other commentators disagree, arguing that the natural phenomenon doctrine provides a unique hurdle for patent validity.[199]

Ultimately, viewing many biotechnology patents through the lens of the natural phenomenon doctrine is overly cumbersome to administer and generally inappropriate. The above analysis on the *Prometheus* decision suggests that part of the struggle in applying the doctrine may be caused by a misunderstanding of what should be considered a natural phenomenon. Even if a natural phenomenon was properly identified, it is not clear that the natural phenomenon doctrine is the best method to control the scope of patentable subject matter and balance inventor incentives. In biotechnology, the distinction between natural and non-natural phenomena is often subtle, and there is no reason to believe a patent on a non-natural phenomenon would be helpful for technological development and a patent on a natural phenomenon would be ultimately destructive.

A. DISTINGUISHING NATURAL AND NON-NATURAL PHENOMENA

Before future courts and inventors can properly evaluate a patent claim for broad preemption or inventive concept under the natural phenomenon doctrine, they must first clearly define the natural phenomenon at issue. A poor definition of the natural phenomenon could cause an application of a natural law to be improperly categorized as the natural phenomenon itself. Such a determination should not be made in hindsight view of the patent claims, although this is often difficult when inventions are created contemporaneously with the discovery of the natural phenomena.

The rapidly growing field of personalized medicine exploits correlations between biomarkers, genes, and synthetic metabolites and the efficacy or toxicity of treatment regimens. *Prometheus* broadly categorized these correlations as natural laws and therefore not patentable subject matter.[200] This was an error.[201] All correlations can ultimately be expressed as a simple mathematical relationship between two or more variables and, as such, cannot be patentable under *Benson*. But this view may be too simplistic for the developing Information Age. *Chakrabarty* delineated inventions "made by

198. *See id* at 598.
199. *See* Ghosh, *supra* note 63, at 357–58.
200. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1297 (2012).
201. *See supra* Section II.C.1.

man" from discoveries of pre-existing natural phenomena.[202] Therefore, correlated variables invented through human efforts should be distinguished from those naturally existing or entirely abstract. The variables in *Benson* and *Flook* were too abstract to allow the algorithm to be considered non-natural.[203] In contrast, many biological correlations can be distinguished by examining the non-natural variables. When a variable itself is non-natural and inventive, such as the 6-MP drug in *Prometheus*, a correlation arising form this variable is likewise non-natural and inventive. In these circumstances, the correlations would not exist without human influence, and these correlations should not be considered natural.

Medical diagnostics often analyze either natural or non-natural biomarker correlations to evaluate an appropriate therapeutic treatment for a patient.[204] Diagnostics that determine the onset of a disease or a probability of contracting a disease are generally natural correlations. These associations remain true whether or not a doctor has exerted any human influence on the patient. When the correlation is between a synthetically introduced compound and an observed result, however, the correlation can no longer be considered natural. Such correlations do not exist in nature because, by their very definition, they are controlled by a non-natural variable.

Once natural and non-natural correlations are properly distinguished as a factual matter, the significance of applying the natural phenomenon doctrine can be considered as a matter of policy. Discovery of both natural and non-natural correlations are important for medical technology and, as such, should be encouraged under the constitutional mandate. However there is no clear indication that a patent incentive for non-natural correlations but not natural correlations would be the most efficient mechanism for inducing their discovery. Both natural and non-natural correlations used to diagnose a patient may be more appropriately defined as methods of diagnosis rather than the "basic tools of scientific and technological work."[205] This questions the utility of the natural phenomenon doctrine in the biotechnology field.

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202. *See* Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (holding that which is "made by man" as patentable subject matter); *see also* Funk Bros. Seed Co. v. Kilo Inoculant Co., 333 U.S. 127, 130 (1948).

203. *See* Diamond v. Diehr, 450 U.S. 175, 186 (1981) ("The [*Flook*] claims were drawn to a method for computing an 'alarm limit.' An 'alarm limit' is simply a number and the Court concluded that the application sought to protect a formula for computing this number.").

204. *See, e.g.*, Agata Zieba et al., *Molecular Tools for Companion Diagnostics*, 29 NEW BIOTECHNOLOGY 634 (2012) (describing how biomarkers can be used to determine the appropriateness of administering Herceptin to a particular patient).

205. Gottschalk v. Benson, 409 U.S. 63, 67 (1972). This Note focuses on the economic incentive theory of patents and does not consider the public policy rationale of categorically

B. NATURAL CORRELATIONS AND DISEASE DIAGNOSTICS

Doctors diagnose many diseases by correlating the presence or absence of naturally existing biomarkers with a particular disease. HIV, for example, is commonly diagnosed by detecting antibodies present in a patient. These antibodies would not exist without infection, although they would exist without human interaction with the patient. The presence of an antibody biomarker is a natural result of HIV infection, and the correlation of biomarker with HIV diagnosis is a natural correlation. Likewise, diagnosing a disease by comparing the abnormal level of a naturally occurring biomarker to the normal level is an observation of a natural correlation.[206] For example, an elevated hemoglobin A1c measurement (> 6.5%) in a patient may allow a doctor to diagnose diabetes.[207] Since the onset of diabetes is a natural process, the physiological response (elevated hemoglobin A1c levels) is likewise a natural phenomenon.

Justice Breyer was correct in *Metabolite* when he unequivocally stated that the correlation between elevated homocysteine levels and vitamin deficiency was a natural phenomenon.[208] While measuring homocysteine levels is an indirect measurement of vitamin deficiency, the correlation would exist without human knowledge or discovery of the correlation. Furthermore, no human action is required to bring the correlation into existence. It is therefore a natural correlation and not patentable subject matter under the natural phenomenon doctrine.

C. CORRELATIONS WITH GENETIC SEQUENCES

Genetic markers can also be used to diagnose a disease through correlation, although the ability to construct synthetic manifestations of the genetic material poses an added complication to the natural correlation analysis. The genetic sequence of an individual can be compared to a genetic

banning methods of diagnosis from patentable subject matter to increase medical access, as other patent systems have done. *See, e.g.*, Convention on the Grant of European Patents, art. 53(c), Oct. 5, 1973, 1065 U.N.T.S. 254 (as amended Nov. 29, 2000), *available at* http://documents.epo.org/projects/babylon/eponet.nsf/0/7bacb229e032863dc12577ec004ada98/$FILE/EPC_14th_edition.pdf.

206. *See In re* Grams, 888 F.2d 835 (Fed. Cir. 1989) (describing the diagnosis of an abnormality by comparing level of a marker in an individual to normal levels as a mathematical algorithm).

207. Christopher D. Saudek & Jessica C. Brick, *The Clinical Use of Hemoglobin A1c*, 3 J. DIABETES SCI. & TECH. 629, 632 (2009).

208. Lab. Corp. of Am. Hlds. v. Metabolite Labs., Inc, 548 U.S. 124, 135 (2006) (Breyer, J., dissenting). Even the patent owners acknowledged this correlation is a natural phenomenon because "[i]t is an observable aspect of biochemistry in at least some human populations." *Id.*

sequence from a non-diseased individual, and certain differences in the sequence can be correlated with a disease. This type of genetic comparison was at issue in *Association Molecular Pathology v. U.S. Patent and Trademark Office* (*Myriad Genetics*).[209] In *Myriad Genetics*, the inventors claimed an "isolated DNA coding for a BRCA1 polypeptide" and a method of comparing *BRCA1* gene in a tumor sample to a *BRCA1* gene in a non-tumor sample.[210] Three different types of genetic manifestations were covered by the claim: DNA, mRNA, and cDNA. DNA is the genetic material that is passed from parent to child and retains information pertaining to how the body functions. Parts of the DNA, called genes, serve as templates for the formation of mRNA through a natural biochemical process called transcription. Not all parts of the gene are used as a template for the final mRNA product,[211] but only those parts that will actually be used by downstream cellular processes to express proteins. mRNA is therefore generally shorter than the DNA gene in humans, but exists as a result of natural cellular processes. cDNA can be synthesized by scientists using an mRNA template, forming a more stable manifestation of the mRNA.[212] cDNA does not exist naturally, as it can only be synthetically generated through laboratory manipulation.

Myriad Genetics distinguished "natural DNA" from "isolated DNA," with the former being unpatentable subject matter and the latter being patent eligible.[213] The Federal Circuit noted the different chemical makeup of isolated DNA[214] and cDNA and determined they were both non-natural "man-made composition[s] of matter."[215] The Federal Circuit also held, however, that methods of "comparing" a genetic sequence of a tumor sample to a genetic sequence of a non-tumor sample, and correlating this difference to a genetic alteration of the tumor sample, are unpatentable "abstract mental processes."[216] While this step of comparing genetic

209. Ass'n Molecular Pathology v. U.S. Patent and Trademark Office, 689 F.3d 1303 (2012), *cert. granted*, 133 S. Ct. 694 [hereinafter *Myriad Genetics*].

210. *Id.* at 1309–10.

211. The gene serves as a template for RNA transcription, but sections of the RNA transcript are excised through a process called splicing. Additional biochemical modifications are made to the RNA transcript before it is considered mature mRNA.

212. cDNA contains bases complementary to those found in the mRNA. mRNA is highly prone to degradation, whereas cDNA generally can last longer in a laboratory environment, making it the preferred method of storing information contained within mRNA.

213. *Myriad Genetics*, 689 F.3d at 1333.

214. Isolated DNA is removed from naturally occurring DNA through the breakage of covalent phosophodiester bonds in the backbone of the DNA. *See id.* at 1328.

215. *Id.* at 1330.

216. *Id.* at 1334.

sequences may be an unpatentable mental step, the Federal Circuit did not directly confront the issue of whether the correlation itself should be considered a natural phenomenon.

By clearly distinguishing natural and non-natural correlations, the method claims in *Myriad Genetics* can be analyzed for patentable subject matter under the natural phenomenon doctrine in addition to the abstract mental steps doctrine. The correlation between naturally occurring DNA and mRNA with disease diagnosis or disease propensity is not difficult to establish as a natural correlation. Such a correlation would exist without inventive effort because the variables of the correlation naturally exist. Since both the disease and the DNA are naturally occurring, the correlation between the two can properly be categorized as a natural correlation. Isolated DNA and cDNA, however, are not naturally existing molecules, and any correlation between these molecules and a disease diagnosis cannot naturally exist. Therefore the existence of a non-natural correlation is dependent upon the status of the DNA being correlated: either a naturally occurring DNA sequence or a non-natural isolated DNA or cDNA. The patent eligibility of isolated DNA and cDNA molecules is currently pending review by the Supreme Court,[217] and a reversal of *Myriad Genetics* likely will affect the correlations' status as non-natural.

The result that a correlation between a natural DNA and a disease should be a natural phenomenon while the correlation between an isolated DNA and a disease should be considered a man-made phenomenon is surprising. After all, the genetic information used to generate the correlation is fully contained within the naturally occurring DNA. This is dissimilar to the drug metabolites in *Prometheus*, which disseminate information that no natural metabolite could provide. When the *Myriad Genetics* examined similar process claims comprising "analyzing" or "comparing" genetic sequences, it found them to be unpatentable subject matter because they were "abstract mental steps."[218] The mental steps doctrine, not the natural phenomenon doctrine, led the Federal Circuit to its result.[219] The mental steps of simply observing a man-made correlation may be independently unpatentable subject matter, but this does not make the man-made correlation a natural phenomenon.

217. Ass'n Molecular Pathology v. Myriad Genetics, 133 S. Ct. 694 (2012).

218. *Myriad Genetics*, 689 F. 3d at 1334.

219. *Id.*; *see also* Donald S. Chisum, *The Patentability of Algorithms*, 47 U. PITT. L. REV. 959, 981 (1986) ("[T]here is no basis for lumping together phenomena of nature and abstract concepts with 'mental steps.' A process consisting partially or wholly of 'mental steps' does not exist in nature and can be quite specific.").

In some cases, the correlations exploited by medical diagnostics are properly categorized as natural phenomena. This often occurs, for example, when the correlation used to diagnose a particular disease, for example diabetes or HIV. With the advancement of technology, however, medical diagnostics exploit correlations between diseases and genetic material. Proper categorization of these correlations as natural phenomena or man-made correlations is dependent upon how the courts categorize DNA molecules as either natural or non-natural. After the Federal Circuit's decision in *Myriad Genetics*, these correlations ought to be considered non-natural and should not be excluded under the natural phenomenon doctrine.

D. CORRELATIONS IN PERSONALIZED MEDICINE

Personalized medicine is a general umbrella term used for designing medical treatments more specifically tailored to an individual's need than is available in current practice.[220] An individual patient may be more or less responsive to a particular drug than any other patient. Many different factors may be responsible for drug efficacy including bioavailability, diet, environment, age, physical activity, or genetic makeup.[221] Personalized medicine can increase treatment efficacy, reduce side effects, lower healthcare costs, and bring drugs to market faster.[222] Drugs may also be more likely to pass FDA screening with a companion diagnostic because the diagnostic can identify particular subpopulations for which the drug is effective, eliminating those subpopulations for which the drug may be ineffective.[223] This can reduce healthcare costs by ensuring that each patient gets the appropriate treatment instead of being treated on a trial-and-error basis.

Personalizing a dosage regimen may require iterative testing of a biomarker or metabolite and adjusting the drug dosage in accordance with a

220. *See* Margaret A. Hamburg, *The Path to Personalized Medicine*, 336 NEW ENGLAND J. MEDICINE 301 (2010).

221. *See, e.g.*, Qiang Ma & Anthony Y. H. Lu, *Pharmacogenetics, Pharmacogenomics, and Individualized Medicine*, 63 PHARMACOLOGICAL REVS. 437, 438 (2011).

222. *See* Christopher P. Leamon & Mike A. Sherman, *The Rise of Companion Diagnostics: A Step Towards Truly Personalized Medicine*, ONCOLOGY BUS. REV. 6 (May 2012), *available at* http://www.oncbiz.com/documents/OBR_0512_v3_COMPDIAG.pdf; *A Push for Personalized Medicine Encourages New Companion Diagnostics*, GLOBALDATA.COM (June 25, 2012), http://www.globaldata.com/PressReleaseDetails.aspx?PRID=215&Type=Industry&Title=Medical+Devices.

223. For example, the drug Selzentry, marketed by Pfizer, is effective in CCR5-tropic HIV-1, but not CXCR4-tropic HIV-1. An important companion diagnostic would be able to determine which viral tropism a particular patient is infected with. *See Viral Tropism*, SELZENTRY, http://www.selzentry.com/hcp/viral-tropism.html (last visited Nov. 3, 2012).

known correlation. As can be seen from the *Prometheus* claims, 6-thiopurine drug dosage may be increased or decreased in order to increase the efficacy of the drug or reduce side effects in accordance with 6-TG metabolite levels.[224] Another method is the growing field of pharmacogenomics, where a patient's genome can be correlated with drug efficacy or toxicity.[225] By sequencing a patient's genetic code, the treating physician can more appropriately select an effective drug treatment.

Often, a natural biomarker is iteratively used to determine drug efficacy. Hemoglobin A1c levels, for example, are not only used to diagnose diabetes, but are regularly measured to assess the treatment regimen. Two different correlations can be considered in this circumstance. The first correlation is a natural correlation between hemoglobin A1c level and the disease of diabetes, as discussed in *supra* Section III.B. The second correlation is a correlation between hemoglobin A1c level and drug efficacy. But determining whether or not this second correlation is a natural phenomenon or not is largely semantic. Is this a correlation between drug efficacy and the diabetic state? Or is this second correlation little more than monitoring the drug's impact on the first correlation and therefore should not be thought of as a separate, man-made correlation? This correlation may still be a patent eligible application of the natural correlation as the use of the correlation is non-conventional under *Prometheus*.

A growing trend in personalized medicine focuses on a patient's individual genetic information to select the appropriate drug or dosage regimen. Pharmacogenetics studies the efficacy or toxicity of a drug correlated to an individual's variation of a particular gene, while pharmacogenomics studies how a larger system of genes may affect drug efficacy or toxicity.[226] The inventors of the *Prometheus* claims found genetic variation of the TMPT gene correlated with different metabolic rates of the thiopurine drug, developing one of the first applications of pharmacogenetics.[227] Given the rapid growth of pharmacogetics and pharmacogenomics in developing drug treatment regimens, along with the ever-increasing ease of genome sequencing, it is important to carefully

224. *See supra* Section II.B.1.

225. *See* William E. Evans & Mary V. Realling, *Pharmacogenomics: Translating Functional Genomics Into Rational Therapeutics*, 286 SCIENCE 487 (1999).

226. *See generally* Richard M. Weinshillboum & Liewei Wang, *Pharmacogenetics and Pharmacogenomics: Development, Science, and Translation*, 7 ANNUAL REV. GENOMICS & HUMAN GENETICS 223, 224–25 (2006).

227. *See* Dubinsky, *supra* note 117. The correlation referred to here is different correlation than at issue in the *Prometheus* claims discussed in *supra* Section II.C.1. The pharmacogenetic correlation relates the genetic variation to the rate of drug metabolism.

consider when such correlations should be patentable subject matter. But when the drug analyzed is non-naturally occurring and the isolated genes being analyzed are themselves non-natural under *Myriad Genetics*, it seems difficult to consider the correlation between the variables as a natural phenomenon.

E. INVENTION AND DISCOVERY OF BIOLOGICAL CORRELATIONS

Natural phenomena were excluded from patentable subject matter because, in part, the applicant did not invent anything and the mere discovery of the natural phenomenon did not warrant a patent.[228] At the same time, it is believed to strike the proper balance between inventor incentives and ensuring other inventors can further innovate in the field. This justification, however, fails to exclude the discovery of a man-made correlation from patentable subject matter, even if such a discovery is neither invented nor applied. The fact that the correlation would not exist without human creation of the variables means that it cannot be natural. A man-made correlation cannot be said to "broadly preempt" any natural law or "basic tools of scientific and technological innovation" because it is itself synthetic. For this reason, judges and patent examiner should proceed cautiously before labeling any correlation a natural phenomenon.

Distinguishing between natural and non-natural correlations provides a starting point for courts applying the natural phenomenon doctrine but still does not establish whether or not the doctrine is even necessary for inventions in biotechnology. Both natural and non-natural correlations in the field of biotechnology serve overlapping goals of diagnosing and treating patients. There is little reason to believe they should be approached differently with respects to a patent incentive. At the same time, the non-natural correlations should not be deemed unpatentable subject matter because they are not the "basic tools of science and technological work." Natural correlations useful for diagnosing HIV, diabetes, or vitamin deficiency allow doctors to treat patients and are inarguably beneficial for society. There are many other diseases, lupus for example, for which natural biomarker correlations are still being sought to help improve diagnosis.[229] Yet

228. *See* Funk Bros. Seed Co. v. Kilo Inoculant Co., 333 U.S. 127, 130 (1948) ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end.").

229. Lupus has historically been difficult to diagnose, with no clear biomarker or set of biomarkers currently known. *See* George K. Bertsias et al., *Therapeutic Opportunities in Systemic Lupus Erythematosus: State of the Art and Prospects for the New Decade*, 69 ANNALS RHEUMATIC DISEASES 1603 (2010).

despite numerous researchers in the field, the need for an efficient lupus diagnostic has not been met.[230] If a correlation is to be found it will likely be a natural correlation, and a patent would be prohibited by the natural phenomenon doctrine. Perhaps the patent incentive is what is needed to continue encouraging investment and research in the field.

IV. CONCLUSION

The natural phenomenon doctrine attempts to strike a necessary balance between incentivizing inventors to develop new and useful processes and ensuring too many patents are not granted, generating more hurdles to innovation than incentives. If the boundary of patentable subject matter is set at natural phenomena, however, it is prudent that courts be clear on what precisely is a natural phenomenon. Unfortunately, the *Prometheus* decision did not provide such clarity. In addition to confusing what must be added to a natural phenomenon to make it patentable subject matter, *Prometheus* confused the very understanding of a natural phenomenon itself. As this Note attempts to demonstrate, it is improper to call any correlation a natural phenomenon. In many cases, the correlation would not exist if it were not for the activities of man, and such correlations are no more natural than its synthetic components. Personalized medicine is a growing sector within the biotechnology industry and relies, in significant part, on correlations. Some of these correlations may be described as natural, but many arise only through human activities and should not be considered as a type of natural phenomenon.

230. *See id.*