FROM *BILSKI* BACK TO *BENSON*: PREEMPTION, INVENTING AROUND, AND THE CASE OF GENETIC DIAGNOSTICS

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INTRODUCTION

This was supposed to be the end of an era. After prolonged uncertainty regarding the patentability of claims drawn to business methods, *Bilski v. Kappos* was expected to provide guidance on when they constituted patentable subject matter. But while the Court explicitly laid to rest both the Federal Circuit's broad approach in *State Street Bank & Trust Co. v. Signature Financial Group,*

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Inc. and its narrow approach in *In re Bilski*,[1] the Justices otherwise provided little information on how to determine whether particular subject matter is statutory. In a fractured set of decisions, the Court appeared to do no more than state the obvious. The patent act should be read broadly, but "laws of nature, physical phenomena, and abstract ideas" are not within the ambit of protection.[2]

The Justices' opinions featured a series of anomalies. The majority insisted on strict construction of the statute.[3] However, the three exceptions it recognized (laws of nature, physical phenomena and abstract ideas) had all been imposed judicially. S*tate Street*—the case approving business method patents—was deemed bad law, but it was impossible to attract five votes for the proposition that business methods are not patentable.[4] And even though business methods are, apparently, patentable, the hedging claims at issue in *Bilski* were all held invalid—not just the broadest claim, but even the narrow ones.[5] Furthermore, while the Court held the Federal Circuit's "M-or-T test" (holding that inventions are unpatentable unless they were tied to a *M*achine or *T*ransformed an article into a different state or thing) to be a mere "clue" to patentability,[7] it never indicated how that clue should be used. It is clear that a claim that fails the test is not *necessarily* invalid, but it remains uncertain whether a claim that passes the test is necessarily *valid*. Nor did the Court indicate what other clues might be relevant. Amici suggested a "technical effect" test,[8] a "technological arts" doctrine,[9] greater attention to the usefulness of the art,[10] or a return to the "mental steps" doctrine.[11] But aside from references to the "technological arts" in Justice Stevens' concurrence, none of these approaches was discussed. As Justice Stevens put it "The Court . . . never provides a satisfying account of what constitutes an unpatentable abstract idea."[12] In fact, the Court seemingly went out of its way to say nothing. Justice Kennedy's plurality opinion empha-

1. 149 F.3d 1368 (Fed. Cir. 1998); 545 F.3d 943 (Fed. Cir. 2008), see Bilski v.Kappos, 130 S.Ct. at 3231 & 3226.

2. *Bilski*, at 3221 (Kennedy, J.).

3. Id.

4. IIC

5. *Id.*, at 3329-30..

7. See *Bilski,* 130 S.Ct. at 3227.

8. Brief of TELES AG as Amicus Curiae in Support of Neither Party, 2009 WL 2445762 (Aug. 6, 2009)(arguing for harmonization with European law).

9. Brief Amicus Curiae of International Business Machines Corporation in Support of Neither Party, 2009 WL 2418481 (Aug. 6, 2009). This test was also favored by the PTO, *Bilski*, at 3233, and "numerous scholars," *id.,* at 3244 (Stevens, J., concurring).

10. Brief of Regulatory Datacorp, Inc, American Express Company, Palm Inc., Rockwell Automation, Inc., and SAP America, Inc. as Amici Curiae in Support of Neither Party, 2009 WL 2441070 (Aug. 6, 2009).

11. Brief of Amicus Curiae Law Professor Kevin Emerson Collins in Support of Neither Party, 2009 WL 2441064 (Aug. 6, 2009).

12. *Bilski*, at 3236.

sized "that the Court today is not commenting on the patentability of any particular invention."[13]

The Justices did, however, agree on one thing: a patent that "preempts" something (a mathematical formula, an approach, commonly used ideas, a wide swath of technological developments, the public's access) is very bad indeed. "Preempt" (or "pre-empt") is used in every one of the *Bilski* opinions.[14] Convergence on the term could provide an important hint to the Court's concerns—if, that is, the term had a meaning within scientific and technological discourse. Instead, its use is entirely within the legal domain, most often to describe the displacement of one law (such as state law) by another (federal law),[15] and in an earlier time, also to describe various technical issues arising in claim drafting and prosecution.[16] Justice Douglas elevated the concept to center stage in *Gottschalk v. Benson* when the issue of protecting computer programs first reached the Supreme Court.[17] Since then, it has caused endless confusion.[18]

Nonetheless, we are apparently now back to *Benson* and with the return of preemption, it is time to operationalize the concept. Part I briefly recounts the Supreme Court's attempts to define patentable subject matter, with the aim of identifying the concerns that led the *Bilski* Court to invoke the language of preemption. It concludes that the real question is not "whether" an advance is in a field where patenting is appropriate, but "how" claims are drafted: claims that "preempt" competitive development—that cover prospects that cannot be efficiently mined by individual right holders—are barred. Part II moves on to consider, as a case study, the field of genetic diagnostics. This is an area particularly ripe for attention. Justice Breyer's dissent from the dismissal of certiorari in *Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc.*,[19] which ignited the debate over the patents issuing under *State Street,* was a medical diagnostics case. Considerable empirical work on the effect of patenting as been done in this area,[20] there are cases waiting in the wings,[21] and promising

13. *Id.,* at 3228

14. See note 45, *infra.*

15. See, e.g., Bonito Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141 (1989).

16. See, e.g., In re Collins, 75 F.2d 1000, 1002 (C.C.P.A. 1935)(using preemption for what is now considered enablement and written description issues); Pangborn Corp. v. American Foundry Equipment Co., 159 F.2d 88, 89 (3d Cir. 1946).

17. 409 U.S. 63 (1972).

18. See generally, Pamela Samuelson, Benson Revisited: The Case Against Protection for Algorithms and Other Computer-Related Inventions, 39 Emory L.J. 1025 (1990).

19. 548 U.S. 124 (2006).

20. See Patently Complicated: Case Studies on the Impact of Patenting and Licensing on Clinical Access to Genetic Testing in the United States, 12 GENETICS IN MED. S1–S211 (Supp. 2010), available at http://journals.lww.com/geneticsinmedicine/toc/2010/04001; Robert Cook-Deegan & Christopher Heaney, Gene Patents and Licensing: Case Studies Prepared for the Secretary's Advisory Committee on Genetics, Health, and Society, 12 GENETICS IN MED. S1–S2 (Supp. 2010), available at http://journals.lww.com/geneticsinmedicine/Fulltext/2010/04001/Gene_patents_and_licensin

medical and scientific advances are on the horizon.[22] The case study suggests that at its core, the preemption problem arises when an advance cannot be invented around. When such advances cover broad prospects, patenting would, as Justice Breyer suggested in *Metabolite,* "impede rather than 'promote … Progress.'"[23] Part III concludes with thoughts about other indicia for determining when a claim is preempted.

I. PREEMPTION

It is not especially surprising that this has been an era of uncertainty in patent law. As new technological opportunities emerge, it is inevitable that there will be questions about how the law applies. It happened when the power of steam was first exploited,[24] when the effects of oxygen were discovered,[25] when it became possible to manipulate electric current,[26] and when differential solubility was understood.[27] The recent rapid development of new sciences—molecular biology, genomics, electrical engineering,[28] information and communication technology[29]—creates many fresh challenges. In theory, each technology raises two categories of questions. The first is *whether*—whether existing patent law is appropriate to the new field or whether a different—or entirely novel—intellectual property system is necessary. The second is *how*—how the requirements of the system should be applied to the new technology.

g__Case_studies_prepared.1.aspx; Sec'y's Advisory Comm. on Genetics, Health, and Soc'y, Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests, available at http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf [hereinafter Report on Gene Patents].

21. Prometheus Laboratories v. Mayo Collaborative Services, _ F.3d _ (Fed. Cir. Dec. 17, 2010); Classen Immunotherapies, Inc. v. Biogen IDEC, 304 Fed. Appx. 866 (Fed. Cir. 2008), *cert. granted, judgment vacated, and remanded*, 130 S.Ct. 3541 (2010); Association for Molecular Pathology v. US PTO, 702 F. Supp.2d 181 (S.D.N.Y. 2010). See also Intervet Inc. v. Merial Ltd, 617 F.3d 1282, 1294 (Fed. Cir. 2010(Dyk, J., concurring in part).

22. James P. Evans, Putting Patients Before Patents, 12(4) Genetics in Medicine, S3-S4 (April 2010), available at http://journals.lww.com/geneticsinmedicine/Fulltext/2010/04001/Putting_patients_before_patents.2.aspx.

[23] *Lab Corp,* 548 U.S. 124, 126 (Breyer, J., dissenting from denial of certiorari).

24. Hornblower v. Boulton, 8 T.R. 95 (K. B. 1799).

25. See, e.g., Neilson v Harford, [1841] 151 ER 1266.

26. See, e.g., O'Reilly v. Morse, 56 U.S. 62 (1854); The Telephone Cases, 126 U.S. 1 (1888).

27. See, e.g., Tilghman v. Proctor, 125 U.S. 136 (1888).

28. See, e.g., Diamond v. Chakrabarty, 447 U.S. 303 (1980); *Benson*; Parker v. Flook, 437 U.S. 584 (1978); Diamond v. Diehr, 450 U.S. 175 (1981).

29. See, e.g., AT&T Corp. v. Excel Comm'ns, Inc, 172 F.3d 1352 (Fed. Cir. 1999); Microsoft Corp. v. AT&T Corp., 550 U.S. 437 (2007).

A. *The "whether" inquiry*

One might have thought that the first issue would be labeled the "statutory subject matter question," and the second would be conceived of as addressing issues on the interpretation and application of other provisions of patent law.[30] And indeed, lawmakers have ostensibly followed that approach. Thus, advances in computer science initially raised the question whether software should be considered a literary work for copyright purposes. A national commission was appointed. After it answered in the affirmative, copyright law was amended to deal with foreseeable problems.[31] As it became clear that copyright protection would be highly limited,[32] the action moved to patenting—leading to a large number of cases on whether software fit within that realm.[33] Similarly, in *State Street*, the Federal Circuit was confronted with the question whether business methods are patentable. Taking its cue, perhaps, from *Diamond v. Chakrabarty*'s hospitality to patenting in emerging technologies,[34] the court answered with a broad holding: anything that achieves a concrete, useful, and tangible result is patentable.[35]

Because *State Street* led to the patenting of highly diverse advances, from medical diagnostics to tax-minimization strategies[36] and methods for training janitors to dust,[37] the Supreme Court used the dismissal of certiorari in *Metabolite* to signal a need to reevaluate. In a series of cases, the Federal Circuit considered a variety of formulations. [40] Eventually, *Bilski* was taken en banc.[41] In that decision, the Federal Circuit narrowed the criteria for patent-eligibility. Adopting a test that it thought derived from the Supreme Court's software cas-

30. *See, e.g.,* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1650 (2003).

31. See 1978 Nat'l Commission of New Tech. Uses of Copyrighted Works 12 (July 31, 1978)(discussing whether computer programs ought to be considered copyrightable works); 17 U.S.C. § 117 (later also amended to deal with problems encountered by the coverage).

32. See, e.g., Computer Associates International Inc. v. Altai Inc., 982 F.2d 693 (2d Cir. 1992)(propounding the abstraction-filtration-comparison test, which substantially restricts the scope of copyright protection).

33. See generally, A. Samuel Oddi, Assault on the Citadel: Judge Rich and Computer-Related Inventions, 39 Hous. L. Rev. 1033 (2002)(describing the developments leading up to *State Street*).

34. *Chakrabarty*, 447 U.S. at 309 (noting that Congress intended the 1952 Patent Act "to include anything under the sun that is made by man").

35. *State Street,* 149 F.3d 1373.

36. *See, e.g.,* ABA Section on Taxation, Tax Strategy Patenting Task Force, http://www.abanet.org/dch/committee.cfm?com=TX800000.

37. See In re Bilski, 545 F.3d 943, 1004 (C.A.Fed.2008)(Mayer, J., citing also methods for making reservations for toilets and dating).

40. See In re Comiskey, 499 F,3d 1365 (Fed. Cir. 2007); In re Nuijten, 500 F.3d 1346 (Fed. Cir. 2007); In re Bilski, 264 Fed. Appx 896, 2008 WL 417680 (Fed. Cir. 2008)(nonprecedential).

41. In re Bilski, 545 F.3d 943 (Fed. Cir. 2008)(en banc).

es, the court held that a process is statutory when it is tied to a machine or transforms materials to a different state or thing,[42]

The Supreme Court granted certiorari in *Bilski* and at oral argument, the same analytical framework prevailed. Thus, the Justices asked whether a series of enterprises were suitable for patent protection.[43] The decision, however, deviated substantially from that approach. Beyond a firm rejection of *State Street,* the Supreme Court provided little concrete guidance on the endeavors eligible for patenting.[44] It held that the M-or-T test was overly restrictive, but nonetheless considered it a "clue to patentability." It did not, however, indicate how the clue should be used. The main limit the Court identified was an old one—that "laws of nature, physical phenomena, and abstract ideas" are not protectable.[45] In addition, the Court resurrected the preemption trope developed in *Benson*, the first case on the patentability of a computer method.[46] But while every Justice who wrote an opinion used the term preemption, no one explained what it meant. Instead, the Court appeared to rely on the "nutshell" with which Justice Douglas summed up *Benson*:

> The mathematical formula involved here has no substantial practical application except in connection with a digital computer, which means that if the judgment below is affirmed, the patent would *wholly pre-empt* the mathematical formula and in practical effect would be a patent on the algorithm itself.[47]

After *Bilski*, the question is thus what the Court means by preemption. The law subsequent to *Benson* had not been a model of clarity. In part, the problem was that Justice Douglas not only adopted the term "preemption," he also deployed another new concept, the "algorithm." Although he defined it as "a procedure for solving a given type of mathematical problem,"[48] it was a word entirely unfamiliar to law and the definition itself left much to be desired. The reference to a *mathematical* problem was misleading: in common parlance, any set of steps to solve a problem is an algorithm. Douglas may have been trying to get at the notion of scientific truth,[49] but not all algorithms, mathematical or otherwise, necessarily state a scientific truth. (Nor is it always clear what, in science, constitutes "truth.") As a result, courts went back and forth on the sig-

42. *Id.*, at 958-61.

43. Justice Sotomayer asked about speed dating; Justice Scalia, to "books on how to win friends and influence people" and training horses; Justice Breyer, to techniques for teaching students without putting them to sleep, 2009 WL 3750776 (Official Transcript of Oral Argument. The majority listed several technologies: advanced diagnostic medicine techniques, inventions based on linear programming, data compression, and the manipulation of digital signals *Bilski*, at 3227.

44 *Bilski*, at 3231.

45. *Id*, at 3225.

46. *Id.*, at 3227, 3228, 3229, 3230 (including language from the nutshell) 3231 (Kennedy, J.); 3235, 3253, 3255 (Stevens, J.); 3258 (Breyer, J.).

47. *Benson*, 409 U.S. at 71-72 (emphasis added).

48. *Id.*, at 66.

49. See, e.g., *Benson,* 409 U.S. at 67.

nificance to attach to the presence or absence of a mathematical equation in a patent application.[52] *Bilski*'s reliance on preemption ends that fight: all processes (including business methods) are now subject to the same test of patentability.

Unfortunately, it is equally difficult to decide whether an algorithm—once identified—is "preempted." After *Benson,* drafters had a field day. Some attempted to waive rights over particular uses of the algorithm, hoping that if some uses (such as for academic research) were left in the public domain, the claim would not be considered preemptive.[53] Others confined their claims to specific fields (much as Bilski did). Some drafters added data gathering steps or post-solution activities.[54] Alternatively, they embedded the algorithm in a traditional industrial process where patenting was common[55] or claimed the machine that implements the steps of the algorithm.[56] Some of these attempts were successful; others were not.[57] Prior to *State Street*, the courts and the patent office formulated a series of tests, each designed to create a procedure (ironically—an algorithm) for identifying advances that did not qualify for protection.[61]

In retrospect, it is evident why it was so difficult to get a handle on preemption. In fact, the concept does not answer the question whether a particular field is suitable for patenting.[63] Or as Judge Rader suggested in his dissent to the Federal Circuit's decision in *Bilski*, nothing explains "[w]hy … some categories of invention deserve no protection."[64] Justice Kennedy's *Bilski* analysis is no better. In deciding that the hedging claims were too abstract to patent, the Court did not discuss hedging as a category. Rather, what it determined was that Bilksi's hedging claims had not been framed in a way that was acceptable. In other words, the question the court answered was not the *whether* question, but a *how* question—how should claims in this field be drafted?

Significantly, a close look at prior subject matter decisions reveals a similar pattern. There was probably very little doubt about whether the technology in many of the early cases—blast furnaces, electrical and chemical innovations—

52. See generally, Oddi, supra note 33.

53. See Samuelson, supra note 18, at 1101.

54. See, e.g., In re Phillips, 608 F.2d 879 (C.C.P.A. 1979).

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

56. See, e.g., In re Bradley, 600 F.2d 807 (C.C.P.A. 1979), aff'd by an eqally divided court sub nom. Diamond v. Bradley, 450 U.S. 381 (1981).

57. Compare Parker v. Flook, 437 U.S. 584 (1978) (unsuccessful) with Diamond v. Diehr, 450 U.S. 175 (1981)(successful).

61. In re Freeman, 573 F.2d 1237 (CCPA 1978); In re Walter, 618 F.2d 758 (CCPA 1980); In re Abele, 684 F.2d 902 (CCPA 1982); US PTO, Examination Guidelines for Computer-Related Inventions, 61 Fed. Reg. 7478 (Mar. 29, 1996).

63. See, e.g., Application of Christensen, 478 F.2d 1392, 1395 (CCPA 1073)("after stating [the patentability] question, the Supreme Court opinion does not again advert to it and never decides it…")(Rich, J., concurring).

64. In re Bilski, 545 F.3d. at 1012 (2008)(Rader, J., dissenting).

was patentable subject matter; the only questions in those cases were "how" questions. For example, the issues in *O'Reilly v. Morse* and *The Telephone Cases* were in reality about how to disclose and claim advances in the inventors' respective fields: Morse lost because he claimed all the ways of "printing intelligible characters … at any distance," but had not identified all of the ways;[66] Bell won because his claims were limited to methods for "transmitting vocal … sounds telegraphically" that he described.[67]

It is improbable that successive generations of Supreme Court justices have overlooked the "whether" question; something else appears to be going on. Perhaps attempts to define patentable subject matter question are doomed to failure because there is nothing categorical that can be said about the fruits of innovation. Hence the rejection of "technical effect," "technological arts," or "useful arts" tests, and the Court's refusal, despite clear misgivings, to exclude business methods. In a sense, then, the real problem with *Bilski* isn't that it rejected *State Street* without providing a substitute; the real problem is that it *approved* the broad holding in *State Street* without acknowledging that it was doing so. As long as the nation is committed to using the patent system to spur creative development, perhaps the best the Supreme Court can do is keep all fields open to patenting—exactly what Judge Rich was trying to accomplish in *State Street*.

B. *The "how" inquiry*

To put this another way, Judge Rader's question on why some categories of invention deserve no protection cannot be answered by examining specific *endeavors*. Rather, certain *claims* do not deserve protection—and the way to understand what the Court means is by formulating a reason why. Judge Rader tried, saying:

> Natural laws and phenomena can never qualify for patent protection because they cannot be invented at all. After all, God or Allah or Jahveh or Vishnu or the Great Spirit provided these laws and phenomena as humanity's common heritage. …. An abstract idea must be applied to (transformed into) a practical use before it qualifies for protection.[70]

Invocation of a higher authority will not appeal to those with a more secular bent. But the passage is critical for two reasons. First, it recognizes that issues like abstractness cannot be answered in the abstract—one needs to understand the goal the exception is there to further in order to apply the rule correctly. Second, Rader provides important hints at what that goal is: claiming "before" something has been "transformed."

The issue, in short, is timing. Patent claims cannot be made too early in the

66. 56 U.S. 62, 129 (1853).
67. 126 U.S. 1, 531 (1888).
70. *Bilksi,* 545 F.3d at 1013.

development of a field and the reason why is preemption: exclusive rights may preempt others from competing and thusly diminish the vibrancy of the marketplace or the vigor of the creative environment. To use the language of *Morse*, early claiming can pose an obstacle to the "the onward march of science"[71] (or business) and it does so by limiting the number of approaches, experiences, bodies of knowledge, and interests that can be brought to bear in mining the initial insight.[72]

To be sure, other requirements for patentability can also be construed as aimed at timing. For example, *Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co.,*[74] on exploiting the properties of the protein complex, NF-κB, was decided on the ground that the applicant filed before it could supply a written description of the substances that could be used to achieve the claimed result. The case could have been equally well argued along preemption lines—that knowledge about NF-κB, which appears to play a role in a wide variety of conditions, including memory loss and susceptibility to diseases such as cancer,[75] is not patentable because the patent would preempt those who would follow on, elucidate the impact of NF-κB, and find ways to utilize the information to treat patients. Rebecca Eisenberg and Robert Merges have similarly argued that the utility issue is aimed at delaying the onset of patent protection to the point where more is known about the invention.[76]

Claim construction also plays a role in trimming the impact of a patent. Thus, Merges and economist Richard Nelson have questioned the traditional broad protection accorded to pioneer inventions.[77] While they recognized that incentives can be important at the inception of a new field, and that centralizing control over an opportunity can improve planning and reduce wasteful duplication, their examination of a wide variety of fields led them to conclude that competitive development is the superior approach to promoting progress:

> "When a broad patent is granted …, its scope diminishes incentives for others to stay in the invention game, compared again with a patent whose claims are

71. *Morse,* 56 U.S. at 113.

72. See, e.g., Heidi L. Williams, *Intellectual Property Rights and Innovation: Evidence from the Human Genome*, NBER Working Paper 16213, *available at* http://www.nber.org/papers/w16213; Kenneth G. Huang & Fiona E. Murray, *Does Patent Strategy Shape The Long-Run Supply of Public Knowledge? Evidence From Human Genetics*, 52 ACAD. MGMT. J. 1193 (2009); Fiona Murray & Scott Stern, *Do Formal Intellectual Property Rights Hinder the Free Flow of Scientific Knowledge: An Empirical Test of the Anti-commons Hypothesis*, 63 J. INDUS. BEHAV. & ORG. 648 (2007).

74. 598 F.3d 1336 (Fed. Cir. 2010).

75. See TD Gilmore, *Introduction to NF-κB: Players, Pathways*, *Perspectives* 25 Oncogene 6680 (2006)("the study of NF-κB … is essentially an industry").

76. Rebecca S. Eisenberg & Robert P. Merges, Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences, 23 AIPLA Q.J. 1 (1995). See also Robert P. Merges & John F. Duffy, Patent Law and Policy: Cases and Materials 88 (4th ed. 2007)(explaining Morse as a timing case).

77. Robert P. Merges & Richard R. Nelson, On the Complex Economics of Patent Scope, 90 Colum. L. Rev. 839 (1990)

> trimmed more closely to the inventor's actual results. … This would not be undesirable if the evidence indicated that control of subsequent developments by one party made subsequent inventive effort more effective. But the evidence, we think, points the other way.[78]

But even though there are other doctrines that can be used to protect competitive development, a preemption doctrine is nonetheless critical. All the other requirements permit patents—they will simply be narrower than might otherwise claimed, or delayed until a use is identified. Yet because patents—once issued—cover all uses, there will be situations where even very narrow patents block off too much, especially in areas (like computer science and genetic diagnostics) where applications flow easily from basic discoveries.[79]

Armed with that understanding, the anomalies in *Bilski* largely disappear. The Court did not outright invalidate business methods, but it was skeptical about them because concentrating a broad business opportunity in a single entity can distort the market and harm the economy.[80] The Court rejected *State Street*'s "useful, concrete, and tangible result" test because insights into broad technological opportunities are clearly "useful" and some will have "concrete and tangible results." Thus, that approach could lead to too much control over important prospects. In contrast, the M-or-T test was accepted as a clue because once an insight is instantiated in a product or in a physical transformation, the claims are unlikely to have such a broad reach that they cut off lines of inquiry or limit competition. But since they can have that effect—for example, tying a process to a general-purpose computer may not reduce the reach of the process significantly—it is unlikely that the Court meant to convert the M-or-T test into a safe harbor.

It is also possible to understand the courts' attitude toward other the other attempts to limit patenting. Thus, the impulse behind the mental steps doctrine, which would bar patents on processes that can be accomplished in the mind, appears based on the idea that thinking usually comes "before" (in the Judge Rader sense) applying fundamental insights to concrete problems. The flaw in the reasoning is that not all thought is of that character; some thoughts are highly complex and so focused on a particular problem, they can be privatized without doing damage to innovation. Still, if the Supreme Court is endorsing the use of clues, that a claim is drawn to a process of thinking might be consi-

78. *Id.,* at 916 (rejecting the prospecting theory propounded in Edmund Kitch, The Nature and Function of the Patent System, 20 J.L. & Econ. 265 (1977)).

79. See Allen Newell, Response: The Models are Broken, the Models are Broken, 47 U. Pitt. L. Rev. 1023, 1026-27 (1986)(discussing the narrowness of the gap between upstream and downstream research in the computer field).

80. Rochelle Dreyfuss, Are Business Methods Patents Bad for Business? 16 Santa Clara Computer & High Tech. L.J. 263, 274-277 (2000). In some countries, competition law may prevent distortion, but U.S. antitrust law does not, *see* Verizon Comm'ns Inc. v. Law Offices of Curtis V. Trinko, 540 U.S. 398 (2004).

dered a clue that it is likely *not* patentable.[81]

Claim limitations are similarly ambiguous. For example, attempts like Bilski's to limit claims to particular sectors will not work as a general rule because competitive development can be important even within a specified field. The genetics case study in the next Part furnishes an example. However, if the true concern is with fostering multiple pathways to development, waiving rights over research uses is closer to the mark. When the cases on waiver were decided, there was a broad common law research exemption; waivers thus contributed little to innovation. Now that the Federal Circuit has largely eliminated the exemption,[82] a waiver is significant. But it is probably not significant enough to furnish a clue to patentability. Because patentees and followers are unlikely to agree on what was relinquished, a waiver could foster litigation, dampen innovation, and impair business.

References to data gathering or post-solution activity may, in contrast, furnish somewhat better clues as there may be some activities that are specific enough to limit the reach of a broad claim. But their use must be handled carefully because, as *Bilski* implicitly recognized,[83] these activities may be too generic to release a prospect for general use. For example, because all diagnostics start by drawing blood and end with associating a variable to disease, the steps in *Metabolite*—"assaying fluid" and "diagnosing" are not limiting.[84] In contrast, the method for optimizing therapeutic efficiency at issue in *Prometheus Laboratories, Inc. v. Mayo Collaborative Services*, which requires the administration of a drug prior to assaying and diagnosing, is arguably a sufficiently specific limitation.[87]

Significantly, cases like *Metabolite* and *Promotheus* can be distinguished in another way. In *Metabolite*, there is no way around the claim: the practice of medicine is all about the activities at issue there—examining patients and interpreting findings in light of "associated" symptoms. The "limiting steps" thus do nothing to reduce the power of the claim to prevent scientists or physicians from understanding biology or treating patients; in *Prometheus*, however, there are arguably other ways to achieve the goals of the patent. In short, a better way to grapple with preemption may be to ask whether the claim can be practiced in other ways—or as patent lawyers say, "invented around."[88] Judge Rich condemned the approach early on as "an essentially illogical distinction unwar-

[81] Cf. Prometheus Laboratories v. Mayo Collaborative Services, _ F.3d _ , Slip Op. at 21 (Fed. Cir. Dec. 17, 2010)(suggesting that mental steps are not patent-eligible).

82. Madey v. Duke University, 307 F.3d 1351 (Fed. Cir. 2002).

83. *Bilski*, 130 S.Ct., at 3231.

[84] *Metabolite,* 548 U.S., at 129. But see *Bilski,* 545 F.3d, at 1014 (Rader, J. concurring and suggesting these as limits in the *Metabolite* case).

[87] *Prometheus*, Slip Op. at 16.

88. *See, e.g.* In re Tarczy-Hornoch, 397 F.2d 856, 857 (C.C.P.A. 1968). See also Oddi, *supra* note 33, at 1062, citing the lower court decision in In re Flook, 559 F.2d 21, 23 (C.C.P.A. 1977)

ranted by, and at odds with, the basic purposes of the patent system."[89] Nonetheless, there is much to recommend "inventing around" as a clue to patentability. The ability to work around the patented method limits the patent holder's grip—it sets a cap on the price that can be charged and makes it possible for others to mine a prospect even when the patentee refuses to do so.[90] Furthermore, since science must deal with the natural world, the inability to invent around is also a clue to *Bilski*'s other exclusions: laws of nature and natural phenomena. Indeed, as the next Part demonstrates, the inability to invent around may be the best evidence of what the Court means by preemption.

II. GENETIC DIAGNOSTICS

Some have complained that *Bilski* provides so little guidance, a *Bilski* defense will be raised in every case.[92] The above suggests, however, that the Court's concerns are fairly specific: the opinion is aimed at fostering business by protecting the competitive environment and at promoting innovation by assuring public access to broad technological prospects. To be sure, identifying the claims that pose a danger to business or innovation will not always be easy, but once courts start looking at the problem in a more directed way, they will surely develop a better grasp of the issue.[93] Further, they may consider other strategies, such as new defenses to infringement or denial of injunctive relief,[94] to protect business and innovation without sacrificing incentives to invent.[95]

While it is likely that the way forward will be somewhat sector-dependent, a study of issues arising in genetic diagnostics is illuminating. This is a field where the impact of patenting genes and diagnostics has been examined, so it is possible to see how exclusivity affects "the onward march." Furthermore, this area is of interest in its own right: there are pending cases and the scientific promise is considerable.

A. *The Science of Genetics*

The field of genetics is concerned with the storage, expression and transmission of biological information. In the most general terms, genetics seeks to

89. *Tarczy-Hornoch* at 897.

90. See, e.g., U.S. PTO, Interim Guidelines for Determining Subject Matter Eligibility for Process Claims in view of *Bilski v. Kappos,* 75 Fed Reg. 43923, 43925, col. 3 (July 27, 2010) (using monopolization as a criterion).

92. *See* Tony Dutra, Patent Community Applauds Supreme Court's *Bilski* Restraint But Rules Lack of Guidance, Patent, Trademark & Copyright Law Daily (June 30, 2010).

93 See, e.g., Research Corp. Technologies v. Microsoft Corp., _ F.3d _ (Dec. 8, 2010), Slip Op. at 15 (using claim drawn to improvement as indicative of patentability).

94. See eBay v. MercExchange L.L.C., 547 U.S. 388 (2006), which was cited by both the majority and the dissent in Bilski, see 130 S.Ct. at 3229 (Kennedy, J.); 3256 (Stevens, J.).

95. See, e.g., Rochelle C. Dreyfuss, The Patentability of Genetic Diagnostics in U.S. Law and Policy (forthcoming).

explain why children look like their parents but also why they are unique. Genetics illuminates both the diversity of life on earth and its unity: on one hand the differences between the genome of a chimp and that of a human are responsible for our unique attributes as distinct species; on the other hand genetics demonstrates that we share a common genetic code (and indeed the molecular details of life) with earth worms, gazelles and bark beetles.[96]

At the root of genetics is deoxyribonucleic acid or DNA. DNA is a long chain of nucleotides—chemical subunits. The DNA chain that encodes the instructions for a human being consists of about 3 billion nucleotides and is about 6 feet long. A single copy of this chain, intricately folded upon itself, resides in each of the approximately 10^{14} (one hundred million million) cells in the human body. DNA has only two jobs in the living organism. It serves as a store of information and it instructs the cell how to synthesize proteins (which execute the work necessary for living cells) and RNA (which carries information and possesses regulatory functions). DNA performs both of these tasks by encoding information via a digital code, represented as the order of the individual nucleotides in a given stretch of the DNA chain.

If one travels along the 3 billion-link chain that is the human genome, one encounters particular linear stretches of DNA, usually extending several thousand nucleotides, that encode the instructions for making a particular protein. After traveling along the entire length of the chain one would have encountered about 25,000 intervals in which a distinct protein or RNA molecule is encoded. That is, one would have encountered approximately 25,000 human genes. Between the "coding" intervals of DNA that each specifies a unique RNA or protein molecule reside "non-coding" regions. Some of this non-coding DNA is regulatory in nature, directing the cell as to which genes to activate and which to leave dormant (for example, a white blood cell does not need to activate or "transcribe" a gene that encodes the instructions for skin pigment, so it leaves that gene in a dormant state). Much of the non-coding DNA appears to simply be "junk" left over from evolution; unnecessary to the function of the genome. But scientists continue to sort out the meaning (and lack thereof) of non-coding DNA.

Non-coding DNA not only exists between genes, but the vast majority of genes themselves are interrupted by stretches of such non-coding DNA. Within a given gene (that is, a stretch of DNA which encodes a particular RNA or protein molecule) there thus exist "introns" (interrupting non-coding DNA) and "exons" (expressed segments of DNA). It is primarily in the exons where the meaningful information resides for directing the synthesis of a protein or RNA molecule. Indeed, the introns can typically be readily removed from a gene without materially altering its informational content. This is the difference between a cDNA version of a gene and a "genomic" copy of a gene. The cDNA

96. See also James Evans, Lisa Susswein & Cecile Skrzynia, Genetics, in SCIENCE FOR LAWYERS 175 (Eric Y. Drogin, ed. 2008).

version has simply had the unnecessary interrupting segments (introns) snipped out and is shorter and easier to manipulate. It is worth pointing out that the cell machinery splices out the introns on a routine basis as the process of snipping out introns occurs in nature every time a cell expresses a given gene.

The way in which a linear stretch of DNA specifies the synthesis of a protein or RNA molecule is though the unique order in which the nucleotides are arranged along that stretch of DNA. Within any given gene, each successive triplet of three nucleotides specifies a particular amino acid, the building blocks of proteins. Thus a uniquely ordered stretch of nucleotides along the DNA molecule specifies (encodes) a unique protein. The only difference between a stretch of DNA that directs the synthesis of a skin pigment protein (i.e. a "pigment gene") and a stretch of DNA that encodes a globin chain (a "globin gene") which carries oxygen in the blood, is the particular order of the nucleotides that make up that stretch of DNA.

Elucidation of the double helical structure of DNA by Watson and Crick (based on data unwittingly provided by Rosiland Franklin) in 1953 immediately illuminated the way in which DNA serves as a store of information and is transmitted from generation to generation.[97] In essence, by consisting of two chains, the double helix contains a copy (or more precisely, a mirror image) of itself. Each of the two chains in the double helix is made up of 3 billion nucleotides arranged in a particular order. There are only four types of nucleotides, designated as A, T, G and C. Thus, one short stretch of a nucleotide chain might read: AATGGCTCGGAT and so on. The two chains of the double helix are held together by the fact that A binds specifically to T and G binds specifically to C. So if one chain has an A at a particular site along its sequence, we know that the other chain will have a T in the corresponding position. Likewise, if a G is located in a particular site, the other chain will have a C at that corresponding site. When a cell divides, it sends one chain to one daughter cell and the "complementary chain" to the other daughter cell. The cells can then easily reconstruct the double helix by building the other, complementary, chain based on this base pairing.

Modern molecular techniques have been developed which allow for the "isolation" of any given gene. This simply means purifying (or using enzymes to construct in a test tube) a particular stretch of DNA that represents a given gene. For example, the gene for insulin is 1,430 nucleotides long and the part that actually encodes the insulin protein is 153 nucleotides. There are two introns which are snipped out or "spliced" in the process of expressing the gene. When the human insulin gene is isolated, investigators may also snip out these introns to produce a cDNA as above.

A mutation is simply an error in the DNA sequence which disrupts the ability of the gene to encode a functioning protein. A mutation may consist of a

97. See James D. Watson and Francis H.C. Crick, A Structure for Deoxyribose Nucleic Acid, 171 Nature 737 (1953); Anne Sayre, ROSALIND FRANKLIN AND DNA (1975).

single missing nucleotide, deletion of several (or several thousand) nucleotides, an insertion of a single or many nucleotides or the substitution of a nucleotide (e.g. a "T" where there should be a "C"). A mutation in a gene disrupts the ability of that gene to encode a protein and may result in disease. For example, a mutation in the human *CFTR* gene causes cystic fibrosis. The field of DNA diagnostics hinges on assaying a gene for its sequence integrity. The most common and generally most effective means of assaying a gene is to "sequence" it—that is, determine the precise order of the nucleotides which comprise that given gene in an individual. If a patient who has a family history of early onset breast cancer has a mutation in the *BRCA1* gene (for example an extra nucleotide, a missing nucleotide or the wrong nucleotide at a given position), the gene cannot regulate cell growth and the patient is at an increased susceptibility to breast cancer. Geneticists refer to an individual's underlying genetic sequence as their "genotype." The "phenotype" of an individual refers to the ultimate effect of that genotype on the individual organism. Thus, an individual's genotype may indicate that they carry a mutation in the *BRCA1* gene. The resulting phenotype of that individual is their marked propensity towards breast cancer at a young age.

Geneticists have discovered many disease-gene linkages in which mutations in a given gene are responsible for a given disease. This involves studying the relationship between phenotypes and genotypes. Typically, this process involves looking at families or a large number or individuals with a given disease and sequencing the patients' genes to detect mutations that track with (in technical jargon are "linked to") the presence of the disease. For such purposes large numbers of individuals with the disease in question are necessary or large families who are transmitting a predisposition to the disease must be assayed. While in classic genetic diseases the relationship between harboring a mutation and developing the corresponding disease is very strong (e.g. 100% of people with a mutation in the Huntington gene eventually develop Huntington disease) geneticists are now learning about many weaker associations which *predispose* an individual to develop the corresponding disease (but do not guarantee that the disease will occur).

Finally, geneticists are learning that individuals differ in their nucleotide sequence at many sites throughout the genome and many (if not most) of these differences are unimportant to their health. Thus, any one individual will, on average, differ from their neighbor at over 1 million sites in their genome. For example at a particular site one individual may have a "G" whereas others will have an "A". These subtle differences among individuals are called "single nucleotide polymorphisms" or "SNPs." Sorting out innocuous polymorphisms with no health implications from those which have health effects is a major challenge for the future of genomic medicine and will be a difficult task, requiring the pooling of sequence information and health information from many individuals.

Because genetic research requires broad access to both phenotype and ge-

notype information, researchers have a strong commitment to putting sequencing data into publically available databases.[98] This commitment does not, however, mean that genetic information cannot be involved in patents. In fact, about twenty percent of the genes in the human genome are associated with patents.[99] Some patents claim products covering "purified DNA" – essentially, cDNA sequences comprising specific genes or mutations; others claim processes, such as for detecting a specific sequence or for using the sequence to diagnose a predisposition to disease.

B. *The Effect of Patenting*

Because patenting behavior in this field has been highly variable, it is possible to conduct a natural experiment on the effects of patents on both the "business"—i.e. practice—of medicine and on innovation in medical science. In a series of eight case studies conducted at the behest of the Health and Human Services Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), Robert Cook-Deegan and his associates chose ten clinical conditions involving heritable disorders for which genetic tests were available.[100] Some of the conditions were associated with patents, some not; some patents were widely licensed, others were not; some of the conditions studied have high prevalence in the population; others afflict small groups. In each case, the associations were known for at least ten years—long enough for the use of the diagnostics to be well established within the medical community and for the effects of patenting to become evident. [103] By comparing the experiences under a variety of patenting and licensing strategies, the investigators isolated and quantified the effects of patents on the development of gene diagnostics and on their availability to patients.[105]

The results demonstrate how upstream patents can impact downstream activities. In cases where there was broad access (either because there were no patents or the patents were widely licensed), there were many laboratories conducting diagnostic tests, spanning the spectrum from academic labs to industry.[106] In settings where numerous labs offered genetic diagnostic tests for the same condition, these laboratories competed on the basis of quality, price, in-

98. See, e.g., Eliot Marshall, Bermuda Rules: Community Spirit, With Teeth, 291 Science 1192 (Feb. 2001).

99. Kyle L. Jensen & Fiona E. Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCI. 239–240 (2005).

100. See note 20, *supra*. The conditions were: (1) breast/ovarian cancer, (2) colon cancer; (3) hearing loss, (4) cystic fibrosis (CF), (5) inherited susceptibility to Alzheimer disease: (6) hereditary hemochromatosis (HH); (7) spinocerebellar ataxias (SCA); (8) long QT syndrome (LQTS); (9) Canavan disease; and (10) Tay-Sachs disease.

103. *Id.* at 9.

105. The studies were peer-reviewed, patent holders were permitted to correct factual errors, and outside comments were solicited, *id*. at 10.

106 *Id.* at 3, 31-35.

novation and the specific nature of the test employed (for example sequencing vs. looking only for specific mutations). In contrast, when there were patents held exclusively by a single entity, both clinical practice and scientific development were impaired.[107]

On the practice end, exclusivity for a given genetic test was associated with a number of harms: Patent holders (who, significantly, were never the first to market in any of the case studies), sometimes cleared the field once their patents issued.[108] Doctors and patients could no longer get second opinions on tests that can carry considerable medical implications (such as a recommendation for major surgery or life-long surveillance). In addition, laboratorians expressed concerns about the quality of genetic diagnostic tests. When only a single lab offers a given test it is impossible to apply the "gold standard" of quality assurance—proficiency testing—which requires analysis of the same sample by more than one provider.[109]

In some cases, tests deemed necessary for patient care were simply not available. For example, patent holders did not always develop tests needed by a segment of the population deemed insufficiently large, but nonetheless enforced the patent against academic labs that routinely cater to such small populations.[110] Some providers failed to offer prenatal screening.[111] Most disturbingly, when exclusive providers did not have relationships with insurance providers (such as state Medicaid offices) poor patients were denied access to testing. Charity testing programs, which are difficult to use, were generally insufficient to make up for the insurance shortfall.[112] Finally, in at least one example, a test for a life-threatening cardiac condition (Long QT syndrome) was practically unavailable for eighteen months when the exclusive rights holder failed to either offer the test clinically or license it so that another lab could perform it.[113]

The SACGHS report and its underlying case studies focused more on health delivery questions than on innovation concerns. Still, the report pointed out several potential impacts on research. Because many clinically identical diseases can result from mutations in widely disparate genes, fears were articulated that patent thickets and holdouts could obstruct the development of new diagnostic methodologies, such as multiplex testing (testing multiple genes simultaneously) and new therapeutic techniques. For example, while sequencing an individual's whole genome will soon be a practical reality, it may be a legal impossibility, given the number of patents that would be infringed in one fell

[107] *Id.* at 33.
[108] *Id.*
[109] *Id.* at 3 & 44.
[110] *Id.* at p. 20-21.
[111] *Id.*
[112] *Id.* at 42-44.
[113] *Id.* at F-26.

swoop.[114]

Other evidence on the effect of patents on basic research tends to support these fears. Proponents of patenting cite the work of Wesley Cohen and coauthors, who conducted surveys of scientists in a variety of fields. Their work suggests that research is unimpeded by patents, largely because scientists tend to ignore them.[115] However, the Cohen studies have limited application to diagnostics. Whereas researchers were rarely sued in most of the fields Cohen studied, the case studies (and Cohen) found that geneticists do receive threatening letters.[116] Furthermore, although Cohen's interviewees did not think patents were hindering research, they mentioned other impediments, such as withholding research results or key physical materials,[117] which may be linked to patenting in ways the interviewees did not appreciate. Significantly, a type of this "self-help exclusivity" is also occurring in the diagnostics realm, where it takes the form of failing to deposit new mutations and human variants in public databases.[118] That activity is particularly damaging in that any understanding of gene function and the role of a given gene in health and disease has an absolute dependency on broad sharing within the scientific community. Finally, there is other empirical work suggesting that patents do impede research. Using event studies, Fiona Murray showed that patenting is associated with a decline in research and a decrease in the number of lines of research pursued.[119] Similarly, Heidi Williams found that product development involving genes subject to exclusive rights lags behind the development of genes in the public domain.[120] In any event, it is hardly a ringing endorsement of the patent system that its functioning depends on its being ignored.

It may seem surprising that the downstream impact of gene patents is so profound. As Judge Markey, the first Chief Judge of the Federal Circuit, took

114. Report on Gene Patents, supra note 20, at 3, 41, & 49-52.

115. Wesley M. Cohen & John P. Walsh, Real Impediments to Academic Biomedical Research, 8 Innovation Pol'y & Econ. 1 (2007); John P. Walsh, Ashish Arora, and Wesley M. Cohen, Effects of Research Tool Patents and Licensing on Biomedical Innovation, in PATENTS IN THE KNOWLEDGE BASED ECONOMY 285 (National Academies Press (2003) (Wesley M. Cohen and Stephen A. Merrill, eds). See also Jane Kaye, Naomi Hawkins, & Jenny Taylor, Patents and Translational Research in Genomics, 25 Nature Biotechnology 739 (2007).

116. Walsh et al, supra note 115, at 312 & 317; Report on Gene Patents, supra note 20, at 31, 32, & 40.

117. Cohen & Walsh, supra note 115, at 19-22. The Hawkins study cited in 115, supra, was conducted in England, where there is a strong research exemption.

118. See Julia Carbone et al., DNA patents and Diagnostics: Not a Pretty Picture, 28 Nature Biotechnology 784 (2010) (noting that after 2004, Myriad stopped contributing data to public databases).

119. Fiona Murray et al., Of Mice and Academics: Examining the Effect of Openness on Innovation (Nat'l Bureau of Econ. Research Working Paper No. 14819, 2009), available at http://www.nber.org/papers/w14819; Kenneth G. Huang & Fiona E. Murray, supra note 72.

120 Williams, supra note72.

pains to stress, patents are rarely true monopolies; usually alternative ways exist to achieve a result similar to the one for which the patented invention is utilized.[121] Richard Epstein has applied that idea to the genetics landscape, arguing that it is possible to sidestep the use of a patented gene by relying on another gene involved in the same condition.[122] Genetics is, however, hostage to biology. Genes evolved over millions of years to serve a specific biological purpose; that is why disruptions by mutation result in disease. These evolved genes are unique and the key value in isolation and purification is to produce the identical sequences to the genes found in nature.

Thus, there is no possibility of sidestepping. While many genetic conditions demonstrate the phenomenon of "genetic heterogeneity," in which a mutation in one of any number of different genes can result in a clinically identical disease, the mutations are not substitutes for each other. A prominent example is that of *BRCA1*, and *BRCA2*, and *p53.* Each of these genes is associated with early-onset breast and ovarian cancer. But each gene has a distinct function. When a patient's family exhibits characteristics of hereditary breast and ovarian cancer, it is necessary to assay *all* the patient's genes since a derangement of *any one* of them can cause the phenotype of breast cancer. It is not possible to bypass *BRCA 1* and *2*, which are patented, and assay only for mutations of *p53,* which is not. Doing so would be medical malpractice because the testing would fail to detect *BRCA 1* and *2* mutations, which account for more than 2/3 of early-onset breast cancers. It is thus necessary for clinicians to deal with Myriad Genetics, one of the firms identified in the SACGHS Report as raising barriers to patient access to breast cancer diagnoses,[123] and which is also failing to deposit new mutations in the public database.[124]

Arguably, there are other ways to invent around patented genes in order to identify hereditary conditions. However, for most genetic conditions, none can supplant the direct analysis of genes. Thus, some have suggested exploiting the phenomenon of linkage disequlibrium (LD), an association between a specific mutation (e.g. in a disease gene) and DNA sequence variants that reside some distance from the mutation in question and can thus act as "markers" for the presence of the disease gene.[125] In theory, LD allows one to evade the constraints of a patent by assaying for the marker that is "linked" to the patented

121. Howard T. Markey, Why Not the Statute, 65 J. Pat. & Trademark Off. Soc'y 331, 333 (1983).

122. Richard A. Epstein, Steady the Course: Property Rights in Genetic Material, in PERSPECTIVES ON PROPERTY OF THE HUMAN GENOME PROJECT 153, 162-68 (F. Scott Kieff ed. 2003).

123. Report on Gene Patents, supra note 20, at 23-24; Robert Cook-Deegan, Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers, 12 GENETICS IN MEDICINE S15–S38, S20 (Supp. 2010).

124. See Carbone, supra note 118.

125. *See* Robert L. Nussbaum et. al, THOMPSON & THOMPSON'S GENETICS IN MEDICINE 213–16 (Saunders/Elsevier Press 2007).

gene. But while it is indeed true that sometimes such associations exist, there are two fundamental—and biologically insurmountable—problems with using such a strategy in the real-world diagnostic arena. First, the linkage between a marker and a gene is always imperfect: as the distance between the linked marker and the mutation of interest grows, LD testing becomes increasingly imprecise. A testing strategy with a high (and known) error rate is wholly inadequate for diagnostic purposes. Second, even if one were (perversely) satisfied with a laboratory test guaranteed to give wrong answers for a subset of patients, the biology of the situation makes it impractical for the majority of genetic tests: the linkage between a disease-causing mutation and a marker depends on historical and genetic contingencies that are only sometimes met. It is a distinct minority of genetic conditions that even demonstrate consistent linkage between a common mutation and a marker.

Finally, it has been argued that one could circumvent a gene patent by instead analyzing the protein the gene produces ("expresses").[126] For a number of reasons, this is an entirely infeasible alternative to genetic testing in the vast majority of situations. Proteins are often only expressed in specific tissues at specific times. For example, many genes are expressed only in the brain or only for a short period of time during fetal development. In contrast, the DNA of any of the body's cells reflects the mutational status of all others. Thus, to detect mutations in a gene which is expressed only in the brain is a simple matter of analyzing the DNA from blood cells or material from a cheek swab. If one were forced to examine the pertinent protein it would necessitate a brain biopsy. Likewise, to query the genetic reasons why a child has multiple malformations would be impossible if one were reliant on protein analysis since many of the critical proteins are no longer expressed anywhere in the child's body, having done (or not done) their job during a specified period during the child's embryonic development.

Of course, there may be situations where avoiding a patent will be possible. Sometimes, an LD or protein test will work; some day new forms of imaging may make sequencing unnecessary. From a legal perspective, some process or product claims are so narrowly drawn, they can be circumvented.[127] Work can also be done offshore and the results sent back to the United States.[128] But alternative strategies are not regularly available.[129] And not all patents are nar-

126. See, e.g., Christopher M. Holman, Learning from Litigation: What Can Lawsuits Teach Us About the Role of Gene Patents in Research and Innovation?, 18 WTR Kan. J.L. & Pub. Pol'y 215, 244 (2009).

127. See, e.g., Genentech v. Wellcome Foundation, 29 F.3d 1555, 1557 (Fed. Cir. 1994); Regents of the Univ. of Cal. v. Dakocytomation, 517 F.3d 1364 (Fed. Cir. 2008).

128. See, e.g., Bayer AG v. Housey Pharmaceuticals, 340 F.3d 1367 (Fed. Cir. 2003).

129. Even Christopher Holman, a strong advocate for gene patenting, has noted that "there is no positive example of patent circumvention" in the diagnostics arena, supra note 126, at 242, and that claims framed as associations between mutations and predispositions to disease are broad enough to encompass "any and all later developed genetic testing metho-

row—patentees claim as much as possible and learn from earlier cases how to draft new claims more broadly. From a clinical perspective, offshoring is impractical and for research, it could undermine U.S. competitiveness in global markets.

Given the difficulty in finding effective substitutes for genetic information, it is no wonder that courts have begun to question the validity of these patents. In *Association for Molecular Pathology (AMP) v. US PTO*,[131] product claims to *BRCA1* and *2* mutations were invalidated on subject matter grounds, as were process claims for methods of diagnosing a predisposition to breast cancer from *BRCA* sequences. *AMP* was decided while *Bilski* was pending in the Supreme Court. However, one Federal Circuit judge has already suggested that *Bilski's* preemption test raises serious questions about patents on isolated DNA molecules.[132] And as noted earlier, Justice Breyer has been skeptical of claims on associations between patents and disease. When a process or a product patent cannot be invented around, both product markets and innovation markets are badly distorted.

III. LESSONS

The problems encountered in the application of patented genomic advances in both clinical and research settings illustrate why the Supreme Court is wary of claims that preempt rivals from competitive development. Admittedly, these effects are most evident through the kind of study described above: after the patents have issued and the inventions are widely distributed. Thus, it can be argued that even if a preemption approach to patentability is desirable in theory, there is no way for the Patent and Trademark Office (PTO) to administer a system that requires such highly evidence-based decisions.

There are two responses. First, there are many issues in patent law that cannot be fully implemented by the PTO. For example, application of the novelty and nonobviousness doctrines requires knowledge of the prior art. Some of that art (e.g. prior use and sale) is of a form that examiners have difficulty finding.[133] Yet the requirements are nonetheless maintained; in cases where the art comes to light later, the requirements are implemented through post-issuance challenges.[134] Second, as the *Bilski* Court intimated, there are clues to patentability that both the PTO and courts can use. The M-or-T test, mental steps doctrine, and absence of claim limitations were discussed in Part I. The genetics case studies suggest others.

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dologies, including those in no way contemplated by the patentee," id at 246.

131. 702 F. Supp.2d 181 (S.D.N.Y. 2010).

132. Intervet Inc. v. Merial Ltd, 617 F.3d 1282, 1294 (Fed. Cir. 2010)(Dyk, J., concurring in part)(subject matter issued not raised by the parties).

133. See 35 U.S.C. §§ 102(a) & (b), 103.

134. Patents (unlike trademarks, see 15 U.S.C. § 1065) never become incontestable.

A. *The ability to invent around.*

A critical feature of patents in the context of diagnostics is that claims to gene sequences and associations between sequences and predisposition to disease cannot be easily invented around. Patent holders can raise prices, refuse to license laboratories, or fail to develop needed tests without fear that an alternative technology will usurp the market for their advance. If society's interest in the development of the field is not aligned with the patent holder's, then it is society that is the loser: it is "preempted" from finding alternatives or leapfrogging over the existing invention to achieve results that are substantially better.[135] In genetics, the problem is that geneticists must work with the physical phenomena of the genes, but the same problem—the fundamental impossibility of circumventing—arises when claims are drawn in the abstract or to principles of nature.

The inability to invent around can, however, be no more than a clue to patentability. After all, patents are intended to produce exclusivity; at some level, no claim can be invented around. The issue then, is one of degree. Furthermore, the determination is sensitive to context. In the genetic realm, for example, the case study demonstrates how patents on *diagnostic processes* can impede the delivery of healthcare. However, patents on *therapeutic products* could be circumvented. When genetic information is used for therapeutic purposes, new substances are introduced into the body. These could differ from the patient's own sequences to improve their efficacy or reduce side effects. Because inventing around is not only possible but desirable, product patents on isolated genes would be acceptable if the rights could be limited to therapeutic uses—for example, by creating exemptions for diagnostic and research uses, or by limiting patent scope.[136]

Applying an inventing-around criterion to the subject-matter issue will thus require both a grasp of the field and an understanding of the patented invention's epistemic significance within it. These are not easy tasks. The National Academies has suggested the PTO convene panels of experts to advise it on patent policy; [137] that idea could be extended to the development of guidelines on the possibilities for inventing around within particular sectors. As previously noted, however, many of these decisions will likely be made post-issuance, when the impact of the patent on the field is evident. Significantly however, in that context, the question may not be terribly different from the inquiry made

135. See, e.g., Hilton Davis Chemical Co., v. Warner-Jenkinson Co., Inc., 62 F.3d 1512, 1533 (Fed. Cir. 1995)(Newman, J., concurring), *rev'd*, 520 U.S. 17 (1997).

136. See, e.g., Report on Gene Patents , supra note 20, Recommendation 1A & B; Gesetz zur Umsetzung der Richtlinie über den rechtlichen Schutz biotechnologischer Erfindungen [Statute Implementing the European Council's Biotechnology Directive], Jan. 21, 2005, BGBl. I at 146, §1a (4) (F.R.G.).

137. See National Research Council of the National Academies, Reaping the Benefits of Genomic and Proteomic Research 10 (2006).

when remedies for patent infringement are calculated and the issue of noninfringing substitutes arises.[139] In both situations, the issue is whether there are other ways to reach the ends achieved by the claimed invention. A quick look at the remedies cases suggests that district courts are able to accurately follow the criteria laid down by the Federal Circuit. Of the cases appealed since 1978 (when the current regime went into effect[140]) to the present, the trial court's decision was reversed only 8.7% of the time.[141] In contrast, Jeffrey Lefstin has computed overall reversal rates in the neighborhood of 14%.[142]

B. *Interoperability.*

A closely related concern is interoperability—the demand for equipment that can easily interact. The most familiar example is in the computer arena, where consumers want software that works with the hardware of their computers, computers that work with their printers, and backwardly-compatible upgrades. In science, researchers need to compare their results and so require wide access to the same (or compatible) research tools.[144] Similarly, the hope of synthetic biology is that a stable set of "parts" (synthesized DNA sequences) will become—like mechanical parts, such as sockets and plugs—interchangeable elements that can be utilized in a wide array of products.[145] In these situations, there may be a variety of ways to achieve a particular result. However, once a choice is made, those who come later are hostage to earlier decisions in much the way that geneticists are hostage to biology.

In an important paper on reverse engineering, Pamela Samuelson and Suzanne Scotchmer analyzed this problem in the software sector. Although the authors conceded that intellectual protection can be necessary to encourage the development of platforms, they concluded that net welfare is enhanced when application developers are permitted to utilize and build upon the work of others. More applications are developed, there is less waste, and a competitive marketplace is preserved.[146] As with genetic diagnostics, it is socially prefera-

139. See, e.g., Grain Processing Corp. v. American Maize-Products Co., 185 F.3d 1341 (Fed. Cir. 1999; New England Medical Center Hospitals, Inc. v. Peprotech, Inc., 1994 WL 16781102 (D.N.J. 1994).

140. See Panduit Corp. v. Stahlin Bros. Fibre Works, 575 F.2d 1152 (6th Cir. 1978).

141. Data available from author. It should, however, be noted, that the reversal rate when the trial court found acceptable noninfringing substitutes was higher than in cases where it did not.

142. Jeffrey A. Lefstin, The Measure of Doubt: Dissent, Indeterminacy, and Interpretation at the Federal Circuit, 58 Hastings L.J. 1025, 1064 (2007).

144. See, e.g., Fiona Murray, The Oncomouse that Roared: Resistance & Accommodation to Patenting in Academic Science, 116 Am. J. Soc. 341 (2010).

145. Drew Endy, Foundations for Engineering Biology, 438 NATURE 449, 449 (2005).

146. Pamela Samuelson & Suzanne Scotchmer, The Law and Economics of Reverse Engineering, 111 Yale L.J. 1575, 1613-27 (2002).

ble to put the first developer's advances into a legal domain where they can be utilized by all. While the authors restricted their policy prescriptions to copyright and contract law,[147] within the patent regime, interoperability concerns may, like the inability to invent around more generally, be taken as a clue to nonpatentability.

C. *Breadth of prospects.*

Of course, there is a sense in which every invention is unique. Accordingly, the inability to invent around cannot be taken as dispositive of preemption. As important is the patent's dominance. As we saw, information about genetic sequences and about relationships between phenotypes and genotypes open many important opportunities to both clinicians and researchers. In none of the cases studied did it appear that these opportunities were fully utilized when the patent was controlled by a single patent holder or licensee. Indeed, especially in the realm of relating genotype to phenotype, a lack of broad distribution has a profound quelling effect on future development. The number of opportunities a claim produces thus furnishes another, related, clue to the possibility that the claim is preemptive and should not be regarded as patentable.

Admittedly, there are counterarguments. Thus, it has been suggested that research is never stymied: patentees are rational; if they are uninterested in developing a prospect, they will license it out.[148] However, the case study suggests that broad licensing is not always the norm. It is easy to understand why. Rationality is bounded by intellectual and information and capacity. Patentees may, for example, have a difficult time understanding the potential for their advance in fields that are remote from their own area of expertise. There can also be significant barriers to licensing, especially between entities like universities and commercial firms that have very different goals.[149] Further, some decisions to hold out are highly rational: the right holder may be afraid that superseding inventions will destroy its market, especially with products that are not encompassed by the patents and therefore escape demands for royalties. Finally, potential *licensees* can be risk-averse and fail to seek licenses when the likelihood is low that their ideas will pan out.[151]

147. *Id.* at 1651.

148. See, e.g., Robert P. Merges, Of Property Rules, Coase, and Intellectual Property, 94 Colum. L. Rev. 2655, 2675-58 (1994). Cf. Richard J. Gilbert & Steven C. Sunshine, Incorporating Dynamic Efficiency Concerns in Merger Analysis: The Use of Innovation Markets, 63 Antitrust L.J. 569, 599 (1995)(suggesting that there are usually markets for innovation opportunities).

149. See e.g., Rebecca S. Eisenberg, Bargaining Over the Transfer of Proprietary Research Tools: Is the Market Failing or Emerging?, in EXPANDING THE BOUNDARIES OF INTELLECTUAL PROPERTY 223 (Rochelle Dreyfuss, et al. 2001).

151. See, e.g., Fiona Murray et al., supra note 119 (demonstrating that oncomice bred fewer lines of cancer research when they their patents were enforced as compared to when they became freely available to researchers).

D. *The identity of the inventor.*

Another useful clue may be gleaned from the status of the inventors named in the patent. For example, the genetics case studies show that associations tend to be identified by academics.[152] From a practical perspective, that finding is significant because these inventors are not primarily motivated by the promise of patents.[153] More important for the purpose of determining preemption, academic rewards tend to depend on "abstract knowledge production."[154] Accordingly, work that comes out of academia is likely to be fundamental—and thus raise preemption concerns. Of course, this will not necessarily be the case—an academic who has discovered a broad prospect may also be the one to identify narrow applications. Nonetheless, academic involvement furnishes a clue to preemption concerns.[155]

Academics can also be considered examples of a broader class of inventors whose work requires greater scrutiny: what Eric von Hippel calls user (or lead user) innovators.[156] These are inventors who develop technology for their own use. Thus, they are not primarily working for the rewards associated with patents.[157] More important, the advances they make are often penultimate in the sense that they are made for the purpose of achieving other goals. In the case of diagnostics, for example, clinicians develop associations in order to treat their patients, find new cures for diseases, understand the biology of disease (and to reap the reputational awards that will advance their careers). Similarly,

152. Report on Gene Patents, supra note 20, at 22. Thus, Mary-Claire King and coworkers first detected linkage to *BRCA1* while at the University of California at Berkeley, see J.M. Hall et al., Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21, 250 Science 1684 (21 Dec. 1990). Ernest G. Seidman, the inventor of the diagnostic at issue in *Prometheus*, is at McGill University, see http://academic.mcgill.ca/crc/2005/seidman.htm; the inventors of the diagnostic in *Metabolite* were university doctors, 548 U.S. at 128. Further, several inventions in cases that could have been argued on preemption grounds are academics, see Ariad Pharmaceuticals, Inc. v. Eli Lilly and Co., 598 F.3d 1336 (Fed. Cir. 2010)(MIT, the Whitehead Institute and Harvard University); University of Rochester v. G.D. Searle & Co., 358 F.3d 916, 929 (Fed. Cir. 2006)(explicitly considering the academic nature of the work).

153. See, e.g., Katherine J. Strandburg, Curiosity-Driven Research and University Technology Transfer, in 16 Advances in the Study of Entrepreneurship, Innovation and Economic Growth 97 (2005). Cf. Waverly W. Ding, Fiona Murray & Toby E. Stuart, Gender Differences in Patenting in the Academic Life Sciences, 313 Sci. 665 (2006)(discussing motivation in medical sciences).

154. See, e.g., Scott Stern, Do Scientists Pay to be Scientists?, 50 Mgmt. Sci. 835 (2004).

155. Cf. EBay v. MercExchange, 547 U.S. 388, 393 (2006)(suggesting "university researchers" as a criterion for deciding when injunctive relief can be denied).

156. Eric von Hippel DEMOCRATIZING INNOVATION (2005); Glen L. Urban & Eric von Hippel, Lead User Analyses for the Development of New Industrial Products, 34 Mgmt. Sci. 569, 571-72 (1988).

157. See Katherine J. Strandburg, Users as Innovators: Implications for Patent Doctrine, 79 University of Colorado L. Rev. 467 (2008).

research tools are primarily developed to facilitate further research. As Fiona Murray and her coauthors have shown in connection with the oncomouse, which is used in cancer research, patents on research tools can reduce lines of research and retard technological development.[158] Accordingly, they will often raise the same concerns that underlie the *Bilski* Court's focus on preemption.

CONCLUSION

At the end of the day, the question is whether to foster a culture of innovation or a culture of intellectual property. They are not the same because patenting far upstream can yield royalties while also delaying innovation. The *Bilski* Court's willingness, despite a commitment to statutory language, to read three exceptions into the subject-matter requirement, suggests that the Court understands the statute as promoting a culture of innovation.

As new technological opportunities emerge, and as universities and other upstream innovators become increasingly aggressive in pursuing patent protection, promoting a culture of innovation becomes ever more difficult. There are many ways to preserve a robust creative environment, including through the disclosure and utility requirements, defenses to infringement, discretion over injunctive remedies, and antitrust law. Many of these approaches may be easier to apply than *Bilski*'s preemption doctrine, but the courts have significantly narrowed two of them—defenses to infringement and antitrust law. The result is significant pressure on the subject matter doctrine. And there are core advances that should remain in the public domain. The hallmark of such an advance is an invention so close to nature that it creates broad prospects that cannot be exploited by inventing around the patent. Other clues include the absence of physicality (the M-or-T test), claims that recite only steps performed in the mind, the absence of claim limitations, the demand for interoperability, and academic or user-innovator involvement. Presumably, as the Federal Circuit begins to apply *Bilski*, it will identify other ways for determining when a claim is too preemptive to patent.

158. Murray et al., supra note 119.