ARTICLE

Patents, Genomics, Research, and Diagnostics

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ABSTRACT

Two kinds of currently available genomic patents may significantly interfere with medical research: (1) patents such as those on specific single nucleotide polymorphisms (SNPs), which may include claims that control the inference of phenotypic characteristics from specific genotypes, and (2) patents on computer-based genomic information, databases, or manipulation procedures. These will create more serious encumbrances than will patents on expressed sequence tags (ESTs). Two approaches should be considered vis-à-vis these genomic patents: (1) Reconsideration and redefinition of the recent extensions of patentable subject matter into more and more intangible areas. This could be pursued by legislation or by test litigation to seek Supreme Court reversal of certain of the decisions of the Court of Appeals for the Federal Circuit (CAFC). (2) A narrow legislative exemption protecting the ability to use SNPs and phenotypic–genotypic relationships in medical research, including contexts in which medical research and clinical practice are substantially intertwined.

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This paper is intended to inform deliberations on the patenting of genomic sequences and genomic information. The paper takes a pragmatic perspective, i.e., its arguments are based on research, economic, and legal–administrative concerns, rather than on considerations as to whether or not genomic patents are ethical.

THE ISSUES

Genomic patenting poses two quite different groups of questions in the medical and medical research area. The first group, which has so far received more attention, involves the ways that genomic patenting may affect the development of therapeutics based on natural proteins. Most of those individuals closely associated with medical and pharmaceutical research believe it essential to permit effective patent coverage of specific protein products and processes for producing specific proteins (and perhaps, therefore, of the corresponding gene sequences) in order to encourage private-sector investment in the research and clinical trials needed to bring such products to the market. There is much less unanimity on the patent protection of other genomic sequences, for example, of expressed sequence tags (ESTs), single nucleotide polymorphisms (SNPs), or receptors that are more important as targets than as therapeutics.[1] These sequences may be useful in therapeutic discovery. In general, their patentability is defended by genomics firms that are developing them and seeking to market information derived from them to pharmaceutical firms, but their patentability is opposed by the pharmaceutical firms themselves. A new generation of questions is coming in this area, involving computer programs for the analysis of genomic information, the "annotation" of the genome, the conditions of expression of the different genes, and the structures and roles of the various proteins encoded by the genes.

The second group of issues involves the use of genomic information in medical research and in diagnosis. This is complicated because research and diagnosis may be totally interdependent in academic medical settings, and almost indistinguishable; one contributes to knowledge as a whole and the other to knowledge about an individual patient. In this area, the key ultimate applications, analogous to therapeutic proteins, are diagnostic tests designed to detect particular SNPs (and other variable sequences) that may affect susceptibility to particular diseases or to particular therapeutics. The genome that is examined may be that of a human or,

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in some cases, that of a pathogen that may have several strains. And the technology to detect the characteristics of the particular genome may require only a simple laboratory process. In this context, patents on SNPs are likely to interfere with medical research. A medical researcher will want, for example, to be able to measure the expression of different genes under different circumstances and to be able to correlate these expressions with the specific characteristics of the patient that are revealed by a specific SNP. This may be impossible if patents cover the particular SNP, and the patent holder is unwilling to grant a license. Moreover, since the regulatory structure for diagnostic testing imposes less severe approval requirements on testing conducted in-house than on distributed products, a patent holder is more likely to require that samples be sent to the holder's own lab than to provide a more convenient kit.[2]

Very likely, future clinical practice, like some current research, will use a matrix chip containing the ability to look for many specific sequences and alternatives. Here, the possibility that licenses may have to be sought from a variety of different holders of sequence patents may pose prohibitive complications in developing, marketing, or using a multipurpose chip. Moreover, whether for individual tests or for matrix chips, the economics here creates a less overwhelming argument for product patent protection than in the case of therapeutics, for clinical trial development costs are significantly smaller than those for therapeutics.

CURRENT STATUS OF THE LAW

Patents were granted quite early for naturally occurring proteins and the genes that coded for them. At the time, the sequencing of genes was difficult, and often took place together with the identification and purification of the protein product. Although the types of claims (the formal descriptions of the precise areas of exclusivity) varied from patent to patent, among those that might be included were claims for the genetic sequences in isolated form, for complementary sequences and probes, for various vectors for inserting the sequences into cloning organisms, for the cloning organisms used for mass production of the protein, for the various production processes, for the proteins themselves, and for the medical use of the protein. The patent law's requirement of "novelty"—that the patented invention be new and not anticipated in previous literature or in nature—was met by the theory that the product had never before existed in isolated (concentrated) form, and that the gene sequence had never before been isolated. Although protection of the protein (which is essential to the pharmaceutical industry) does not necessarily require protection of the sequence, the sequence claims have been regularly granted.

The public and private human genome programs completely changed the research pattern that underlay this early body of law. Genome sequences now became available on a large scale, often without full understanding of the functions of the sequences. This led to new legal issues. One group involves sequences that are believed to code for a protein whose function may be unknown or only estimated from homology to known sequences. In the revised *Utility Examination Guidelines*, 66 *Fed. Reg.* 1092 (Jan. 5, 2001) and the *Revised Interim Utility Guidelines Training Materials*, the Patent and Trademark Office (PTO) has indicated that it will require a "specific and substantial utility that is credible." Its examples (*Training Materials*, examples 4 and 5) imply that a sequence for a protein whose function is unknown is unpatentable, as is one identified only as able to bind with another specific protein where the further protein has no known utility. In spite of strong opposition from the National Institutes of Health (NIH) and many in the scientific community, however, the PTO decided that patents may continue to be available for sequences whose function is biologically significant although known only from homology.[3] The guidelines, however, cannot be taken as a final statement of the law, for they are not binding on the Court of Appeals for the Federal Circuit (CAFC), which has sometimes declared patentable types of inventions, e.g. business methods, that the PTO had declared unpatentable. Assuming that the guidelines hold up, genomic patents will then be available only for genes whose function is known.

There has been significant public debate over the CCR5 gene patent, in which a key biological function was discovered by researchers not associated with those who filed the patent, and yet the patent is regarded as validly covering the new application.[4] This is a result of applying traditional chemical patent law principles to biotechnology. Under chemical patent principles, a patent on a novel chemical covers all uses of that chemical, whether or not discovered by the original patent holder. The discoverer of a new use may have a right to file a further patent, claiming use of the chemical for the particular new purpose, but will still have to obtain a license from the initial patent holder before using the chemical for the new purpose. It is not clear that it is wise to apply such chemistry-based legal principles to the genomic context, but there was no active debate on the issue until recently. The law here may, however, come under pressure as a result of genomic evidence that a single "gene" may code for a number of different proteins, presumably through different splicing mechanisms. This is a possible implication of the recent publication that there are far fewer genes than expected.[5] If this is the case, the different proteins coded for by a gene are not chemically identical, and the chemical analogy would imply that discovery of a gene and one of the proteins it codes for should *not* give rights over the other proteins coded for by the sequence.

For ESTs, the key issues are whether the discoverer of an EST should have a right (1) to a patent covering the use of that EST as a probe to help in identifying the entire gene or (2) to a patent that would be infringed by the entire sequence or protein, regardless of whether or not the EST is used to identify the protein. In technical patent law, the question of whether the latter scope should be available is that of whether a "comprising" claim should be granted—the meaning of a "comprising" claim is that a claim to a sequence "comprising" the identified EST sequence is infringed by the entire gene (or other longer sequences) that includes the patented sequence. If such comprising claim were granted and valid, a pharmaceutical firm seeking to use a protein would infringe any patents held by firms that had identified ESTs included in the overall protein sequence (whether or not these had been used by the pharmaceutical firm in identifying the protein). The new utility guidelines strongly indicate that no further EST patents will be granted, with either narrow or broad claims[6] (*Training Materials*, Example 9).

SNPs and similar diagnostic sequences present a much different issue. Here, there is greater utility than for ESTs, assuming that the implications of the specific SNP have been identified.[7] There has been a number of patents covering, for example, the BRCA1 and BRCA2 mutations predisposing to breast cancer.[8] These were based on early research and extensive use of genetic linkages and the like. And there has been one patent for SNPs, in which the value of the polymorphisms was unspecified other than that they could be used for forensic identification purposes.[9] Although this patent does not seem to have the specific utility needed under the new guidelines, SNPs that have a clear diagnostic role seem likely to be patentable. There is a growing number of examples.[10] Under current principles, it is essentially certain that there will be patents on all kinds of genotypic–phenotypic linkages, completely covering the use of particular genomic information to infer characteristics of the organism. They will, effectively, be patents on the use of the information and inference logic, not just on particular methods of identifying the specific genotype. Indeed, there may not need to be a disclosure of a specific method or diagnostic kit. Moreover, just as genome sequencing has facilitated the filing of a large number of gene patents, so also large-scale population studies looking for correlations between genomic and phenotypic information will facilitate similar large-scale filings in the diagnostic area. Although none of these patents has yet been discussed by the CAFC, previous cases strongly suggest that they will be upheld by that court.[11]

The post-genome era of biological research raises further patent issues. Patents in which the invention consists of new software, or statistical or other analytic approaches, have been granted and are likely to continue to be granted. Such patents will certainly cover particular approaches to the development of annotations, to the analysis of genomic data or gene expression data, or to protein structure calculation. Whether there will be other efforts to protect annotations themselves (other than through contractual restrictions on access to databases) is not yet clear, but at least one of the software-oriented patents has very broad claims on use of databases that include protein functions and may therefore indirectly restrict annotation.[12] There is also an important new line of applications, seeking claims that would control the use of genomic information in machine-readable form.[13] One even seeks to restrict use of the information for comparison purposes in order to search for homologies.[14] Such patent claims seem absolutely inimical to the very concept of the patent system and are unlikely to be issued outside the United States, but they will be very hard to avoid under contemporary U.S. patent principles, as will be noted below.

PATENT LAW DOCTRINES

Several legal doctrines underlie the patents just discussed. Some could be changed or be interpreted in ways more favorable to the conduct of research.

A. Novelty and Non-obviousness

A first relevant set of principles is that set governing the way the prior art affects patentability. An invention must be "novel," meaning it has not been disclosed in the prior art, and it must be "non-obvious," meaning not obvious "to a person having ordinary skill in the art" (35 U.S.C. § 103). There is certainly a reasonable argument whether a gene sequence is any longer "non-obvious," considering that it can be determined in a known way with known (albeit elaborate) equipment and computer programs. Put a different way, does identification through a sequencing machine constitute invention or discovery within the meaning of the patent act?

The patent act does state that patentability "shall not be negatived by the manner in which the invention was made" (35 U.S.C. § 103), but this language need not be read to require acceptance of a sequence derived in a predictable way. Conceivably, then, the argument could be made that all the sequences deriving from the large-scale gene sequencing programs are obvious, while the early sequences deriving from relatively laborious laboratory work remain non-obvious. If such an argument were taken too far, it might undercut patentability for therapeutic proteins yet to be discovered in the human genome. That will depend, of course, on the extent to which there is a non-obvious link between the gene sequence and the function of the protein, a link

that, as noted above, may be less well understood than was previously thought.

There is a more plausible alternative—that the sequence, and perhaps sequences generally, should not be regarded as patentable, but that the proteins they code for might remain novel (at least in purified form), and pharmaceutical production organisms with the gene inserted artificially would also be novel. This would protect the pharmaceutical industry while leaving it possible to use sequences in research. It would not, of course, protect the diagnostic industry. There are several possible theories that might support such an approach, although none of these theories is accepted under current law. Thus, it could be argued that the sequences, because they are found in nature, are not novel or that, because they are not subject to direct application, they are not useful in the same sense as a composition of matter. Or one might go to the subject matter limitations discussed below by reviving the position that products of nature are not patentable, or by defining a position that information itself is not patentable (and viewing the gene sequence more as information than as a molecule).

B. Enablement and Written Description

The enablement doctrine has long required that a patent applicant demonstrate how to perform the invention. This has recently been supplemented by a "written description" requirement, also based in the statute, and recently clarified by *The Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (CAFC 1997), as well as by new guidelines.[15] Although the proposed written description guidelines argue otherwise, there is a good chance that these doctrines may defeat broad-claim patents on ESTs, i.e., those that would cover the entire protein in which the EST was found, for the entire protein is neither adequately described nor enabled. However, as noted above, such EST patents are unlikely to be issued anyway. And these enablement and description doctrines pose no barrier to the patenting of SNPs.

C. Utility

Utility also derives from the statute, 35 U.S.C. § 101. It was most fully clarified in a Supreme Court case that, in essence, dealt with the rights to be accorded to relatively abstract inventions, *Brenner v. Manson*, 383 U.S. 519 (1966). Thus, this doctrine deals with the balance that has to be maintained to encourage both initial and subsequent innovation. The proposed guidelines speak of a "specific and substantial utility that is credible," and, under current law, identification of one adequate utility is enough to control use of the invention for all purposes. As noted above in the discussion of the proposed guidelines, an EST may not have adequate utility if its only described function is as a probe to search for a relevant gene. On the other hand, a SNP almost certainly has adequate utility if related to a particular disease, but probably not if related only to forensic identification applications.

D. Experimental Use (the Research Exemption)

The principles just reviewed are those applied by the PTO in deciding whether to grant patents. There are other principles applied by courts in determining that a patent has been infringed. One doctrine that courts have discussed here is that inventions can be used for academic-type research without infringing the patent.[16] Because there is not often an infringement suit unless the infringement has significant commercial consequences, the doctrine is more often discussed as a possible defense than applied to actually provide a defense; hence it tends to appear only as a legal dictum.[17] In addition to this judicial doctrine, there is a very specific statutory exemption, enacted in 1984 as part of the Hatch–Waxman Act's rebalancing of the research-based and the generic pharmaceutical industries, to allow certain testing of patented products shortly before those products go off-patent, 35 U.S.C. § 271(e)(1).[18]

The CAFC has just given the judicially-created component of the research exemption a very narrow reading, and one of the judges has argued in concurrence that there is no such exemption—*Embrex, Inc. v. Service Engineering Corp.*, 216 F.3d 1343 (CAFC, 2000).[19] This is extremely significant, for it may produce pressure for legislation to modify the patent law, and that legislation might be a vehicle for reforms that benefit clinical medical research.

Any new exemption, however, would certainly be designed to allow experimentation to understand or improve on the patented product or process, but not experimentation to use it. This responds to the perceived need to allow patents for developing new research tools and instrumentation. Thus, a patented approach to making an analytic balance might be used in an attempt to design an improved balance, but not to weigh things, even in research. This is the pattern emerging in Europe, where, in some cases, the research exemption applies to industrial research as well as academic research; the issue is not whether there is ultimately an academic or commercial motivation, but whether the invention is used only for understanding or improvement of the invention. Under the global norms emerging in this area, a broad research exemption would help in many aspects of medical research, but would probably not cover use of patented genomic information for diagnostic purposes in clinical medical research, nor would it assist one seeking to assemble rights in different SNPs. A stronger, special-purpose

exemption would almost certainly be necessary for such purposes.

E. Patentable Subject Matter

The subject matter limitations on patentability have evolved radically in recent years and pose extremely important issues in the genomic context. The statute authorizes patents on "any new and useful process, machine, manufacture, or composition of matter," 35 U.S.C. § 101. This was long held to prohibit patents on naturally occurring products, on the grounds that they were not new, and, it was also interpreted as prohibiting patents on laws of nature, scientific principles, or methods of doing business. In the face of a number of ambiguous Supreme Court cases,[20] and a perceived need to adapt the patent system to a software-based world, the CAFC has radically changed this law.

The case that has received the most attention is *State Street Bank & Trust Co. v. Signature Financial Group*, 149 F.3d 1368 (CAFC 1998), which overthrew the traditional principle that business methods are not patentable. That case has now been supplemented by *AT&T v. Excel Communications, Inc.*, 172 F.3d. 1352 (CAFC 1999), which, in essence, removed the tangibility requirements from patents for computer programs, and therefore effectively permits patents on algorithms themselves.[21] The latter is probably the more important case in its implications for genomics. When these cases are read together, the implication is that all of the following are almost certainly patentable (assuming novelty and non-obviousness, etc., in the specific case):

- The use or measurement of a specific genetic characteristic to infer a specific phenotypic characteristic
- The use of a specific genetic characteristic in deciding whether to administer a specific pharmaceutical product
- The use of a particular receptor as a pharmaceutical target
- A technique of statistical analysis for use in evaluating clinical data
- The use of a specific equation in predicting levels of a particular enzyme in the body
- A computerized—or non-computerized—process of comparing two gene sequences to look for homologies (assuming one of the sequences is novel, or the computer algorithm is novel)

This extension of the patent system is likely to create enormous problems, and it will quickly become dramatic in medical research. We are in a situation in which any new Krebs cycles will be patented! This raises very serious issues because, for the first time, the patent system is effectively controlling the use of natural information, and taking out of the public domain information that is there for anyone to measure. We are now issuing patents with claims analogous to claims on the use of blood pressure to evaluate health as distinguished from the more traditional claims on the use of a specific device to measure blood pressure. This has serious implications for both medical care and medical research.

Many believe that the system has gone too far, especially in the context of business methods, and significant opposition has arisen, within the business community as well as the academic community. Consider, for example, the public proposals of Jeff Bezos, the CEO of Amazon.com, for a shorter term for some patents,[22] and the PTO's effort to explore business method patents more fully.[23] Unless there is a Supreme Court case reversing the CAFC's move toward these patents, it is possible that Congress will respond to certain of these criticisms. There certainly was some interest before September 11, 2001, as exemplified by the fact that the House Committee on the Judiciary Subcommittee on Courts and Intellectual Property held hearings on business method patents in April 2001 and on gene patents and other genomic inventions in July 2000.[24] Moreover, Congresswoman Lynn Rivers introduced legislation in March 2002 calling for restrictions on the enforcement of genomic diagnostic patents.[25] But it must also be recognized that the businesses gaining such patents are, along with the patent bar, strong supporters of the existing trend, and that intellectual property will receive less attention than terrorism.

A key problem in reform is defining and agreeing upon a reasonable standard to replace the CAFC's broad standard. The approach used for computer software before *State Street* and *Excel* was basically one of tangibility, i.e., one could patent software that actually operates on a computer or led to a change in the real world, but one could not patent the underlying algorithm.[26] Thus, anyone could still legally use the algorithm in paper-and-pencil form. There may well be a strong effort to restore this principle, but such a reform probably does not go far enough. It would, for example, eliminate some of the business concept patents, but, unless accompanied by an increase in the standard for non-obviousness, would leave available patents governing software that would do the same thing as the business concept (and, for many business applications, implementation is feasible only in software form). Moreover, again without a raising of the non-obviousness standard, it would not prohibit patents on routine manipulations of machine-readable genomic information. And it is not at all clear that it would reach the needed reforms in the genomic diagnostic area.

Thus, at least for medical research, it is essential to go further. What seems plausible is to prohibit patenting of information about the world or of abstract methods of using such information. Thus, it would be impossible to patent a genome per se or fundamental understandings about biochemical pathways; but it would still be possible to patent a

pharmaceutical and its use for a particular indication. In the medical research context, it would, under this principle, be impossible to patent, for example, the information that a particular bit of information about the human body serves to reveal something important, while leaving it possible to patent a specific device to detect that bit of information. Thus, a particular kind of chip to detect an SNP or a particular sequencing machine would be patentable, but the information underlying the usefulness of an SNP would not be patentable.[27]

F. Special Exemptions

Finally, special exemptions are possible. This has already happened for surgery, with the Frist-Ganske medical procedures exemption statute, 35 U.S.C. § 287(c). This statute, passed in 1996, exempts medical practitioners and their related entities from infringement actions based on medical or surgical procedures.[28] Whether this section can be interpreted to cover use of genetic information about a research subject depends on whether such use is a "medical or surgical procedure" on a "body," and whether such use is excluded from the exclusion because it is "the practice of a process in violation of a bio-technology patent." It is unlikely that an exemption can be obtained for all diagnostics, similar to that for surgical procedures, but there might be a more narrow exemption, for example, providing for use of information in tests being carried out in which there are substantial research purposes (as distinguished from tests performed exclusively for clinical purposes), or for compulsory licensing of information relevant to diagnostic testing. (See also note 25.)

REALISTIC ALTERNATIVES

Based on this review of the law, there is little likelihood that EST patents will be a substantial barrier to the advance of medical technology; unless the CAFC makes a surprising decision, ESTs will not be patentable. The real issues and problems for medical research arise with uses of SNPs and more broadly in the diagnostic and information areas.

The analysis suggests two plausible directions of response:

A. Narrow Diagnostic Exemption

The first direction is to seek a narrow diagnostic exemption, presumably by statute. One approach would be that just suggested and would be the narrowest exemption plausible to free medical research while responding to the needs of the diagnostic industry. This would be to allow patented genomic information to be used freely *when the research purpose is substantial compared with the diagnostic purpose*. This would, for example, allow laboratory sequencing to be done freely in medical research, even though a patented SNP might be used. This would protect the diagnostic industry by restricting the application to contexts with a substantial research purpose. Conceivably the statute might be written so that kits would have to be used if they were supplied by the patent holder on reasonable terms. This would help medical research, but it would not solve the commercial chip producer's problem of assembling substantial rights in a marketed product. Passage might be furthered by the perceived needs for Congressional action in response to the *Embrex* decision on research tools or *Florida Prepaid Postsecondary Ed. Expense Bd. v. College Savings Bank*, 527 U.S. 627 (1999), the Supreme Court case giving states (including state university medical schools) sovereign immunity against certain aspects of the federal patent laws.

A somewhat broader, but still narrow, legislative exemption would be an exclusion from patentability or infringement or a compulsory licensing process for information *for use for all diagnostic purposes*. This would not only help academic medical centers; it would also help those in industry seeking to assemble diagnostic chips for various purposes. Moreover, patients' groups would be quite supportive. The chip manufacturing industry would certainly be divided—some would probably prefer to compete on the basis of chip quality and others on the basis of patent rights in the SNPs included in the chips. The pharmaceutical industry might benefit and might like easier access to pharmacogenomic data, but may resist any approach involving compulsory licensing. For medical research, the more narrow of these narrow approaches is probably more feasible.

B. Broader Reform

The broad reform is to re-narrow the scope of patentable subject matter and to restore principles restricting the patentability of abstract concepts, of information, or of principles of nature. This would provide greater freedom to use genotypic–phenotypic links, and would also decrease patent-based controls on use of genomic information in computer programs. This might be done through litigation, which would have to go to the Supreme Court in order to reverse or modify certain of the decisions that have been taken by the CAFC. Or it could be done by Congress in an effort to restate the traditional principles. There is an important difference between the two in that a Court decision is likely to be effective retroactively, while an act of Congress would almost certainly grandfather all existing patents.

The judicial approach may have a good chance of success. A number of important lines of argument are available: The concept of the patent system requires disclosure, 35 U.S.C. § 112. Patents should not take information out of the public domain if they are to achieve the Constitutional goal of

"promot[ing] the Progress of Science and useful Arts." Principles of nature (i.e., information about nature) have traditionally not been patentable. Patents on such information, as opposed to new methods or compositions of nature, are likely to fail the cost–benefit analysis comparing the incentive they create with the complications they pose for subsequent researchers. The recent business method and algorithm holdings of the CAFC are clearly inconsistent with this direction. The obvious question is whether the Supreme Court, which has not recently displayed its hand on this kind of patent law question,[29] would in fact restate traditional doctrine or would accept the direction in which the CAFC has been changing the law. Almost certainly, in this approach there would be significant support from the scientific community, from significant parts of the medical research community, and, depending on the context, from those members of the business community who believe that software patents are more a nuisance than an incentive. The opposition would come from those who benefit from business method patents, and from those whose business plans involve control over specific genomic sequences.

The legislative approach would have to build on this opposition to the extension of patents to business methods and perhaps to genomic patents as well. Save for the patent bar itself, this is probably a much broader group than the group supporting such patents. The approach requires Congress to agree on a specific positive response, rather than simply to react to current decisions that many dislike (but each of which favors some specific group), and the text will necessarily be a compromise among different interests. The following proposed statutory language (revising 35 U.S.C. § 101) focuses some of these issues:

> Revised § 101: Inventions Patentable: Whoever invents or discovers any new and useful *tangible* process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title. *Patents shall not be available for principles of nature, including principles related to human diagnosis or therapy, nor shall the discoverer of specific information be entitled to patents that restrict its use by others. This shall not be read as preventing the patenting of computer programs designed to implement specific algorithms, but the algorithms or scientific principles embodied in the programs shall not be patentable except as embodied. Nor shall this section be read as preventing the patenting of machines, manufactures, or compositions of matter, or any new and useful improvement thereof, based upon principles of nature or specific information.*[30]

The first three sentences are intended as straightforward statements of what the law was some years ago. The word "tangible" in the first sentence and the second sentence as a whole are intended to restrict patents of the information contained in gene sequences or of principles such as "the use of gene sequence X to identify statistically proclivity to disease Y." They are also intended to end the patentability of business methods. The third sentence is designed to restore the tangibility requirement for computer programs. And the last sentence is designed to ensure the patentability of pharmaceuticals, including those based on natural proteins, and of specific devices for the collection or analysis of diagnostic information, including that in gene sequences.[31] (Presumably some of these points would also be spelled out in the legislative history.)

Under this approach, a DNA sequence would not be patentable, nor would information about inferences that can be drawn from DNA information be patentable. The provision that the discoverer of such information is not entitled to restrict others from using the information implies that a discoverer of the importance of a specific DNA sequence would be unable to keep others from using that sequence or complementary sequences in diagnostic tests. On the other hand, the inventor of a chip using the sequence or of a new method of identifying sequences would be entitled to a patent on the chip or the new method.

Although this broader reform appears more ambitious on its face, it may actually be more feasible because of the shared concern of several communities about the impact of recent extensions of patent law.

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ENDNOTES

[1]Patents on receptor proteins may seek to control use of the receptors as assays for new pharmaceuticals (or even as targets). Although these are important applications in the pharmaceutical context and in research, they pose quite different issues from those discussed in this paper with respect to genomics patents and clinical medical research.

[2]A. Huang, FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship, 53 *Food & Drug L. J.* 555 (1998); N. Holtzman & M. Watson (eds). *Promoting Safe and Effective Genetic Testing in the United States; Final Report of the Task Force on Genetic Testing* (1998); Institute of Medicine, *Assessing Genetic Risks* (1994).

[3]In 1998, the PTO issued one patent on a group of *partial* sequences whose function was known from homology; Au-Young et al., (Incyte), 5,817,479, *Human kinase homologs*, Oct 6, 1998. There is debate over such patents and the PTO is not known to have issued more in this pattern.

[4]Human Genome Sciences Press Release, *Human Genome Sciences Receives Patent on AIDS Virus Entry Point*, Feb. 16, 2000.

[5]J. Venter et al., The Sequence of the Human Genome, *Science*. 291: 1304(16 Feb. 2001).

[6]The "written description" guidelines, issued at the same time as the utility guidelines, also imply that, even if an EST were patentable, the PTO would not issue "comprising" claims designed to control the whole gene on the basis of identifying the EST subsequence. In such a case, where it is the whole gene that has utility, identification of just the EST does not place the inventor "in possession of the claimed invention as a

whole," Revised *Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1 "Written Description" Requirement, 66 Fed. Reg.* 1099 (Jan. 5, 2001). A different principle will, of course, be applied when the subsequence itself has an identified utility, e.g., as a promoter or as an immunogenic epitope. In such cases, it is appropriate to permit a comprising claim based on the sequence to protect the inventor of a promotor, for example, from others who would use the promotor to encourage expression of genes not named in the patent.

The European Union *Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions*, takes a position on the patentability of ESTs very similar to that now found in U.S. law, Article 5 and Preambular Comments (22)–(24). It does not explicitly discuss SNPs.

[7]There are, of course, utility issues analogous to those posed with respect to gene sequences:what is the probabilistic level of confidence of a specific utility necessary to obtain a patent, and what if a particular SNP is useful for several different purposes?

[8]E.g., Skolnick et al., (Myriad), 5,710,001, *17q-linked breast and ovarian cancer susceptibility gene*, Jan 20, 1998. These patents typically include claims covering comparison of a person's gene sequence with the identified mutation. There is also a patent on the "consensus sequence," Murphy et al. (OncorMed), 5,654,155, *Consensus sequence of the human BRCA1 gene*, Aug. 5, 1997. Litigation between the two firms was settled in 1998. Another example of claim scope is Tsuchihashi, (Mercator Genetics), 5,712,098, *Hereditary hemochromatosis diagnostic markers and diagnostic methods*, Jan. 27, 1998. The key claim speaks broadly of assessing DNA or RNA from the individual for the presence or absence of the identified mutation.

[9]Chee & Fan, (Affymetrix), 5,856,104, *Polymorphisms in the glucose-6 phosphate dehydrogenase locus* (Jan 5, 1999).

[10]E.g., Lalouel etc., (U. of Utah), 5,998,145 *Method to determine predisposition to hypertension*, (Dec. 7, 1999) (specific mutation in the angiotensinogen gene, held by Myriad).

[11]E.g., *AT&T Corp. v. Excel Communs., Inc.*, 172 F.3d 1352 (CAFC 1999) (to be discussed below), and *Arrhythmia Research Technology v. Corazonix Corp.*, 958 F.2d 1053 (CAFC 1992).

[12]Seilhamer et al., (Incyte), 6,023,659, *Database system employing protein function hierarchies for viewing biomolecular sequence data*, Feb. 8, 2000.

[13]E.g. Rosen et al., (Human Genome Sciences), EPO App. 786,519, filed July 30, 1997, *Staphylococcus aureus polynucleotides and sequences*.

[14]White et al., (The Institute for Genomic Research), European Patent Office Application 756,006, January 29, 1997, *Nucleotide sequence of the mycoplasma-genitalium genome, fragments thereof, and uses thereof*. Among the claims sought are:

> 1. Computer-readable medium having recorded thereon a nucleic acid sequence selected from the group consisting of [specified sequences]
> 14. A method for identifying commercially important nucleic acid fragments of the Mycoplasma genome comprising the step of comparing a database comprising a nucleotide sequence as described in claim 1 with a target sequence to obtain a nucleic acid molecule comprised of a complementary nucleotide sequence to said target sequence, wherein said target sequence is not randomly selected

[15]*Supra* n. 6.

[16]See R. Eisenberg, Patents and the Progress of Science: Exclusive Rights and Experimental Use, 56 *U. Chi. L. Rev.* 1017 (1989).

[17]The law arose in a world in which academic-type research was not expected to have commercial implications. That world, of course, is changing. Not only is the line between academic research and commercial research blurring, but research is becoming a significant market, as in the case of PCR (polymerase chain reaction) reagents, and the patent system is moving to cover inventions that are useful only as research tools.

[18]This derives from the Drug Price Competition and Patent Term Extension Act of 1984, and was given a broad reading by the Supreme Court to include medical devices in *Eli Lilly & Co. v. Medtronic, Inc.*, 496 U.S. 661 (1990). There was serious PTO discussion of creating a statutory research exemption during the early 1990s. See *Public Hearings and Request for Comments on Economic Aspects of the U.S. Patent System*, 58 *Fed. Reg.* 68394 (Dec. 27, 1993).

[19]The concurrence rests on a theory, partially supported in previous Supreme Court cases, that intention is irrelevant to patent infringement.

[20]E.g. *Diamond v. Diehr*, 450 U.S. 175 (1981); *Parker v. Flook*, 437 U.S. 584 (1978); *Gottschalk v. Benson*, 409 U.S. 63 (1972).

[21]On remand, the patent involved in this case was held invalid for anticipation and obviousness, *AT&T Corp. v. Excel Communs., Inc.*, 52 USPQ2d 1865 (D. Del. 1999).

[22]*An open letter from Jeff Bezos on the subject of patents*, posted on March 9, 2000 at ⟨http://www.amazon.com/exec/obidos/subst/misc/patents.html/002-6082976-8604867⟩. (Accessed June 10, 2001, now inactive.)

[23]*Automated Financial or Management Data Processing Methods (Business Methods)*, White Paper, March 29, 2000.

[24]See ⟨http://www.house.gov/judiciary/4.htm⟩, accessed June 6, 2002.

[25]See ⟨http://www.house.gov/rivers/news_geneintrod.html⟩, accessed June 21, 2002.

[26]*Examination Guidelines for Computer-Related Inventions*, 61 Fed. Reg. 7478) (February 28, 1996)

[27]Part of the problem here is drawing a line between abstract information (that would be unpatentable under the proposal in text) and tangible uses of that information (that should, in at least some cases, be patentable). The distinction is hard enough for therapeutic discovery and invention; it is even harder for diagnostic discovery and invention, for the objective of diagnosis is precisely information (as distinguished from therapy in which the objective is a material change in the body). Europe has struggled with a somewhat similar issue in its effort to apply the European Patent Convention that attempts to prohibit patents on therapeutic and diagnostic methods, while permitting patents on devices and drugs:

> Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application. . . . This provision shall not apply to products, in particular substances or compositions, for use in any of these methods.

European Patent Convention, Article 52 (4).

[28]Although there are further definitions in the provision, the key exclusion from infringement suit is of "medical activity," defined in 35 U.S.C. § 287(c)(2)(A) as

> . . . the performance of a medical or surgical procedure on a body, but shall not include (i) the use of a patented machine, manufacture, or composition of matter in violation of such patent, (ii) the practice of a patented use of a composition of matter in violation of such patent, or (iii) the practice of a process in violation of a biotechnology patent.

The distinction between medical procedures and use of patented machines or compositions of matter (i.e. pharmaceuticals) is very similar to that made in the European Patent Convention.

[29]The recent decisions are not very helpful in estimating the likely response of the Court. They include the state sovereign immunity case noted in text, *Markman v. Westview Instruments, Inc.*, 517 U.S. 370 (1996) on the scope of jury trial in patent litigation, and Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd. , 122 S.Ct. 1831 (2002), and *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997), both on the doctrine of equivalents, a technical claim interpretation doctrine.

[30]The length of this draft is inelegant! If one is confident that the courts will develop the difficult detailed principles needed in application, the goal might be well achieved just by adding the word "tangible" as suggested in the first sentence and also, perhaps, adding the first proposed new sentence.

[31]In drafting language such as this, there are at least three dimensions in which lines can be drawn to distinguish what is reasonably patentable from which should not be patented: (1) Is the invention itself "tangible or not" (i.e., embodied on a computer or an abstract algorithm, as the distinction was made in some traditional software patent law)? (2) Is the invention a principle of nature (e.g., information such as a relation between a genotype and a phenotype) or an application of such a principle (e.g., a specific diagnostic test)? (3) Is the invention a surgical or diagnostic method or process, or a device or composition of matter designed to facilitate that method or process (the distinction made in the European Patent Convention between surgical procedures and medical devices)?

Although the consistency of this proposal with TRIPS was not analyzed, it is unlikely to pose a problem. Most of the exclusions are contained in one or another major nations' laws or interpretations, and there is a strong argument that the areas excluded from patent protection do not involve inventions or are not "capable of industrial application" within the meaning of TRIPS Art. 27.