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GENE PATENTS AND THE PRODUCT OF NATURE DOCTRINE

JOHN M. CONLEY*

INTRODUCTION

Michael Crichton is not the first person to be shocked and appalled by gene patents. Indeed, it seems to be a standard reaction among almost everyone but patent lawyers. In an extreme version of this reaction, Congressman Xavier Becerra of California has introduced a bill that would virtually ban new gene patents.1 While the bill probably has little or no chance of passage in anything like its present form,2 its introduction is symptomatic of an unease with current patent law and practice that is both wide and deep. Scientists, economists, and law professors worry about the impact of gene patents on future biotechnology research.3 Ethicists lament the apparent commodification of human tissues, especially when others make money

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2. The bill was referred to the House Subcommittee on Courts, the Internet, and Intellectual Property on March 1, 2007, and no further action has been reported.

without compensating the donors of those tissues. Legal academics (far more than practicing patent lawyers, who seem comfortable with the situation) worry about fidelity to long-established patent law principles. And people of all backgrounds seem to share Representative Becerra’s visceral reaction that patenting genes just is not right.

Any number of gene patent examples might serve to bring these diverse objections into focus, but the one that may do it best is the so-called breast cancer gene patent. Issued to Mark H. Skolnick and several University of Utah colleagues in 1998 and assigned to Myriad Genetics, Inc. (Skolnick’s company), the patent “relates to methods and materials used to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer.” The broadest of twenty allowed claims—the operative parts of the patent, which define specifically what is patented and what others may not do—covers “an isolated DNA coding for a BRCA1 polypeptide... having the amino acid sequence set forth in SEQ ID NO:2 [a listed amino acid sequence].” The allowance of this claim means that Myriad Genetics can exclude anyone else from making, using, or selling the breast cancer gene outside the body. (This is what “isolated” means.)


9. Id. claim 1.

10. The relevant definition reads as follows: “Isolated” or “substantially pure”. An “isolated” or “substantially pure” nucleic acid (e.g., an RNA, DNA or a mixed polymer) is one which is substantially separated from other cellular components which naturally accompany a native human sequence or protein, e.g., ribosomes, polymerases, many other human genome sequences and proteins. The term embraces a nucleic acid sequence or protein which has been removed from its naturally occurring environment,
quence is that doctors wishing to test patients and their families for the presence of the cancer-predisposing form of the gene must obtain a license from Myriad and must persuade the patients' insurance companies to pay for that license. But because U.S. patent law lacks a meaningful research or experimental exception, anyone wishing to do research on the gene outside the body must also obtain a license. Moreover, because the patent claim covers any and all DNA sequences that code for the BRCA1 protein, if multiple genes are found to perform this function, Myriad will control all of them for the twenty-year life of its patent.

A patent such as this evokes a strong response from just about every category of skeptics, whether their particular focus is the foreclosure of research, the potential denial of healthcare, or the proper application of the patent laws. It is also likely to trigger an elemental response that lies at the core of almost every objection: You should not be able to patent a gene!

This paper will focus on the latter point, restating it as a question of legal doctrine: Why is it that the law has routinely treated genes as patentable inventions rather than unpatentable natural phenomena? Part I of this article will review the basics of patent law, with particular emphasis on patentable subject matter and the long-established product of nature doctrine. Part II will discuss the understanding of genetics that is reflected in the patent case law, an understanding that has led the courts and the United States Patent and Trademark Office (USPTO) to find a material distinction between genes as usually claimed in patent applications and their naturally-occurring counterparts. Part III will review several recent legal developments that, taken together, may portend some future constraints on the virtually unfettered patentability that genes have enjoyed thus far. Finally, I will conclude with some thoughts on the policy implications of these developments.

and includes recombinant or cloned DNA isolates and chemically synthesized analogs or analogs biologically synthesized by heterologous systems.

Id. col.19 ll.8–18.

11. See Madey v. Duke Univ., 307 F.3d 1351, 1361–62 (Fed. Cir. 2002) (holding that experimental exception is extremely narrow, and not applicable to work of research university); Lee, supra note 3, at 86–87 (reviewing narrowing of research exception).

12. See Demaine & Fellmeth, supra note 6, at 416–17 (“The University of Pennsylvania has curtailed much of its genetic research from fear of patent infringement, and at least one Yale University researcher has been forced to withdraw from breast cancer research to avoid infringing license limitations on the BRCA1 and BRCA2 genes patented by Myriad.”).
I. A BRIEF REVIEW OF PATENT LAW

A patent is a right to exclude: specifically, the right to exclude others from making, using, or selling the patented invention for twenty years from the date of issue.\textsuperscript{13} The infringer’s intent is irrelevant. Whereas copyright law requires proof of copying,\textsuperscript{14} inadvertent duplication constitutes patent infringement. The authority to grant patents is provided in the Constitution: Congress is authorized “to promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.”\textsuperscript{15} As this language suggests, the American patent system has an economic rationale, with the government offering a broad exclusionary right as an incentive to invention. The Patent Act further seeks to promote scientific progress by conditioning the grant of the patent on full disclosure of the relevant technology.\textsuperscript{16}

The basic requirements for obtaining a patent are set forth in §§ 101, 102, 103, and 112 of the Patent Act of 1952.\textsuperscript{17} Section 101 specifies two distinct requirements. First, the application must claim the sort of thing on which a patent may be granted; in other words, it must claim patentable or “statutory” subject matter. That category is very broad, encompassing claims by anyone who “invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof.”\textsuperscript{18} As the Supreme Court most famously put it, the realm of patentable subject matter includes “anything under the sun that is made by man.”\textsuperscript{19} Nonetheless, the category is not all-encompassing. As far back as 1889, the Patent Office recognized that it would be wrong “for an element or a principle to be secured by patent,” lest patents might “be obtained upon the trees of the forest and the plants of the earth.”\textsuperscript{20} Almost a century later, the Supreme Court reiterated that “laws of nature, physical phenomena, and abstract ideas” are not patentable subject matter.\textsuperscript{21} The reason is that “such discoveries are ‘manifestations of . . . nature, free to all men and reserved exclusively to none.’”\textsuperscript{22}

\begin{itemize}
\item \textsuperscript{13} 35 U.S.C. §§ 154(a)(2), 271(a) (2006).
\item \textsuperscript{14} 17 U.S.C. §§ 106(1), 501(a) (2006).
\item \textsuperscript{15} U.S. CONST., art. I, § 8, cl. 8.
\item \textsuperscript{16} See 35 U.S.C. § 112 (stating the enabling disclosure requirement).
\item \textsuperscript{17} Id. §§ 101–03, 112.
\item \textsuperscript{18} Id. § 101.
\item \textsuperscript{19} Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (citations omitted).
\item \textsuperscript{20} Ex parte Latimer, 1889 Dec. Comm’r Pat. 123, 125–126 (1889).
\item \textsuperscript{21} Chakrabarty, 447 U.S. at 309.
\item \textsuperscript{22} Id. (quoting Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948)).
\end{itemize}
This longstanding prohibition against patenting "physical phenomena" or "manifestations of nature" is often referred to as the "product of nature" doctrine. Although its precise theoretical roots are somewhat murky and still debated, the fundamental point is that the mere discovery of a naturally occurring phenomenon is not patentable because it is not an invention. As the Supreme Court stated in its most recent pronouncement on the subject, "'the relevant distinction’ for purposes of § 101 is . . . ‘between products of nature, whether living or not, and human-made inventions.'"\textsuperscript{23}

Second, § 101, by using the word "useful," imposes a utility requirement.\textsuperscript{24} In the vast majority of cases, it is easily met. As Justice Story wrote in 1817, "[a]ll that the law requires is, that the invention should not be frivolous or injurious to the well-being, good policy or sound morals of society."\textsuperscript{25} The utility requirement has presented a formidable barrier to only two categories of patents: so-called chemical intermediates and genes. In the former category, the Supreme Court has rejected a claim "to a chemical process which yields an already known product whose utility—other than as a possible object of scientific inquiry—has not yet been evidenced."\textsuperscript{26} The typical gene patent claims a gene that codes for a known protein and the utility standard is readily met. However, as I will discuss below, the logic of the chemical intermediate rule has been applied to defeat claims to gene fragments whose ultimate function is not known and whose only present value is as a research tool.\textsuperscript{27}

Section 102 requires that the claimed invention be novel.\textsuperscript{28} "Novelty" has a highly technical meaning that is articulated (albeit not very clearly) in § 102's complex provisions. For example, under § 102(a), the patent will be denied if the invention was known or used by others in this country, patented here or abroad, or described in a "printed publication" in the United States or a foreign country prior to the patent applicant's date of invention.\textsuperscript{29} Section 102(b) creates the "statutory bar" that results in a forfeiture of patent rights if the applicant or anyone else makes public use of the invention, puts it on sale, or engages in other specified conduct more than a year prior to the filing of the application.\textsuperscript{30} Section 102(g) establishes the

\textsuperscript{25} Lowell v. Lewis, 15 F. Cas. 1018, 1019 (C.C.D. Mass. 1817) (No. 8,568) (Story, J.).
\textsuperscript{26} Brenner v. Manson, 383 U.S. 519, 529 (1966).
\textsuperscript{27} See discussion infra Part III.B.
\textsuperscript{28} 35 U.S.C. § 102.
\textsuperscript{29} Id. § 102(a).
\textsuperscript{30} Id. § 102(b).
rules for determining priority when two or more inventors claim the same invention.\textsuperscript{31} American priority rules are virtually unique in international patent law: priority is usually awarded to the person who can prove that he or she was the first to invent, whereas in most other countries the patent goes to the first person to file an application.

The final substantive requirement is "nonobviousness." As set forth in § 103(a), the specific rule is that the invention is unpatentable if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.\textsuperscript{32} The nonobviousness barrier will sometimes trip up applicants who have survived the § 102 novelty inquiry. Under the novelty test, the patent will not be denied unless the very invention that is now claimed has been described, used, etc. in its entirety before the critical date.\textsuperscript{33} Under the nonobviousness rule, by contrast, the patent will be denied if a hypothetical person of ordinary skill in the field, armed with the total knowledge of the field then available to the public (the "prior art"), would have looked at the claimed advance at the time it was invented and deemed it an obvious step.\textsuperscript{34} To date, the nonobviousness requirement has had little impact on gene patents. In fact, the United States Court of Appeals for the Federal Circuit has gone so far as to hold that a claim to an isolated and purified gene (that is, cDNA) is not rendered obvious by prior art that discloses both a method of gene cloning and the partial amino acid sequence of a protein closely related to that produced by the claimed gene.\textsuperscript{35} Nonetheless, there have been some recent hints that nonobviousness may be preparing for a comeback.\textsuperscript{36}

Assuming that these four substantive standards can be satisfied, the application itself must meet certain formal requirements. The most important of these is § 112's "enablement" rule, which is meant to enforce the disclosure part of the patent bargain.\textsuperscript{37} The patent application must describe the invention with enough specificity to enable a person skilled in the rele-

\begin{itemize}
\item \textsuperscript{31} Id. § 102(g).
\item \textsuperscript{32} Id. § 103(a).
\item \textsuperscript{33} See Verdegaal Bros., Inc. v. Union Oil Co. of Cal., 814 F.2d 628, 631 (Fed. Cir. 1987) (holding that anticipation requires that "each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.").
\item \textsuperscript{34} See KSR Int'l Co. v. Teleflex Inc., 127 S. Ct. 1727, 1740 (2007) (Supreme Court's most recent restatement of obviousness doctrine, discussed infra text accompanying notes 112-115).
\item \textsuperscript{35} In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995).
\item \textsuperscript{36} See discussion infra Part III.C.
\item \textsuperscript{37} 35 U.S.C. § 112 (2006).
\end{itemize}
vant field to make and use it. It is not necessary for the inventor actually to have built the invention before filing the application; it is enough that the description provided in the application will enable someone else to build it. Meeting the enabling disclosure requirement also proves that the applicant is actually in possession of the invention. 38

II. WHY ARE GENE PATENTS NOT BARRED BY THE PRODUCT OF NATURE DOCTRINE?

To understand the answer to this question, one must begin with Diamond v. Chakrabarty, 39 the Supreme Court’s only biotechnology case. Chakrabarty had altered an existing species of bacteria by inserting new DNA rings, called plasmids. The result was a genetically new species with enhanced oil-consuming properties. In a five-to-four decision (it is often forgotten just how close this case was), the Court held that the new species of bacteria was patentable subject matter, notwithstanding that it was alive. Although the specific facts of the case did not involve claims to genes themselves, the Court’s broadly-worded discussion of the boundary between unpatentable natural phenomena and patentable human-made inventions remains the standard for applying the product of nature doctrine. 40

Of greater direct relevance is the Federal Circuit’s 1991 decision in Amgen, Inc. v. Chugai Pharmaceutical Co., 41 which may still be that court’s most significant biotechnology case. In Amgen, three companies fought over the patent rights to the DNA sequences that encode the human erythropoietin (EPO) protein, which stimulates the production of red blood cells. 42 The broadest of the Amgen product claims that was upheld by the Federal Circuit reads as follows: “A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin.” 43 Amgen, in other words, claimed the purified and isolated form of

38. See, e.g., Enzo Biochem, Inc. v. Gen-Probe Inc., 323 F.3d 956, 969 (Fed. Cir. 2002) (stating dual purpose of § 112). Providing an enabling disclosure of a biotechnology invention can sometimes be problematic. See id. at 964–65 (holding that, in case of DNA patent, § 112 requirement may be satisfied by depositing sample of claimed composition in public depository).
40. See supra text accompanying notes 22–23. For recent general discussions of the product of nature doctrine, see Andrews et al., supra note 3; Chin, supra note 6, at 986; Stephanie Arcuri, Note, They Call That Natural? An Analysis of the Term “Naturally Occurring” and the Application of Genes to the Patent Act, 40 VAL. U. L. REV. 743, 757–60 (2006); Fox, supra note 6, at 1012.
41. 927 F.2d 1200 (Fed. Cir. 1991).
42. Because it enhances the blood’s ability to carry oxygen, EPO has played a prominent role in many sports doping scandals. For example, the 1996 Tour de France winner, Bjarne Riis of Denmark, has recently admitted that he used EPO that year. See Associated Press, Riis Admits Doping During 1996 Tour Victory, NBC SPORTS, May 25, 2007, http://nbcspports.msnbc.com/id/18864080/.
43. Amgen, 927 F.2d at 1204 (quoting U.S. Patent No. 4,703,008 (filed Nov. 30, 1984)).
any gene that codes for the EPO protein. As used in the Amgen patent, “purified and isolated” meant that the coding region of the relevant DNA had been identified and had been reproduced outside its natural environment.

That Amgen’s patent was directed to statutory subject matter was taken for granted and not at issue in the case. However, the Federal Circuit did take pains to point out why this was the case: “It is important to recognize that neither [competing inventor] invented EPO or the EPO gene. The subject matter . . . was the novel purified and isolated sequence which codes for EPO . . . .”44 The district court emphasized the same point, characterizing human EPO as “a nonpatentable natural phenomenon ‘free to all men and reserved exclusively to none.’”45

Thus, by 1991, the Federal Circuit had acquiesced in the proposition that the words “purified and isolated” were sufficient to distinguish a claimed gene from its naturally occurring counterpart. And it had done so in the context of an extraordinarily broad claim that covers the purified and isolated version of any gene that codes for the vitally important human EPO protein. But what did these qualifying words actually mean? As is clear from a reading of the patent itself, as well as from the district court’s extended discussion, the essence of Amgen’s invention was “the successful cloning of the EPO gene.”46

A clone, or cDNA version of a naturally-occurring gene, differs from the naturally-occurring variant in that the introns, or noncoding regions, are absent.47 This is because cDNA is synthesized by reverse-transcribing messenger RNA (mRNA). mRNA is itself the product of the complete transcription of one strand of an entire active gene, followed by the splicing out of the noncoding regions. Accordingly, the gene claimed in Amgen does not have a precise structural counterpart in the human body. On the one hand, it lacks the noncoding regions that are part of naturally-occurring DNA. And, on the other hand, while cDNA is a faithful reverse transcription of the sequence recorded by the mRNA, it is DNA, not RNA, and thus a different chemical.48 The acceptance of this fundamental distinction by the courts and the USPTO has underlain all subsequent gene patenting.

44. Id. at 1206.
46. Id.
47. For a more detailed review of the science of DNA patents, see Conley & Makowski, supra note 7, at 309–16.
48. Most importantly, RNA substitutes the base uracil for the thymine that is present in DNA. See id. at 311.
The power of this distinction is illustrated even more vividly by the Skolnick breast cancer gene patent.49 Making ingenious use of a variety of known techniques, as well as detailed family medical histories available in Utah, the inventors were able to identify the sequence of base pairs that codes for the protein for which the human BRCA1 gene codes. This discovery led to the first and broadest of the allowed claims: “An isolated DNA coding for a BRCA1 polypeptide [protein], said polypeptide having the amino acid sequence set forth in [an appended listing].”50 In other words, a patent was granted on an isolated DNA sequence (note the absence of the further modifier “purified”) that codes for a protein that is made up of the specified sequence of amino acids.

The only thing that distinguishes the claimed sequence from sequences in living human cells that code for the same protein is the word “isolated.” According to the definition provided in the patent, “isolated” is a synonym for “substantially pure.”51 These equivalent terms denote a “nucleic acid...which is substantially separated from other cellular components which naturally accompany a native human sequence.” In other words, “isolated” “embraces a nucleic acid sequence...which has been removed from its naturally occurring environment.”52 The chemical difference between the claimed sequence and the comparable sequence that actually occurs in the human body is that the “isolated” sequence does not include any noncoding DNA. Nonetheless, what emerges is a patent on a DNA sequence that is defined by the fact that it does exactly the same coding work as the human BRCA1 gene. This claim perhaps represents the gene patent in its most sweeping form.

“Isolated” continues to work its magic, sometimes in combination with “purified” and/or “synthesized.” Several recently-issued patents illustrate the point. For example, a patent issued to Callaghan et al., in 2006 and entitled “Human Tumor Suppressor Gene”53 claims “[a]n isolated nucleic acid comprising a nucleotide sequence selected from the group consisting of’ five different nucleotide sequences—two defined by specific nucleotide listings and the other three by the amino acids or proteins for which they code.54 According to the abstract, the claimed gene “appears to represent a tumour [sic] suppressor gene and the detection of a polymorphism or alteration in the gene from a subject may be useful for the diagno-

50. Id. claim 1.
51. See supra note 10 for a full definition of “isolated.”
54. Id. claim 1.
sis or determination of a predisposition to hyperproliferative disease such as a cancer.” It is clear from the body of the patent, however, that the exact function of the gene is not yet known. The assumption that it has a tumor suppressing function is based on the protein it codes for having a similar amino acid sequence to a fruit fly protein which is, in turn, similar to a family of rat proteins that help to mark cells for degradation and death.

Another 2006 patent, this one issued to Ikawa et al., and entitled “Human p51 Genes and Gene Products Thereof,” claims “[a]n isolated DNA molecule comprising a nucleotide sequence coding for a polypeptide comprising” a listed sequence of amino acids. The p51 gene is believed to be a member of the p54 family of known tumor suppressor genes. The evidence for actual tumor-suppressing activity is stronger than in the Callaghan patent; that evidence includes p51’s involvement in cell growth inhibitory activity and the presence of a suspect mutation in human tumor tissues.

In both of these patents, “isolated” appears to have its everyday meaning. While the Amgen meaning of “with noncoding regions absent” is at least implicit in patents such as these, it is no more than that. Andrew Chin has described the current state of claiming practice as follows:

The claim terms “isolated” and “purified” typically do not refer to an absolutely homogeneous condition but more broadly encompass mixtures in which biological substances and large molecules other than the claimed DNA molecule are substantially absent. To give a typical example, a patent issued in 1998 to Chiron Corporation states that a DNA molecule is “purified” if it “is present in the substantial absence of other biological macromolecules...” while a DNA molecule is “isolated” if it is “separated not only from other [DNA molecules] that are present in the natural source of the macromolecule but also from other macromolecules.” Thus, a DNA molecule excised from a living cell and stored in a saline solution, with no other DNA present, would be “isolated” and “purified” within the meaning of the patent claim.

“Isolated” has become an equally powerful word in the realm of protein patents, often serving as the only distinction between a claimed protein and its naturally occurring counterpart. For example, a patent issued to Turley et al., in 2002, entitled “Hyaluronan Receptor Protein,” relates to “a novel hyaluronan receptor protein involved in cell locomotion or motility and in cell proliferation and transformation and to DNA sequences encod-

55. *Id.* at [57].
57. *Id.* claim 1.
ing this protein.” Significantly, “[t]hese receptors regulate cell locomotion and have been implicated in malignant transformation.” The broadest of the three claims is directed simply to “[a]n isolated protein comprising the amino acid sequence of FIG. 2.” Following the same strategy, a patent issued to Kikuchi et al., in 2006 claims “[a]n isolated gastric cancer antigen protein which comprises [the listed] amino acid sequence.” An alternative claim is directed to “an isolated protein” that is encoded by a specified DNA sequence. The significance of the invention is that the protein in question can stimulate the immune cells of the body to kill cancer cells. Given the language of the claims, the patent would control any research on the antigen protein, whether defined by its amino acid sequence or the nucleotide sequence of the gene that codes for it.

To summarize, Amgen ratified the proposition that claiming genes in isolated or purified form “is not simply a lawyer’s trick.” Interpreting the limitations “isolated” and “purified” in the gene-cloning context of that case, both Amgen courts accepted the prevailing assumption in patent law that a gene that is effectively claimed in cDNA form is materially different on a structural level from its natural precursor.

There are two problems with this assumption, however. First, as should be evident from the recent patents just discussed, the thinking reflected in Amgen has given rise to one of those slippery slopes of which lawyers are so fond. A reader of Amgen may or may not be persuaded by the materiality of the DNA/cDNA distinction. Nonetheless, it was a distinction and thus promised to circumscribe gene patents and limit their preclusive effect on future research. But now, as Chin points out, “isolated” has come to mean nothing more than, well, isolated. We are faced with a proliferation of patents that create proprietary rights in genes and proteins whenever they are used outside the chemical media in which they naturally occur. To make matters worse, genes are successfully defined both in terms of their sequences and the proteins they encode, while proteins are defined both by the amino acids that comprise them and the DNA sequences that encode them. As a practical matter, has the line between natural phenomenon and human-made invention been obliterated?

60. Id. col.1 ll.27-28.
61. Id. claim 1.
63. Id. claim 2.
64. Eisenberg, supra note 3, at 786.
65. See supra note 58 and accompanying text.
A second problem involves the exclusive focus on structural distinctions between natural and human-made genes. There is no doubt that isolation produces, at least in literal terms, a difference in chemical structure. The isolated gene or protein is no longer the same physical entity as its natural precursor. But, as all of the patents I have discussed make clear, the entire utility of the claimed isolate lies in the fact that it is functionally indistinguishable from the natural version. Thus, the breast cancer or tumor suppressor gene patents claim DNA sequences that are defined by the fact that they do exactly the same coding work as the versions that occur in the body. The function of a gene is to carry information that can be used to make a protein. The isolated versions carry the same information—indeed, they are of interest to science only because they do.

Patent lawyers have succeeded in making the chemical structure of genes the sole focus of the patentable subject matter analysis. It is not clear, however, why this should be so. In determining whether a claimed gene is a natural phenomenon or a human-made invention, why should a small structural difference be dispositive, while functional identity—which is the whole point of the patent—is entirely irrelevant? Perhaps it really was a lawyer’s trick after all.

III. ARE THERE ANY LIMITS IN SIGHT?

There is no direct evidence of any tightening of the patentable subject matter rules. As the recent patents discussed in the Introduction suggest, it is business as usual at the USPTO. Nor have any court decisions struck down gene or protein patents on subject matter grounds. There are, however, some indirect hints that change may be in the air.

A. Patentable Subject Matter

The most significant of these hints was the Supreme Court’s near-miss on patentable subject matter in 2006 in the case of Laboratory Corp. of America Holdings v. Metabolite Laboratories, Inc. The case involved:

[A] patent that claims a process for helping to diagnose deficiencies of two vitamins, folate and cobalamin. The process consists of using any


test (whether patented or unpatented) to measure the level in a body fluid of an amino acid called homocysteine and then noticing whether its level is elevated above the norm; if so, a vitamin deficiency is likely.68

The trial court and the Federal Circuit held that the patent was valid and that Laboratory Corporation of America ("LabCorp") was liable for inducing infringement when it encouraged doctors to order diagnostic tests for measuring homocysteine.69

Although LabCorp vigorously defended the case on a number of grounds, including that the patent was invalid for being overbroad and indefinite, it never raised the issue of patentable subject matter in any explicit way in the lower courts.70 However, in its successful petition for certiorari, LabCorp raised the following question:

Whether a method patent [setting forth an indefinite, undescribed and nonenabling step] directing a party simply to 'correlate' test results can validly claim a monopoly over a basic scientific relationship [used in medical treatment] such that any doctor necessarily infringes the patent merely by thinking about the relationship after looking at a test result.71

Thus, at least four Justices—the minimum number necessary to grant certiorari—seemed to have a strong interest in revisiting the product of nature doctrine's first cousin, the longstanding prohibition against patenting "laws of nature."72 Then, in a move that was as startling as its original grant of cert, the Court dismissed the writ as improvidently granted.73 Its one-sentence per curiam order gave no clue as to what had happened. But, in a strong dissent from the dismissal, Justice Breyer, joined by Justices Stevens and Souter, gave some hints as to what the four or more who had wanted to take the case had been thinking.

The dissent began by reciting the longstanding exclusion from patent protection for "laws of nature, natural phenomena, and abstract ideas."74 According to Justice Breyer, the exclusion has nothing to do with the relative ease or difficulty of discovering the laws of nature, or the ultimate utility of such discoveries. The exclusion is, rather, based in the Constitution: allowing such patents would be to grant more protection than is necessary to "promote the progress of science and the useful arts."75

69. *Id.*
70. *Id.* at 2925 ("LabCorp did not refer in the lower courts to § 101 of the Patent Act, which sets forth subject matter that is patentable, and within the bounds of which the 'law of nature' principle most comfortably fits.").
71. *Id.* at 2925 (emphasis added) (citation omitted).
74. *Id.* at 2922 (citation omitted).
75. *Id.* (quoting U.S. CONST., art. 1, § 8, cl. 8).
Breyer characterized the patentable subject matter rules (including the prohibition against patenting phenomena of nature) as an effort "to sail between [the] opposing and risky shoals" of overprotection and underprotection, to balance "the enormous potential for rent-seeking that would be created if property rights could be obtained in [those basic principles] and . . . the enormous transaction costs that would be imposed on would-be users." After a detailed description of the invention at issue and its impact on medical practice, and a thorough review of the "laws of nature" case law, Justice Breyer reached the tentative conclusion that "[a]t most, [the patentees] have simply described the natural law at issue in the abstract patent language of a 'process.'" Regardless of whether he was right or wrong, he concluded, the case presented a significant opportunity for the Court to clarify "whether the patent system, as currently administered and enforced, adequately reflects the 'careful balance' that 'the federal patent laws . . . embed[y].'"

So the three dissenting justices saw in Lab. Corp. an important opportunity to ask whether the current application of the patentable subject matter requirement is providing more protection than is necessary to promote the progress of science and the useful arts. The case dealt specifically with the "laws of nature" exclusion. Nonetheless, a majority opinion along the lines of Justice Breyer's dissent may well have invited a similar rethinking of the product of nature exclusion, with particular focus on its impact on science. One can envision an argument in the Federal Circuit, or perhaps the Supreme Court itself, about whether the USPTO's exclusive reliance on small structural differences between natural and isolated genes is promoting or inhibiting the progress of science. Those of us who would like to participate in that argument can only hope that the Supreme Court will be confronted with another case in which the issue of patentable subject matter is more squarely presented.

A further hint that change may be on the horizon has come from the Federal Circuit's 2005 decision in SmithKline Beecham Corp. v. Apotex

76. Id.
77. Id. at 2923 (quoting WILLIAM M LANDES & RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 305–06 (2003)).
78. Id. at 2928.
79. Id. at 2929 (citations omitted). Interestingly, Justice Breyer all but repudiated the Federal Circuit's holding in State St. Bank & Trust Co. v. Signature Fin. Group, Inc., 149 F.3d 1368, 1373 (Fed. Cir. 1998), that a software-based accounting process comprised patentable subject matter as long as it produced a "useful, concrete, and tangible result." According to Justice Breyer, "this Court has never made such a statement and, if taken literally, the statement would cover instances where this Court has held the contrary." Lab. Corp., 126 S. Ct. at 2928.
The question in the case was whether Apotex’s generic drug compound paroxetine hydrochloride anhydrate (PHC anhydrate) would infringe SmithKline’s patent on another form of PHC, PHC hemihydrate. The two compounds are crystals; PHC hemihydrate includes bound water molecules, whereas PHC anhydrate does not. SmithKline uses PHC hemihydrate as the active ingredient in the antidepressant drug Paxil. When Apotex sought regulatory approval for a generic antidepressant that contained PHC anhydrate, SmithKline sued for infringement of the hemihydrate patent.

SmithKline did not claim that its hemihydrate patent covered the anhydrate form. In fact, PHC anhydrate had been the subject of an earlier, now-expired patent, and had thus been part of the prior art for the PHC hemihydrate application. SmithKline alleged, however, that Apotex’s PHC anhydrate tablets convert naturally into PHC hemihydrate—including upon ingestion by the patient—thus “making” the patented compound. The district court ruled for Apotex, and the Federal Circuit affirmed, although on different grounds. It found that, because PHC anhydrate did indeed convert naturally into PHC hemihydrate, PHC anhydrate “inherently anticipated” the hemihydrate compound. Under § 102(b), the Federal Circuit held, the prior art included all chemicals that were patented or described in a printed publication more than one year prior to SmithKline’s application for the hemihydrate patent, and any compounds that were inherent in those prior art chemicals, regardless of whether their inherency was fully understood prior to the critical date.

As interesting as the inherency issue is, the critical part of the case for the gene patent story is the concurring opinion of Judge Gajarsa. He would have affirmed the district court’s judgment in favor of Apotex on the ground that the claim in question encompassed unpatentable subject matter. Judge Gajarsa reviewed the discovery of the paroxetine compounds and their properties at great length, beginning with the original research on
the anhydrate form in the 1970s. He then focused on SmithKline’s unlimited, four-word claim to “crystallized paroxetine hydrochloride hemihydrate” and the necessary implication that that claim represented an assertion of rights in “all ‘crystallized paroxetine hydrochloride hemihydrate,’ without any exceptions.”

For Judge Gajarsa, the key fact was that:

[A]t some point, likely in late 1984, something occurred in SmithKline’s laboratories that gave rise to two new phenomena simultaneously. The first was a synthetic crystal later named paroxetine hemihydrate, ostensibly a patentable human-made invention under Chakrabarty. The second was a natural physical process whereby paroxetine anhydrate (a pre-existing synthetic crystal that is today in the public domain) could, under normal climatic conditions and with no human intervention, bond with water molecules and convert itself into paroxetine hemihydrate, ostensibly an unpatentable, newly-discovered natural process under Chakrabarty.

The result was an invention that “blur[red] the line between a natural process and a synthetic product . . . [A] synthetic compound, created by humans in a laboratory, never before existing in nature, that is nevertheless capable of ‘reproducing’ itself through a natural process.” In an elaborate hypothetical, Judge Gajarsa analogized to genetically modified corn that was blown by the wind from the field of a single farmer all across the continent. He concluded that the notion that the patent holder would be entitled to collect royalties from every farmer whose field contained even a few patented stalks “cannot possibly be correct.” The problem, in his view, was “the inevitable failure of the patent to provide public notice—which, in turn, stems from the inherently unpatentable nature of the claimed subject matter.” In other words, if a patent claims—without limitation—a product that can result from natural processes beyond the intent or control of a would-be infringer, then that patent cannot fulfill its public notice function. In such circumstances, Judge Gajarsa concluded, its subject matter must be deemed unpatentable.

Judge Gajarsa’s two final points are also noteworthy. First, he stated emphatically that claimed subject matter that falls into both the “nonnaturally-occurring” and “found in nature” categories is not patentable under §

89. Id. at 1347–50.
90. Id. at 1350.
91. Id. at 1352.
92. Id. at 1360 (citations omitted).
93. Id. (citations omitted).
94. Id. at 1361.
95. Id.
And second, he observed that "[m]erely limiting the claim to 'synthetic PHC hemihydrate' would have solved the problem. But SmithKline Beecham did not."  

It is unclear what, if anything, Judge Gajarsa's concurrence portends for the law of gene patents. It is, of course, merely a concurrence, without the force of law. Indeed, his two panel colleagues (Judges Rader and Bryson) reacted dismissively. In two short (and, to this reader, unpersuasive) paragraphs, they accused him of confusing subject matter eligibility with the separate question of the scope of the claims: "The scope of the claims is not relevant to subject matter eligibility. Subject matter does not take on a different eligibility status with adjustments in the scope of the proposed claim." The apparent import of this statement is that, in the majority's view, a human-made compound cannot be rendered unpatentable merely because the claim could also read on a naturally-occurring variant.

In my judgment, Judge Gajarsa has the better argument. How can it be irrelevant to subject matter status that a patent unambiguously claims naturally-occurring subject matter? Would Chakrabarty have won if he had claimed—again, without limitation—an organism that was produced in nature, as well as in his laboratory?

Even if Judge Gajarsa is right, however, his objection may not extend to gene patents. He was concerned that SmithKline's claim covered both the human-made and naturally-occurring versions of PHC hemihydrate, and that these were the very same compounds. As he emphasized, SmithKline could have resolved his objection simply by limiting its claim to "synthetic PHC hemihydrate," but did not do so. Going back at least to Amgen, gene patent claimants have been careful to limit their claims to nonnaturally-occurring genes, using the modifiers "synthesized," "isolated," and/or "purified." Transposing Judge Gajarsa's objection into the gene context, limiting a claim to "synthesized" or "purified" would surely be sufficient to satisfy him, and "isolated" almost certainly would do the job as well. The literal structural identity that so troubled him in SmithKline simply is not present.

Nonetheless, it does seem newsworthy that, in the mind of at least one Federal Circuit judge, the product of nature doctrine is alive and well as a barrier to patentability that is still to be taken seriously. Perhaps the court can someday be persuaded to take a close look at whether the meager struc-

96. Id. at 1362.
97. Id.
98. Id. at 1342.
natural dissimilarity between claimed genes and their natural counterparts is a sufficient distinction in the light of their complete functional identity. 99

B. Utility

In another important 2005 case, In re Fisher, the Federal Circuit invoked the seldom mentioned utility requirement to strike down patents on expressed sequence tags (ESTs). 100 As the court described it, “[a]n EST is a short nucleotide sequence that represents a fragment of a cDNA clone.” 101 cDNA is derived from the reverse transcription of mRNA, which is itself based on the transcription of a gene that is being expressed (that is, in the process of coding for a protein). When an EST is introduced into a mixture of DNA, it may hybridize (its single strand binding to its complement) with a portion of the DNA. If that happens, it is then possible to conclude that the DNA is part of a gene. Fisher claimed ESTs derived from cDNA that had been obtained from maize leaf tissue. He therefore asserted that the ESTs he claimed corresponded to genes that were expressed in that tissue. However, he did not know either the precise structure or function of the genes being expressed or the proteins that they encoded. 102 Rather, he disclosed a variety of uses in genetic research. 103

Citing Brenner v. Manson, 104 the Supreme Court’s chemical intermediate case, the Federal Circuit held that a claimed invention must have a “substantial” and “specific” utility, with the former requiring a “significant and presently available benefit to the public” and the latter “a well-defined and particular benefit to the public.” 105 Noting that “the facts here are similar to those in Brenner,” 106 the court held that Fisher’s asserted utilities fell well short of the Brenner standard. None of Fisher’s asserted uses was either substantial or specific, because all “represent merely hypothetical

99. Additional evidence of the Federal Circuit’s growing interest in the question of patentable subject matter can be found in three recent cases involving inventions that comprise mental processes. See In re Bilski, 545 F. 3d 943 (Fed. Cir. 2008) (en banc) (holding that method for managing the consumption risk costs of a commodity sold at a fixed price does not comprise patentable subject matter, because it is a non-transformative process that encompasses merely mental steps); In re Comiskey, 499 F.3d 1365, 1368 (Fed. Cir. 2007) (holding that mental processes for resolving a legal dispute by the decision of a human arbitrator are not patentable subject matter); In re Nuijten, 500 F.3d 1346, 1348 (Fed. Cir. 2007) (holding that encoded signals are not patentable subject matter).

100. 421 F.3d 1365, 1367 (Fed. Cir. 2005).

101. Id. at 1367. See also Conley & Makowski, supra note 7, at 315–16 (describing the biology of ESTs).

102. Fisher, 421 F.3d at 1368.

103. Id.


105. Fisher, 421 F.3d at 1371.

106. Id. at 1374.
GENE PATENTS AND THE PRODUCT OF NATURE DOCTRINE

possibilities, objectives which the claimed ESTs, or any EST for that matter, could possibly achieve, but none for which they have been used in the real world.” 107 Moreover, “any EST transcribed from any gene in the maize genome has the potential to perform any one of the alleged uses.” 108 As in Brenner, the claimed substances were useful only “as an object of use-testing;” 109 in this case, in the identification of genes that encode unknown proteins of unknown function. As in Brenner, this was simply not enough to meet the standard of “specific benefit... in currently available form...” 110

The holding in Fisher will not, of course, impose any limits on the patenting of genes whose protein-encoding structure is currently known. Nonetheless, gene-patent skeptics were heartened by the fact that the Federal Circuit had taken a stand against the seemingly unfettered expansion of the biotechnology patent portfolio. Moreover, the result was not foreordained, as evidenced by Judge Rader’s strong dissent. 111 At a minimum, one can say that the court is paying attention—at least at the margins.

C. Obviousness

A final hint about the future involves the doctrine of obviousness. In its April 2007 decision in KSR International Co. v. Teleflex Inc., 112 a case that involved an automobile gas pedal assembly, the Supreme Court made it somewhat easier to defeat a patent on obviousness grounds. The specific question was whether the combined teachings of multiple prior art references rendered the applicant’s invention obvious. The Federal Circuit held that, for an invention to be found obvious, the prior art must contain some “teaching, suggestion, or motivation” to combine the references in the way that the applicant did (the “TSM test”). 113 Finding the “rigid approach of the Court of Appeals” inconsistent with its own “expansive and flexible approach,” 114 the Supreme Court reversed. Instead, “a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.” 115 Thus freed from the necessity of finding specific evidence in the prior art to satisfy the TSM test, the USPTO and the courts

107. Id. at 1373.
108. Id. at 1374.
110. Id. at 1371 (quoting Brenner, 383 U.S. at 535).
111. Id. at 1379 (Rader, J., dissenting).
113. Id. at 1734.
114. Id. at 1739.
115. Id. at 1741.
presumably will have more freedom to reject patents that are borderline obvious.

The early evidence from biotechnology suggests that this is exactly what is happening. In one of its first post-KSR cases, *PharmaStem Therapeutics Inc. v. ViaCel Inc.*, the Federal Circuit held that two patents on the collection, preservation, and use of stem cells from umbilical cord blood were invalid for obviousness. The court found that "it was reasonable for the inventors of the patent, like the authors of the prior art references, to infer the presence of high concentrations of stem cells in cord blood, even though the prior art studies did not offer conclusive proof." Citing KSR, the court characterized the inventors' contribution as "[s]cientific confirmation of what was already believed to be true"—"a valuable contribution, but it does not give rise to a patentable invention."

A 2007 decision of the USPTO's Board of Patent Appeals and Interferences suggests the potential impact of KSR on gene patents specifically. In *Ex parte Kubin*, the Board upheld an examiner's section 103 rejection of claims covering a cDNA molecule that encodes "natural killer" proteins that are part of the body's defenses against infection. Given related prior art patents and publications, the Board held, the skilled practitioner would have found it "obvious to try" to isolate the cDNA in question; accordingly, the invention was "the product not of innovation but of ordinary skill and common sense." Under KSR, it held, this was enough to show obviousness. Significantly, the Board did not believe that *In re Deuel* (which had held that the obviousness of a general method of isolating cDNA was irrelevant to the obviousness of a particular claimed cDNA molecule) was controlling "given the increased level of skill in the art and factual differ-

116. 491 F.3d 1342 (Fed. Cir. 2007).
117. Id. at 1363.
118. Id. at 1363–64.
121. 51 F.3d 1552 (Fed. Cir. 1995). See supra text accompanying note 35.
ences.” It seems reasonable to ask whether the evolving “level of skill in the art” will jeopardize a broad range of existing and future cDNA patents.

Finally, the aggressive use of the obviousness doctrine briefly threatened some of the most famous—or infamous, depending on one’s point of view—patents in the whole biotechnology realm. Since 1998, the University of Wisconsin has received a series of patents on embryonic stem cell lines. The purpose of a cell line is to extend the natural life of a living cell for research purposes—as biologists sometimes describe it, “to immortalize the cell.” Cells are first taken directly from an organism and then grown in an artificial medium, or culture. When these cell cultures can be induced to grow for substantially longer than normal, they are referred to as cell lines.

James A. Thomson of Wisconsin is widely credited with having been the first to culture human embryonic stem cells. The broadest of the Wisconsin patents claims a “purified preparation of primate embryonic stem cells” which have several characteristics, including a life expectancy of more than one year, the same genetic composition as the parent species, and pluripotency, or the potential to “differentiat[e] [in]to derivatives [of] endoderm, mesoderm, [or] ectoderm [tissues]”—that is, the ability to turn into any kind of cell. Stated in these terms, this claim would appear to encompass any primate stem cell line.

According to news reports in the spring of 2007, the USPTO was reexamining three WARF patents at the behest of two public domain advocacy foundations and had made a preliminary determination of invalidity. The initial determination of invalidity was reportedly based on the

122. Ex parte Kubin, No. 2007-0819, 2007 WL 2070495, at *7; Board Finds that cDNA Sequence Was “Obvious to Try” Under KSR, 74 PAT., TRADEMARK & COPYRIGHT J. (BNA) 350, 351 (Jul. 20, 2007).


124. See Conley & Makowski, supra note 7, at 316–18 (describing the biology of cell lines).


126. See Pollack, supra note 123. Under 35 U.S.C. § 301 (2006), “[a]ny person at any time may cite to the Office in writing prior art consisting of patents or printed publications which that person believes to have a bearing” on any patent. Section 302 then provides that “[a]ny person at any time may file a request for reexamination by the Office of any claim . . . .” on the basis of prior art cited under § 301. The final decision is appealable by the patent holder but not the challenger. Separately, pursuant to 35 U.S.C. § 311(a), “[a]ny third-party requester at any time may file a request for inter partes reexamination by the Office of a patent on the basis of any prior art cited . . . .” Both patentee and challenger have rights of appeal. Id. § 315. The procedure is rarely used, however. On the one hand, the requester has limited procedural rights, but on the other, the reexamination will have a strong preclusive effect against the requestor in any subsequent infringement action. Reexamination of two of the WARF patents—including the ‘806 Patent cited in the text—was sought under § 302, while a third was reex-
fact that Thompson’s cells “appeared to be the same as, or obvious variations of, cells described in earlier scientific papers or in patents issued to others.”\textsuperscript{127} KSR would presumably lend more weight to this position. However, in final decisions issued this past spring, the USPTO upheld all three patents.\textsuperscript{128} An appeal by the challengers is possible in the case of one of the three patents, but the other two decisions are final\textsuperscript{129}. Despite the outcome, it is worth noting that those who interpret and apply the patent law—from the Supreme Court down to the examiner level—are responding, albeit in a preliminary and tentative way, to the widespread and growing concern about the heretofore inexorable expansion of the biotechnology patent realm.

CONCLUSION: WHY GENE PATENTS MATTER

The tangible impact of gene patents on scientific progress and economic development continues to be hotly debated. Critics warn of the threat posed by the creation of a “patent thicket” or “patent anticommons”\textsuperscript{130} that would make it intolerably inefficient to obtain all the licenses necessary to do research. A particular concern has been “the increasing tendency for biomedical researchers to patent upstream inventions, i.e., research tools and inputs used to conduct basic research and development, as opposed to the products of research and development.”\textsuperscript{131} A related issue is that which was central to both \textit{Brenner}\textsuperscript{132} and \textit{Fisher}:\textsuperscript{133} the risk that broad, upstream, and early patents create rights of presently unknown scope and significance.\textsuperscript{134} In other words, when we grant a patent on a gene, we usually do so with only very incomplete knowledge of what that gene does in the body.

\textsuperscript{127} Pollack, supra note 123.
\textsuperscript{128} See Vanden Plas, supra note 126.
\textsuperscript{129} As reported in supra note 126, the two reexaminations conducted under § 302 cannot be appealed by the challenger, whereas the one conducted under § 311(a) can be. News reports quote one of the challengers as planning to appeal. See Vanden Plas, supra note 126.
\textsuperscript{131} Holman, supra note 3, at 329–30.
\textsuperscript{132} Brenner v. Manson, 383 U.S. 519 (1966); see supra text accompanying notes 26, 104–111.
\textsuperscript{133} \textit{In re Fisher}, 421 F.3d 1365 (Fed. Cir. 2005); see supra text accompanying notes 100–111.
\textsuperscript{134} See Kane, \textit{Splitting the Gene}, supra note 6, at 719 ("One concern is the specter of a patent issuing where the metes and bounds are unclear due to the underdeveloped state of the invention—in other words, an uncertain scope, and possible lack of enablement or written description, or both.").
Not everyone agrees with this assessment. As Christopher Holman has argued, if a patent thicket problem were impeding research, "one might expect that organizations representing the interests of biotechnology... would be advocating for reforms." But he finds instead that "these groups tend to be among the most adamant defenders of the status quo and strong patent rights."

The empirical evidence for the effect of biotechnology patents on research is mixed. Chin, for example, has built an elegant mathematical case that oligonucleotide patents impede downstream research. Similarly, a survey of laboratory physicians found that almost half "reported not developing a test because of the fees associated with it." Yet a 2005 National Academy of Sciences survey of more than 1,500 academic and industry researchers found that none of the respondents had ever stopped a project because of conflicting patent rights, and only a handful had experienced any material delays. By the same token, there are numerous individual reports of clinical physicians avoiding tests or treatments because of patents and associated licensing fees, but it is unclear just how widespread this problem is. Overall, as Linda Demaine and Aaron Fellmeth have concluded, "[t]here has been no conclusive empirical study to support one or the other viewpoint."

Even in the absence of compelling empirical evidence, I remain concerned. Such concern is new for me: for most of my thirty years as an intellectual property lawyer, I have not worried much about shifting tides in legal doctrine. In the early 1980s, I represented the successful plaintiff in one of the first-generation software copyright cases that resulted in expansive protection for the "look and feel" of a program. Many observers expected software progress to grind to a halt. Then, in 1992, Computer...
Associates International, Inc. v. Altai, Inc. dramatically reduced the scope of copyright protection. Many observers expected software progress to grind to a halt. But neither doctrinal trend had any discernible impact on the industry; aided by a nimble licensing community and a flagrant, often flamboyant disregard for the law, it has continued to churn out more, better, and cheaper software. Similar unfulfilled apocalyptic prophesies attended the proliferation of software and business method patents. The technology sector has long seemed the embodiment of the Coase Theorem: "while the delimitation of rights is an essential prelude to market transactions . . . the ultimate result (which maximizes the value of production) is independent of the legal decision." In other words, given a market without transaction costs, the participants will arrive at the most efficient outcomes regardless of the content of legal rules.

But I fear that genes may be different. Based more on instinct than evidence, I share Brenner’s concern about granting patents of unknown and unknowable scope. Every year, we seem to hear more about the multiplicity of tasks that our relatively few genes perform. With each year’s hindsight, last year’s understanding of how genes work looks incomplete and primitive. This, in my judgment, should make us increasingly cautious about granting exclusivity in any gene. I hope that the recent legal developments I have reviewed portend at least a slowing of the rush to monopolize the genome.

146. 982 F.2d 693 (2d Cir. 1992).
148. In April 2003, for example, concern about the impact of such patents led the Federal Reserve Bank of Atlanta to convene a conference on “Business Method Patents and Financial Services,” in which I participated. The conference proceedings are summarized in Clifford S. Stanford, Business Method Patents and Financial Services, FED. RES. BANK ATLANTA ECON. REV, Fourth Quarter 2003, at v.