The Impact of Human Gene Patents on Innovation and Access: A Survey of Human Gene Patent Litigation

Christopher M. Holman†

I. Introduction

While opposition to so-called "gene patents" is nothing new, the rhetoric appears to be heating up. For example, a recent New York Times editorial by popular science fiction author Michael Crichton warns:

> YOU, or someone you love, may die because of a gene patent. . . Gene patents are now used to halt research, prevent medical testing and keep vital information from you and your doctor . . . [B]y now one-fifth of the genes in your body are privately owned.[1]

He goes on to allege that certain unspecified parties have used gene patents to secure "ownership" of diseases and entire genomes, and argues that the patent office and courts have made a mistake by allowing the patenting of genes; in his view, human genes are part of our common biological heritage and the mere discovery of a previously uncharacterized gene is not an invention warranting a patent. Not only does he believe that gene patents have a substantial negative impact on biomedical research and public health, he also suggests that they pose a threat to personal autonomy and an affront to human dignity. Dr. Crichton is far from alone - similar concerns have been voiced by a diverse coalition of gene patent critics that includes prominent scientists, religious leaders, public policy advocates, academics, governmental agencies and members of Congress.[2]

Crichton's editorial appears to have been timed to coincide with the introduction in Congress of the Genomic Research and Accessibility Act (GRAA), a bill sponsored by Congressmen Xavier Becerra (CA-31) and Dave Weldon, M.D. (FL-15) and intended to end the patenting of genes. The GRAA would prospectively bar the patenting of any "nucleotide sequence, or its functions or correlations, or the naturally occurring products it specifies."[3] Although the bill was clearly motivated by concerns over gene patents, its language would appear to encompass all inventions involving polynucleotides, even where the role of the polynucleotide has nothing to do with genetics, or even biology. The scope of the proposed ban on a polynucleotide's "functions or correlations" is

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† Christopher M. Holman, Ph.D., J.D. is an Associate Professor of Law at the University of Missouri – Kansas City.

1 Crichton, Michael, Op-ed, *Patenting Life*, N.Y. Times, Feb. 13, 2007, at A23

2 *See, e.g.*, Who Owns Your Body, http://www.whoownsyourbody.org/ (last visited July 23, 2007), Letter from Bruce Alberts, National Academy of Sciences (Mar. 22, 2000), *available at* http://www.uspto.gov/web/offices/com/sol/comments/utilguide/nas.pdf, Bd. on Sci., Tech., and Econ. Policy, Sci. Tech. and Law, Policy and Global Affairs, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH 125-27 (2006).

3 H.R. 977, 110th Cong. (2007) (actually the bill goes much farther than simply banning gene patents, and would prohibit the patenting of "a nucleotide sequences, or its functions or correlations, or the naturally occurring products it specifies").

ambiguous, but might be interpreted as encompassing any process claim that involves the use of a polynucleotide, genetic information or a biological correlation.

To fully appreciate the import of the proposed ban, bear in mind that U.S. law currently contains no subject matter-specific proscription on patentability.[4] Congress and the courts have steadfastly refused to enact any subject matter specific limitation on patentable subject matter – even attempts to ban the patenting of genetically engineered mammals (including human beings) and human cloning have failed to win Congressional approval.[5] The extreme and unprecedented nature of the proposed legislative fix to the perceived problem of gene patents should prompt questions: What is it about the patenting of genes, and the patenting of human genes in particular, that is so detrimental to the public interest? Have gene patents been asserted in a manner that restricts personal autonomy, offends human dignity, impedes biomedical research, or harms public health? Is the response proposed by the GRAA proportionate to the nature and scope of any problems that might exist, or even sound policy?

The objections that have been raised in connection with gene patents generally fall into two categories, moral and utilitarian. Moral opponents of gene patents tend to be concerned with the implications of gene patents with respect to personal autonomy and human dignity. For many, genes possess a singularly important, perhaps even sacred status as the blueprint of life.[6] The notion that anyone can obtain private property rights in such a fundamental aspect of our common human heritage strikes some as an affront to human dignity.[7] Others have questioned the equity of allowing a researcher who succeeds in chemically characterizing a genetic mutation to obtain exclusive patent rights relating to that mutation, and argue that patients suffering from a genetic diseases should retain control over the mutations associated with their disease.[8] Clearly, some of the concerns arise from widespread misunderstanding of the nature of the patent grant. For

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4 [Cite to Holman Tibtech paper].

5 Rabin, Sanders. *The human use of humanoid beings: chimeras and patent law*, 24 NATURE BIOTECHNOLOGY 517, at 517-519 (2006); Dewar, Helen, *Human Cloning Ban Sidetracked; Senate Vote Deals Amendment Second Setback in a Week*, Wash. Post, June 19, 2002, at A4, Manual of Patent Examining Procedure (MPEP) Section 2105 (The Patent and Trademark Office (PTO) has implemented a policy of refusing to grant patent claims that would encompass a human being, though neither Congress nor the courts have provided any explicit support for the practice.), USPTO: Still No Patent on Life Containing Human Cells, http://www.patentlyo.com/patent/2005/02/uspto_still_no_.html (Feb. 23, 2005), *but see*, S. 681, 110th Cong. (2007) (legislation introduced that would ban the patenting of tax planning methods).

6 Resnik, David B., *DNA Patents and Human Dignity*, 29 J.L. Med. & Ethics 152, 157 (2001), Joint Appeal Against Human and Animal Patenting, Press Conference Text (Washington, D.C.: Board of Church and Society of the United Methodist Church, May, 16, 1995).

7 Id. USPTO Utility Examination Guidelines, 66 Fed. Reg. 1092, *1093 but see*, Bd. on Sci., Tech., and Econ. Policy, Sci. Tech. and Law, Policy and Global Affairs, REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH 64-65 (2006) (stating that others have argued patients suffering from a genetic diseases should retain control over the mutations associated with their disease, rather than allowing a researcher who succeeds in chemically characterizing the mutation to obtain the exclusive ownership of a patent claiming the mutation, Greenfield, Debra L., *Greenburg v. Miami Children's Hospital: Unjust Enrichment and the Patenting of Human Genetic Material*, 15 Annals Health L. 213 (2006).

8 *See, e.g.*, Reaping the Benefits, 64-65, summarizing a dispute between patient families and a hospital over the patenting of the gene associated with Canavan Disease. Greenfield, Debra L., *Greenburg v. Miami Children's Hospital: Unjust Enrichment and the Patenting of Human Genetic Material*, 15 Annals Health L. 213 (2006).

example, it has been suggested that gene patents allow their owners to "do whatever they want with the genes in your body,"[9] or "that a person whose body includes a patented gene could be [found] guilty of patent infringement."[10] Some have even suggested that patents on human genes constitute a form of slavery.[11]

Utilitarian objections, on the other hand, focus more on a perception that human gene patents impede biomedical research and restrict patient access to important therapeutic and diagnostic technologies. For example, some have argued that the proliferation of gene patents threatens to create a patent thicket that will render it difficult to conduct biomedical research, or to conduct follow-on research subsequent to the initial discovery of a gene.[12] By inhibiting biomedical research, it is feared that these patents will substantially delay, or even prevent, the development of potentially life saving cures.[13] It is also feared that gene patents will restrict access to genetic testing services, or at least raise the prices of such testing, reduce the quality of genetic tests that are available, hinder the development of improved versions of the tests, and prevent patients from obtaining a second opinion to confirm an initial diagnosis.[14]

Both moral and utilitarian concerns figure prominently in Congressman Becerra's statement accompanying the introduction of GRAA in Congress.[15] The statement begins by appealing to morality, citing the impact of human genes on personal autonomy and warning that "[o]ne-fifth of the blueprint that makes up you … me … my children … your children … all of us … is owned by someone else, [and] we have absolutely no say in what those entities do with our genes. This cannot be what Watson and Crick intended." However, the Congressman quickly shifts his focus to more utilitarian issues, which appear to be the primary concerns driving the proposed legislation. For example, he asserts that "gene patents interfere with research on diagnoses and cures," that "[h]alf of all laboratories have stopped developing diagnostics tests because of concerns about infringing gene patents, and that [o]ne laboratory in four has had to abandon a clinical

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9 *See* 153 Cong. Rec. E315, E316 (daily ed. Feb. 9, 2007) (statement of Rep. Becerra) (asserting that "who we are is owned by someone else."), Crichton, Michael statements.

10 United States Patent and Trademark Office (USPTO) Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (2001).

11 Greenfield, Debra L., *Greenbert v. Miami Children's Hospital: Unjust Enrichment and the Patenting of Human Genetic Material*, 15 Annals Health L. 213, 230-31 (2006); Gargano, Brian, *The Quagmire of DNA Patents: are DNA Sequences More Than Chemical Compositions of Matter?*, 2005 Syracuse Sci. & Tech. L. Rep. 3 1, [no page numbers on WL]; Resnik, David B., *DNA Patents and Human Dignity*, 29 J.L. Med. & Ethics 152, 157 (2001). Joint Appeal Against Human and Animal Patenting, Press Conference Text (Washington, D.C.: Board of Church and Society of the United Methodist Church, May, 16, 1995).

12 Jensen and Murray, Science 310:239-40, citing Heller and Eisenberg [n. 5 & 6, get cite] Cf. Andrews, L, J Paradise, T Holbrook, and D Bochneak. 2006. "When patents threaten science." *Science* 314:1395-1396.

13 [Crichton and Becerra statements]

14 Myriad BRCA story. Reaping the benefits, Cho, Illangasekare, Weaver, Leonard, and Merz 2003; Merz, Kriss, Leonard, and Cho 2002.

15 153 Cong. Rec. E315-05 (daily ed. Feb. 9, 2007) available at http://www.whoownsyourbody.org/genepatent-intro.pdf

test in progress because of gene patents."[16] He goes on to allege that in "countries where genes are not patented patients get better tests for genetic diseases than in the United States," that patents on disease causing bacteria and viruses might be used to prevent the introduction of "inexpensive, timely public health testing for . . . common infectious diseases," and that during the SARS epidemic researchers "were apprehensive about vigorously studying the disease because three patent applications were pending and they were fearful of possibly facing charges of patent infringement."[17] He also implies that gene patents have contributed to an allegedly high rate at which academic researchers refuse to share "information, data, or materials regarding published research," and that this failure to share has been detrimental to "the training of the next generation of scientists."[18]

Generally speaking, published statements criticizing human gene patents tend to provide little documented evidence of specific instances wherein such fears have actually manifested themselves.[19] The statistic that one-fifth of human genes are "patented" is routinely cited, but what does this actually mean? Human genes are not patentable per se, at least in the form in which they exist in the human body, and patent claims reciting human genetic sequence vary dramatically in scope on a claim-by-claim basis.[20] The repeated assertion that one-fifth of the human genome is "owned" by patent holders has likely led many to assume a greater level of control than actually exists. In fact, although critics such as Dr. Crichton and Congressman Becerra imply that the owner of a gene patent is able to exert control over another individual's body, or to do things with a person's genes that could not be done in the absence of the patent, it is difficult to imagine a situation under which such a scenario could occur.[21]

Regarding utilitarian concerns, the most frequently cited example of a gene patent allegedly adversely impacting research and public health involves Myriad Genetics and its much criticized efforts to enforce patents relating to mutations in the BRCA genes.[22] Genetic testing for these mutations can be used to diagnose for a predisposition to certain forms of cancer, and it has been widely asserted that by enforcing its patents Myriad has elevated the price patients must pay for these important tests and impeded research that might otherwise have improved the testing protocols.[23] But aside from the Myriad example, few other specific cases illustrating the adverse effect of gene patents are cited, at least with respect to patents relating to human genes.[24] Even the Myriad example is

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16 153 Cong. Rec. E315-05 (daily ed. Feb. 9, 2007) http://www.whoownsyourbody.org/genepatent-intro.pdf at page 2

17 Id.

18 Id.

19 For example, no references are provided to support the shocking statistics cited in the statement by Congressman Becerra. Surely there is some basis for the assertions. However, based on the apparent over-interpretation of a study by Jensen and Murray to arrive at the conclusion that one-fifth of our genetic make up is "owned" by someone else, as described below, some degree of skepticism might be in order with regard to the other charges leveled in the Congressman's statement .

20 infra

21 infra

22 [cite]

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24 [cite to Kieff chapter] There have been reports of adverse effects of patents claiming non-human genes, particularly genes of pathogenic microorganism and viruses.

based primarily on anecdotal reports of laboratories voluntarily curtailing their genetic testing services involving the BRCA gene due to fears of patent liability, based on subjective assessments of risk by laboratory directors.[25] In fact, Myriad has rarely asserted its patents in court, and those lawsuits settled before any substantive ruling on the merits.[26]

The paucity of documented examples wherein the fears surrounding gene patents have manifested themselves is striking, particularly when one considers the high level of public concern and the extraordinary nature of Congressman Becerra's proposed legislative fix. In contrast, critics of patents claiming software, information technology and business methods can point to a number of high profile examples where these patents have actually been asserted and successfully enforced in the courts, providing objective validation of the tangible impact of these patents.[27] Likewise, in the biomedical sector, patents on fundamental biological pathways and correlations have led to enforcement actions that clearly raise substantial public policy concerns.[28] In contrast, the case against gene patents is attenuated by its reliance on anecdotal evidence and unsubstantiated assumptions regarding the nature and scope of so-called gene patents and the extent to which these patents adversely impact research and public health.

This article critiques the argument for banning gene patents, and assesses the extent to which the perceived fears surrounding these patents have manifested themselves in the courts. It focuses particular attention on human gene patents, a subset of gene patents which has garnered particularly critical commentary.[29] I begin by discussing with some specificity the nature of the subject matter claimed in so-called human gene patents, and the rights conferred by these patents. I then present the results of a comprehensive search I conducted to identify and characterize, to the extent practical, every instance where a human gene patent has been asserted in a lawsuit. As described in more detail below, patent litigation is posited to function as a useful proxy for a patent's impact. My intent is to inform the debate over the patenting of human genes patents by considering the actual impact of human gene patents, as evidenced by the claim language of specific human gene patents, the frequency with which these patents are asserted in lawsuits, and the outcome and policy implications of these litigations. I conclude by discussing some general observations regarding the results of the study and their policy implications.

II. Owning a gene patent is not the same thing as owning a gene

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[25] Cho study, Perspectives on Properties of the Human Genome Project, Edited by F. Scott Kieff, Chapter 7, Perusing Property Rights in DNA.

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[27] *See Eolas v. Microsoft*, 399 F.3d 1325 (Fed. Cir. 2005), *eBay Inc. v. MercExchange, L.L.C.*, 126 S. Ct. 1837 (2006), *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343 (2001).

[28] *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354 (2004), *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 2007 U.S. Dist. LEXIS 49076 (2007).

[29] For example, although the bill to ban gene patents is not limited to humans, or even to genes for that matter, encompassing as it does any nucleotide sequence, the ire of individuals such as Congressman Becerra's and Michael Crichton seems particularly directed at "human gene patents" and the ownership of human genes. The seminal study by Jensen and Murray also focused entirely on human gene patents, based on those authors' conclusion that human gene patents raised the most compelling policy concerns and were of most interest to the public.

Much of the concern with respect to human gene patents appears to arise out of a perception that a patent claiming a product or process involving a human genetic sequence confers "ownership" of the corresponding gene. In part, the trepidation surrounding gene patents likely results from a failure to appreciate the distinction between the rights conferred by a patent and ordinary personal property rights. The statements by Crichton and Becerra, for example, evidence confusion on this point by asserting that owners of gene patents can do whatever they want with the genes in our bodies, and there is "nothing we can do to stop them."[30] Although routinely characterized as a form of intellectual "property," a patent lacks many of the attributes of "ownership" typically associated with ordinary personal property, such as a car or real property.[31] Ordinary personal property often includes a positive "right to use" the property, whereas the patent grant confers no such right. The patent grant is limited to the right to exclude others from various activities involving the claimed invention, such as making, using or selling the invention in the US.[32]

Importantly, a patent in no way expands the patent owner's ability to do what it wants with the patented subject matter. In general, researchers and others are free to do what they like with genes and genetic information, which might include functional studies of the gene, use of the gene in a recombinant process for protein production, or the performance of a genetic test. Conversely, as a general rule no one has the right to do anything with another person's body, or the genetic material residing in a person's body, and the existence of a patent in no way alters that. To be sure, there are a variety of legal restrictions limiting certain uses of genetic material and genetic information. For example, it would generally be illegal to introduce a foreign gene into a human subject (i.e., to perform gene therapy), or to market a genetic testing kit without first securing FDA approval.[33] Congress is currently considering legislation that would ban certain uses of an individual's genetic information.[34] But because a patent only confers the right to exclude others from using an invention, and does not include any positive right to use, the patent in no way expands upon the patent owners freedom to take any action that would be barred in the absence of the patent.

Furthermore, the patent owner's right to exclude is limited to the patented subject matter as defined by the claims. Many of the patents that have been categorized as gene patents only claim some narrowly defined recombinant product or process involving the use of a genetic sequence. The patent should generally pose no impediment to use of the gene in other contexts. For example, a patent with claims limited to expression of a human gene in certain recombinant mammalian cells culture systems does not restrict

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[30] 153 Cong. Rec. E315-05 (daily ed. Feb. 9, 2007), Crichton, Michael, Op-ed, *Patenting Life*, N.Y. Times, Feb. 13, 2007, at A23 -- Congressman Becerrra and Crichton statements, implied by who owns your body

[31] Perspectives on Properties of the Human Genome Project, Edited by F. Scott Kieff, Chapter 7, Perusing Property Rights in DNA at 127.

[32] 35 USC 271. This distinction between the rights conferred by a patent vs. what most people think of as "ownership," and the implications for policy decisions regarding genetic-based patents, is explained in greater detail by Professor Kieff. Supra, 127-130.

[33] FDA/CBER – Cellular & Gene Therapy, http://www.fda.gov/cber/gene.htm

[34] H.R.493, 110th Cong. (2007) Title: To prohibit discrimination on the basis of genetic information with respect to health insurance and employment. http://www.govtrack.us/congress/bill.xpd?bill=h110-493

research on the gene or other uses of the gene, including expression of the identical gene in an alternate mammalian cell culture.[35] Likewise, a patent limited to a hybridization micorarray employing a defined set of genetic sequences does not restrict the use of those sequences in other contexts.[36] A patent claiming a chimeric gene produced by fusing portions of two or more distinct genetic sequences to encode a non-natural hybrid protein does not otherwise limit the use of the constituent genes.[37] These are just a few of the many examples of gene patents which have been characterized as "claiming the gene,"[38] which some have extrapolated to outright "ownership" of the genes.[39] But it is absurd to characterize patents encompassing such limited uses of a gene as "ownership" of the gene, or to suggest that these patents grant the patent owner the right to do whatever it wants with claimed gene.[40] It would make as much sense to claim that the owner of a patent on a method of welding that involves the use of oxygen "owns" the air we breathe.

III. The rationale for this study

While the literature includes numerous empirical studies of gene patents, often focusing on human gene patents,[41] I am not aware of any that has focused specifically on the small set of gene patents that have actually been asserted in court. For this article I attempted to identify, in a comprehensive and systematic manner, all lawsuits that have been filed based on an allegation of infringement involving a human gene patent, including declaratory judgment actions filed by parties alleging a reasonable apprehension of being sued for infringement of such a patent. The results not only provide a measure of the frequency at which these patents have been the subject of judicial enforcement, but more importantly, by analyzing specific claims that have been asserted, the nature of the alleged infringing activity, the circumstances surrounding the filing of the lawsuit, and ultimate litigation outcomes, I hope to inform the policy debate. It seems to me that much of the concerns arise out of a tendency to consider gene patents in the abstract, and that a serious assessment of the impact of human gene patents should only proceed from the more sophisticated understanding of the phenomenon to be gained by considering the specifics of claims that have actually been asserted.

Of course, one might argue that by focusing solely on litigated patents my study will fail to identify much of the pernicious effects of human gene patents. To be sure, even a patent that has never been formally asserted in court can have a substantial impact. For example, biomedical research and product development might be impacted when a firm agrees to pay royalties to license the use of a patented technology, or decides to modify or even forgo certain uses of human genes for fear of being subjected to an

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35 U.S. Patent No. 5356804, *see* Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094 (Fed. Cir. 2003) (Finding the '804 patent was not infringed by a mammalian cell culture produced using an alternate, later developed technology).

36 Murray Jensen, p. 329.

37 6673562, 5851795, 5844095

38 Murray Jensen study describes these patents as claiming the gene.

39 153 Cong. Rec. E315-05 (daily ed. Feb. 9, 2007), Crichton, Michael, Op-ed, *Patenting Life*, N.Y. Times, Feb. 13, 2007, at A23

40 The point that patents do not confer ownership on genes has been made by PTO. USPTO Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 ("Patents do not confer ownership of genes, genetic information or sequences.").

41 Jensen Murray and studies cite therein

expensive infringement lawsuit. These non-litigation responses to the patent might in turn ultimately affect the availability of life saving cures and genetic testing options. Nevertheless, although litigation is by no means the only measure of the impact of a patent, or class of patents, I would assert that it is an important and useful one. Moreover, it is one that can be addressed in a relatively objective manner, as opposed to, for example, attempts to gauge the extent to which research has been stymied by fears of exposure to patent liability which may or may not be justified.[42]

A recent law review article by Allison et al. argues convincingly that patent litigation, i.e., the filing of an infringement-related lawsuit, is a good indicator of patent value.[43] The authors conclude that commercially valuable patents are more likely to be subject of a lawsuit than other patents, the vast majority of which have little or no commercial significance.[44] In this paper, I posit the corollary that litigation is likewise an indicator of patent impact. The concepts of value and impact are closely related - important patents that are having an impact are likely valuable and valuable patents are likely having an impact. But for the purposes of this paper I am focusing on patent impact, the effect of a particular patent or class of patents on society at large (either positive or negative), as opposed to the value of the patent as experienced by the patent owner. Essentially, I would argue that if patent infringement lawsuits are rarely filed in connection with human gene patents, then perhaps these patents are not having as much impact as has been feared, and do not warrant exceptional and extreme countermeasures. As noted by Allison et al, it seems likely that a patent on which multiple parties are paying substantial license fees will at some point result in the filing of a lawsuit by the one party willing to put up a fight.[45] Furthermore, even if the parties expect to settle the dispute quickly and have no intention of taking a suit to trial, a patentee (or accused infringer) might file a lawsuit as a negotiating tactic, or to preserve their rights.[46] And although patent litigation is expensive, if a patent is truly blocking important research or product development it seems likely someone would be willing to challenge the patent by provoking or filing a lawsuit.[47]

It is important to bear in mind that patents are not self-enforcing. In general, the mere issuance of a patent does not legally restrict the ability of anybody to do anything unless and until the patent owner successfully sues for patent infringement.[48] It is well known that a huge number of patents exist purporting to cover many of the tools, reagents and protocols used in research laboratories throughout the US every day, including human gene patents.[49] Studies have shown that these patents have had a relatively minor

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42 See, e.g., Rowe, Elizabeth A., *The Experimental Use Exception To Patent Infringement: Do Universities Deserve Special Treatment?*, 57 Hastings L.J. 921 (2006) (explaining that although many have expressed the fear that university researchers will be subject to infringement lawsuits, for a variety of reasons universities are unlikely to be sued for patent infringement).

43 Valuable Patents, Allsion, Lemley et al

44 Id at 1.

45 At 10.

46 Id.

47 Id.

48 Exception for drug patent listed in orange book and 30-month stay.

49 Walsh, J.P, A. Arora, and W.M. Cohen. 2003. "The Patenting and Licensing of Research Tools and Biomedical Innovation." Pp. 285-340 in *Patents in the Knowledge-Based Economy*, edited by W.M. Cohen and S. Merrill. Washington: National Academies Press.

impact on basic research, due in large part to the fact that researchers simply choose to remain ignorant of the patents, or at least do not to let the existence of patents dictate research agendas.[50] These researchers are behaving perfectly rationally, because in fact basic research activities have rarely if ever been the subject of a patent infringement lawsuit.[51] Regardless of the number and claim breadth of human gene patents, these patents only have an impact to the extent they are asserted, or to the extent third parties voluntarily choose to avoid certain activities or pay licensing fees for fear of otherwise being sued for infringement. A patent that is ignored and never asserted has no impact on biomedical research or the public interest.[52]

An important advantage of focusing on patent litigation, as opposed to the mere issuance of patents, is that by considering the specific nature of the allegedly infringing activity it is possible to more accurately gauge the actual restrictive effect of the asserted patent. For example, a human gene patent might be asserted in an attempt to shut down the only commercial provider of genetic testing services targeting a gene of unique and compelling clinical significance, e.g., the BRCA genes. Such a scenario (were it found to occur), wherein the patent functions to deny patients access to important medical technology, would provide a compelling example of the negative impact of human gene patents. Likewise, a patent used to block all drug discovery efforts targeting an important gene (or gene product) would raise similar policy concerns, particularly if the patent owner is not actively engaged in the use of the gene in its own drug discovery efforts. On the other hand, a patent asserted to block a competing company's use of a gene in a unique, proprietary protein expression system would be much less problematic, particularly if alternate technologies for achieving the same product are readily available. In fact, the patent might be serving a positive role in incentivizing the necessary investment in the research and development of life-saving therapeutics. While critics might decry the large number of patents claiming human genes, any negative impact of these patents will be attenuated if they are not asserted in a manner contrary public policy.

The scope of this study is restricted not only to litigated gene patents, but more specifically to litigated human gene patents. My decision to focus solely on human gene patents was based in part on a desire to limit the study to a manageable dataset amenable to detailed analysis of each case. Many gene patents claim non-human genetic sequences, such as those of most relevance to agricultural and veterinary biotechnology. Patents claiming to genetic sequences of important human pathogens, such as the hepatitis C virus and HIV, in particular have caused concerns, and some of been the

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Walsh, J.P, A. Arora, and W.M. Cohen. 2003. "Working through the patent problem." *Science* 299: 1020. Walsh, J.P and Wei Hong. 2003. "Secrecy is increasing in step with competition." *Nature*422:801-802. Walsh, John P., Charlene Cho, and Wesley M. Cohen. 2005. "The View from the Bench: Patents, Material Transfers and Biomedical Research." *Science* 309: 2002-2003. Walsh, John P., Charlene Cho, and Wesley M. Cohen. 2005. "Patents, Material Transfers and Access to Research Inputs in Biomedical Research." Final Report to the National Academy of Sciences' Committee Intellectual Property Rights in Genomic and Protein Related Inventions.

[50] Id.

[51] infra

[52] Aside from the psychic injury apparently brought about in some by the mere knowledge that such patents exist. Supra. The patent might also be of some tangible benefit to the inventor, to the extent it is perceived as evidence of productivity.

subject of litigation. However, human gene patents have been the primary focus of the controversy surrounding gene patents and seem to me to provide a useful demarcation to limit the scope of the present study.[53]

IV. What exactly is a "human gene patent"?

As a preliminary to discussing human gene patents, we should stop to consider exactly what it is we mean when we use term "gene." The ambiguity of the term is becoming increasingly clear - the word "gene" is used in a variety of divergent ways, and often has dramatically different meanings for scientists working in different disciplines. In classical genetics, the term gene was used to refer to the fundamental unit of inheritance. It was only later that scientists began to elucidate the molecular basis of genetics, eventually establishing that genes are comprised of DNA and function by encoding proteins.[54]

Today, the term gene is often defined as genetic material that encodes a protein.[55] However, increasingly, the term is being used in a broader sense to encompass not only protein-encoding genetic sequences, but other functional regions of the genome as well. For example, Wikipedia defines a "gene" as:

> a set of segments of nucleic acid that contains the information necessary to produce a functional RNA product in a controlled manner. They contain regulatory regions dictating under what conditions this product is made, transcribed regions dictating the sequence of the RNA product, and/or other functional sequence regions.[56]

The Wikipedia definition seems to me as good as any and highlights many of the issues glossed over in much of the current debate over gene patents.[57] For example, instead of defining a gene as ***DNA*** encoding a protein, it defines it as a ***nucleic acid*** that encodes a functional RNA. Although DNA is the primary genetic material in humans and other higher organisms, the genes of certain viruses such as HIV are comprised of RNA, a related but distinct nucleic acid. More relevant to a discussion of human gene patents, it focuses on the production of a ***functional RNA*** rather than an encoded ***protein***. RNA production is an intermediate step the expression of a gene-encoded protein, so this definition encompasses the traditional notion of a gene as a protein-encoding genetic sequence. But the definition is significantly broader, in that it encompasses the production of RNA that is not subsequently translated into protein. It has long been recognized that certain RNA molecules function directly, rather than as intermediates in protein expression, such as the transfer RNA (tRNA) and ribosomal RNA (rRNA)

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[53] Murray and Jensen note that human gene patents have caused the most controversy and limited their study to human gene patents, also Crichton and beccerrra statements.

[54] At least the genes of in higher organisms such as man, Some viruses, such as HIV, have genomes based on RNA.

[55] [There is a reported decision that defines a gene in this way]

[56] http://en.wikipedia.org/wiki/Gene#_note-Pearson_2006. July 16, 2007

[57] Perhaps more importantly for those considering policy, the converse is also true. DNA is used in a variety of non-genetic and non-biological applications, and attempts to curb gene patenting by banning the patenting of DNA threaten to bar patentability for a number of DNA inventions that have nothing to do with genetic, or even biology.

molecules involved in translating a messenger RNA (mRNA) into the corresponding protein. However, it has recently become apparent that RNA plays a much more diverse and substantial role in biology than was previously recognized, for example in the form of "microRNAs" and other RNA molecules now known to be vital in controlling cellular processes.[58] Although protein-encoding DNA is thought to make up only about 1-2% of the overall genome in humans and other mammals, recent studies suggest that on the order of 60-80% of the genome is transcribed into RNA. Function has yet to be assigned for much of this RNA, but it is becoming increasingly apparent that non-protein encoding RNA can play a substantial biological function. The Wikipedia definition also includes regulatory regions which are not themselves transcribed into RNA, but which regulate transcription, such as promoter and enhancer regions.

The Wikipedia definition would seem to encompass artificial, non-naturally occurring nucleic acid sequences that encode a functional RNA product. For example, it would appear to encompass complementary DNA (cDNA) molecules, i.e., non-naturally occurring DNA molecules that correspond in sequence to a protein-encoding mRNA. Most genes in humans and other eukaryotic organisms contain non-protein coding regions called introns that are removed from the mRNA prior to transcription of the protein from the mRNA template, in a process known as splicing. As a consequence, most of the genes that reside in the human genome do not directly code for a protein, and are of limited practical utility in expressing the protein recombinantly, particularly in prokaryotes, which do not have the biochemical machinery required to remove introns. cDNA molecules, although they do not occur in nature, encode directly for native proteins and are often classified as genes. In fact, some of the earliest reported judicial decisions involved "gene" patents actually involved claims directed to cDNA, not naturally occurring genes.[59] In addition, the Wikipedia definition would include synthetic genes that have little relationship to any naturally occurring gene, including genes encoding totally synthetic proteins or functional RNA products.[60]

Cognizant of the ambiguity inherent in use of the term gene, I will attempt to formulate a working definition for the term "human gene patent" as it is used in this paper. Much of the published commentary on gene patents neglects to explicitly define the term, or even to provide a specific example of a gene patent.[61] Wikipedia defines "gene patents" as "patents on specific sequences of genes, their usage, and often their chemical composition."[62] Again, this seems to me as good a definition as any, at least for a lay audience.[63] Wikipedia's definition includes "usages" of genes, which comports with the GRAA's ban on the patenting the "functions and correlations" of "nucleotide

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59 For example, Regents of UC v. Eli Lilly.

60 GAT gene, http://www.sciencemag.org/cgi/content/abstract/sci;304/5674/1151.

61 This problem is alluded to in Murray and Jensen. *Science* 14 October 2005:

62 http://en.wikipedia.org/wiki/Gene_patents . Accessed July 27, 2007.

63 Although the reference to "specific sequences of genes . . . and often their chemical composition" seems to reflect a misunderstanding of biotechnology patent law. When one refers to a gene "sequence," this generally refers to either the order of nucleotides appearing in the gene, or to the actual molecule itself. A description of a gene sequence is pure information and not patentable per se, so to make sense the definition must be using the term to describe the actual chemical itself, in which case the inclusion of "chemical composition" would seem to be redundant.

sequences." Note that the term "usages" could be interpreted quite broadly to include compositions of matter, such as vectors, cell lines and recombinant organisms, as well as methods employing genetic molecules or genetic information.

Technically, the term "gene patent" is something of a misnomer. In spite of repeated warnings that patents allow others to "own the genes in your body," or even to "own your body", it is black letter law that naturally occurring genes as they exist in their native state (e.g., as they exist in the human body) are unpatentable products of nature, as is raw genetic sequence information.[64] However, longstanding judicial precedent has consistently held that the purification of a natural product from its native environment can confer patentability on the purified biomolecule.[65] Citing to this precedent, the U.S. Patent Office has taken the position that isolated or recombinant forms of naturally occurring genes are patentable, as are synthetic polynucleotides corresponding in structure to native genes, and the courts have shown no inclination to overrule the patent office in this regard.[66] In general, the patent law treats isolated polynucleotides corresponding to naturally occurring genes as it would any other molecular compound, although some have argued that the Federal Circuit has at times applied the law differently to biomolecules.[67]

Some previous studies of human gene patenting have classified any patent that discloses a human gene as a human gene patent.[68] An obvious problem with this approach is that it fails to recognize that the exclusionary potential of a patent is limited by the patent claims.[69] A patent that refers to a human gene sequence in its specification but that has no claims reciting the human gene sequence is not properly considered a

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[64] USPTO Utility Examination Guidelines, 66 Fed. Reg. 1092. http://www.uspto.gov/web/offices/com/sol/notices/utilexmguide.pdf "It might be in your body, but it doesn't belong to you." http://www.mywire.com/pubs/Esquire/2001/06/01/138745?pbl=15. But see 6, 421,613 which claims a data structure supporting computer access to data representing a specified genetic sequence.

[65] USPTO Utility Examination Guidelines, 66 Fed. Reg. 1092. For example, in 1873 Louis Pasteur received U.S. Patent 141,072 claiming "yeast, free from organic germs of disease, as an article of manufacture." Since then, the courts have upheld the validity of claims directed to purified adrenalin and prostaglandin, noting that the isolated forms of these molecules do not exist in nature and have substantial therapeutic utility. Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95, 103 (S.D.N.Y. 1911). In re Bergstrom, 427 F.2d 1394, 1397 (CCPA 1970). Purified native proteins are also routinely patented. Scripps Clinic and Research Institution v. Genentech, Inc., 927 F.2d 1565 (Fed. Cir. 1991).

[66] The point that patents do not confer ownership on genes has been made by PTO. USPTO Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093

[67] *Id.*, UC v. Lilly, Deuel, Despite the established precedent allowing the patenting of purified natural products, some argue that genes should be treated differently. For example, Affymetrix, a leading supplier of DNA hybridization array technology, has argued before the courts that "isolated, purified and synthesized" cDNA molecules should be classified as unpatentable "products of nature," because the mere removal of DNA from its native environment and excision of non-coding regions does not result in any substantial functional difference from naturally occurring DNA or RNA. In re Dane K. FISHER and Raghunath V. Lalgudi, Brief for Amicus Curiae Affymetrix, Inc. in Support of Appellee, 2004 WL 4996615. [Lemley and Burk Policy Levers paper]

[68] Murray Jensen notes 20-22.

[69] supra

human gene patent, since it provides no basis exclude any use of a human gene, and in no sense confers ownership of the gene.[70]

Another complication in defining human gene patents is that patent claims reciting human genetic sequences vary widely in scope, and can be either product or process claims. Some of the broadest product claims assert per se coverage to any isolated polynucleotide corresponding to a naturally-occurring human genetic sequence, which might be a full-length protein encoding gene,[71] a gene fragment,[72] a regulatory region,[73] a cDNA molecule, a transcribed but non-protein encoding region of the genome, or a genomic region of unknown function, i.e., "junk DNA."[74] Many product claims broadly encompass any polynucleotide encoding a naturally occurring protein, or even any polynucleotide claiming any variant of a naturally occurring protein.[75] Note that such a claim would probably not cover the native gene including introns, at laast literally, but rather would cover a cDNA encoding the protein and any other synonymous, non-naturally occurring sequence made possible by the redundancy of the genetic code.[76] These and many other sorts of claims are all commonly referred to as human gene patents.

It is important to bear in mind that because of natural genetic variability there is generally not a single, unique sequence for a given human gene. It is this sequence variation, often referred to as mutations or polymorphisms, that causes the genetic differences between individuals, and many times the discovery and characterization of these differences is as significant as the identification of the gene itself. For example, mutations in the BRCA genes have been associated with a predisposition to certain forms of cancer.[77] In many cases a patent will claim only a single variant, such as the predominant wild-type sequence, or perhaps one or more specific polymorphic forms, [78] such as specific BRCA mutations associated with a predisposition towards cancer.[79] Some claims are drafted in a manner that attempts to encompass any variant of a gene, including as yet undiscovered variations.[80] In some cases these patents broadly claim

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[70] From Murray Jensen study. [examples?] 7,238,376 claims a method of treatment using black tea extract, but the specification recites BRCA sequence fragments for use in PCR protocol. 7,238,469 claims a method of administering carbon monoxide during an organ transplant operation, but specification recites mouse gene sequence fragments for use in PCR protocol.

[71] 5,616,483, (Genomic DNA sequences encoding human BSSL/CEL)

[72] 6,204,020

[73] 6,534,268

[74] Promega v. Lifeprobes

[75] 5,215,892, InCyte patents. Christopher M. Holman "Protein Similarity Score: A Simplified Version of the BLAST Score as a Superior Alternative to Percent Identity for Claiming Genuses of Related Protein Sequences" 21 Santa Clara Computer & High Tech. L.J. 55 (2004).

[76] The claims encompass an astronomical number of different polynucleotides, a consequence of the redundancy of the genetic code. [Holman Protein Similarity Score Paper]

[77] Reaping the benefits

[78] 5,693,473

[79] 5,747,282

[80] This can potentially be accomplished, for example, by claiming the gene in a manner that does not recite a specific sequence, or by claiming any polynucleotide sharing a certain percent of sequence identity, or having sufficiently similar sequence to be able to hybridize to a reference sequence. [cite similarity score paper]. For example, see IGFBP-3 patent in Insmed and claim 7 in Chugai.

any recombinant or isolated form of naturally occurring gene sequence; these are probably the closest thing to a patent claiming a gene, since on their face they would appear to cover any biotechnological product or process making or using the claimed sequence. In many case, however, patents are limited to specific genetic constructs or expression systems, such as a recombinant vector, cell line or host organism comprising the gene sequence. These claims provide more limited coverage, as defined by the language of the claims, in a manner that varies in a multitude of dimensions on a patent-by-patent basis.

Some product claims are not directed to the genetic sequence per se, but rather to a DNA probe capable of specifically hybridizing to and thereby recognizing a genetic sequence, or a specific mutation in the sequence. Other claims recite PCR primers that could be used to amplify the sequence, or some fragment of the sequence. Although these claims do not necessarily cover the genetic sequence directly, they can be extremely effective in covering the necessary reagents required for studying the gene or for conducting genetic testing. In a practical sense, these claims to probes and sequence fragments can provide more expansive patent coverage than claims directed to the full-length gene sequence.

In many cases the most dominating patent claims relating to human genetic sequences are process claims, particularly those that broadly claim methods for identifying mutations. This runs counter to the conventional wisdom that product claims are generally more powerful then process claims. For example, a claim encompassing any method of diagnosing for a medical condition based on identifying the presence of a specified mutation could be difficult if not impossible to design around.[81] Process claims involving the use of human genetic sequence information are often characterized as human gene patents, although they do not physically claim a molecule embodying the genetic sequence.

The term “human gene patent” has been explicitly identified in some previous studies. For example, oneof the most influential and informative empirical studies of human gene patenting formed the basis for a 2003 article by Jensen and Murray in the prestigious journal Science (“Jensen/Murray”). This study has been widely cited in arguments against gene patents, and is presumably the basis for the assertions by Crichton and Becerra that one-fifth of human genes are patented.

For the purposes of their study, which like the current study was limited to human genes, Murray and Jensen defined the term "gene" to mean “a set of cotranscribed protein-encoding exons,” and a "gene patent" as any patent disclosing and claiming a human gene sequence or some fraction thereof. Note that their definition of “human gene" is relatively conservative and much narrower than, for example, the Wikipedia definition, excluding as it does the approximately 98% of the human genome which is not thought to encode for proteins, e.g., regulatory sequences, transcribed sequences which encode RNA that is not translated into proteins, and the vast stretches of genomic DNA having no known function, sometimes referred to as "junk" DNA. The Jensen and Murray definition would encompass human genes residing in the genome, and also cDNA molecules produced in a laboratory corresponding to human genes.

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[81] 5,709,999

On the other hand, their definition of "patented" is fairly expansive, and would include any patent whose claims reference a human gene sequence, regardless of how limited the scope of the claim. For example, their definition would include a patent that only claims a specific gene fusion comprising two or more specific genetic sequences fused to one another, [82] or a hybridization array comprising multiple human gene sequences, or molecules encoding non-naturally occurring variant proteins.[83] These sorts of claims would encompass only a minute fraction of the potential uses of the human gene, but under the Jensen & Murray criterion the scope or practical significance of the claims is not taken into consideration. Although this methodology is perfectly reasonable and suited for what was essentially an automated data-mining survey, gene patent critics such as Crichton and Congressman Becerra appear to have over-interpreted the results, by equating every patent in the database with ownership of a gene, when the scope of many of the patents is in fact quite limited.

To compile their database Jensen and Murray performed an automated search designed to identify all U.S. patents reciting the canonical term "SEQ ID NO:" in the claims, and wherein the "SEQ ID NO." term is used in conjunction with a specific genetic sequence corresponding to a known human gene.[84] Their search identified 4270 patents reciting 4382 human genes, and based on this result they concluded that approximately 1/5 of human genes were claimed in US patents.[85]

While their search strategy has the significant advantage of being amenable automation, permitting them to query the entire set of relevant issued patents, like most search strategies (including those I employed in the current study) there are certain limitations, and when disregarded these limitations can render their conclusions susceptible to misinterpretation. Some of these limitations were explicitly noted by Jensen and Murray. For example, patents frequently claim genetic sequences indirectly, by means of claims that explicitly recite a protein sequence and claim any polynucleotide capable of encoding the protein.[86] But any patent claiming a genetic sequence in this

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[82] 5376367, Fusion proteins comprising MGF and IL-3. A fusion protein comprising MGF linked to IL-3, wherein MGF and IL-3 are linked via a C-terminal to N-terminal fusion. This is another example of a patent that does not claim any polynucleotide sequence

[83] their database includes U.S. Patent No. 5,444,153, whose claims recite non-naturally occurring variant proteins and non-naturally occurring antibodies that recognize these proteins. This patent is one of the data points used to justify the conclusion that 1/5 of human genes are patented. I assume that this patent made its way into the database because it does have seek ID number in the claims, and because the patent contains a seek ID number corresponding to human gene. One of the problems with the search methodology is that it apparently does not discriminate between patents were in the seek ID number relating to a gene sequence appears in the claims, or situations such as this wherein a seek ID number relating to a protein appears in the claims and a seek ID number relating to a gene appears in the patent but not in the claims. To this extent, Murray N. Jensen have fallen into the same trap that they had noted in other previous studies, i.e., a failure to distinguish between patents that merely recite gene in the written description section of the patent but not in the claims themselves.

[84] http://www.sciencemag.org/cgi/content/full/310/5746/239#ref20.

[85] The authors reported that at the time the article was written NCBI's database included 23,688 distinct human genes.

[86] [Holman Similarity Score Paper] The reason for this is that provides much broader protection. Owing to the redundancy of the genetic code, there are an astronomical number of redundant variations of any given gene sequence that will encode exactly the same protein. By claiming any genetic sequence that encodes a specified protein sequence, it makes it more difficult to design around the patent and gives much

matter would not be identified in the Murray and Jensen study, unless, as is often the case, the patent also explicitly claims a specific exemplary nucleotide sequence encoding the protein, e.g., the specific cDNA isolated by the inventor.[87] A more significant limitation stems from the fact that many human gene patents, particularly older ones, do not use the SEQ ID NO format and hence cannot be identified by this search strategy.[88] The SEQ ID NO convention was not introduced until 1990, many years after people began filing patents on genetic sequences.[89] As a result, the oldest patent in the Murray and Jensen database issued in 1993.[90] To this day, patent issue with claims that reference genetic sequences without using SEQ ID NO, e.g., identifying the gene by its common name.[91] In fact, a majority of the litigated human gene patents I identified in this study did not appear in their database.

An alternative approach to defining and identifying gene patents was used in compiling the DNA Patent Database, an online database of DNA patents compiled and administered by the Kennedy Institute of Ethics at Georgetown University.[92] Although the database is identified as a DNA patent database, as opposed to a gene patent database, it is apparent that the focus on DNA and nucleic acids reflects an underlying interest in patents relating to genes.[93] The DNA Patent Database was compiled based on a two stage automated search of the Delphion patent database, and continues to be updated on an ongoing basis. The first stage of the search makes use of the patent classification system, and seeks to identify all patents falling within a classification thought likely to be associated with genes or genetic research.[94] The second stage is to select from that group any patent that includes within its claims any one of a long list of terms specifically associated with DNA, nucleic acids, genetics and the like.[95]

As of March 30, 2007, the DNA Patent Database included 43,456 patents, roughly 10 times more patents than found in Jensen/Murray, which reflects the significantly

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broader patent protection. Cite to BLAST paper for principle that genes can be claim in terms of encoded protein.

[87] For an example, see US Patent No. 7196172 claim 11. An isolated ***polynucleotide*** molecule encoding a first ***polypeptide*** and a second ***polypeptide*** as shown in claim 1.

[88] UC v. Lilly

[89] M&J supporting materials. See for example 4,363,877, asserted in Genentech v. Eli Lilly

[90] 5,215,892 (June 1, 1993) 1. An isolated DNA sequence which codes for the IL-6 gene expression inducing nuclear factor C/EBP2, wherein said DNA sequence is selected from the group consisting of the nucleotide sequence set forth in SEQ ID NO:30 and a nucleotide sequence which hybridizes thereto, and which encodes a polypetide which is capable of binding to the following nucleotide sequence: ACATTGCACAATCT.

[91] 4,703,008, Amgen v. Chugai, 4,431,,740, UC v Lilly. 4,766,075 Genentech v. Wellcome, 6,025,126 (2000) and 6,414,133 (2002), asserted in Ventana v. Vysis.

[92] http://kennedyinstitute.georgetown.edu/index.htm. The center identifies itself as the world's oldest and most comprehensive academic bioethics center.

[93] For example, the website states that the "database serves as a resource for members of the general public interested in fields like genomics, genetics and biotechnology."

[94] [describe patent classification system]

[95] For search algorithm see http://dnapatents.georgetown.edu/SearchAlgorithm-Delphion-20030512.htm. The specific terms searched are: antisense cDNA centromere deoxyoligonucleotide deoxyribonucleic deoxyribonucleotide DNA exon gene genetic genome genomic genotype haplotype intron mtDNA nucleic nucleotide oligonucleotide oligodeoxynucleotide oligoribonucleotide plasmid polymorphism polynucleotide polyribonucleotide ribonucleotide ribonucleic "recombinant DNA" RNA mRNA rRNA siRNA snRNA tRNA ribonucleoprotein hnRNP snRNP SNP.

greater inclusivity of the DNA Patent Database search strategy. The database is not limited to human genes or genetic sequences identified by means of the SEQ ID NO: format, nor is it limited to DNA that serves a genetic, or even biological function; in fact, many of the patents are directed to inventions that only tangentially involve DNA, or which involve the use of DNA in non-biological applications. For example, some of the inventions appearing in the database relate to nanotechnology rather than genetics or biotechnology.[96] The DNA Patent Database's inclusivity is its primary virtue, since it is not likely to miss any patent having a relation to DNA or genes. At the same time, it would be a mistake to view the number of patents appearing in the database as anything more than a crude indicator of the extent to which genes are being patented, since a large percentage (probably the vast majority) are not what one would normally consider gene patents.

Bearing in mind the limitations of previous attempts to define gene patents, for the purposes of this study I decided to act as my own lexicographer and define a "human gene patent" as any patent with a claim directed to a product or process that includes a single, specific human genetic sequence.[97] The sequence can be naturally occurring, or a synthetic sequence created by biotechnology but based on a naturally occurring human sequence. The definition is much narrower than that employed by the DNA Patent Database, but substantially broader than that employed in Jensen/Murray. For example, the definition encompasses any DNA sequences that occur naturally in the human genome, regardless of whether it encodes a protein. My definition most closely resembles the Wikipedia definition, in that it includes any sequence that is transcribed into RNA, as well as regulatory sequences, but is broader in that it also includes so-called "junk DNA," i.e., DNA that is not known to be transcribed and that has no known function. Although "junk DNA" has no known biological function, it can be useful for molecular genetic identification technologies used in forensics and paternity testing, and hence can be of commercial significance warranting patent protection. My definition also includes polymorphisms and mutant forms of genomic DNA sequence, regardless of the frequency at which it occurs, non-DNA polynucleotides such as RNA, and non-naturally occurring DNA sequences that code, either directly or indirectly for a naturally occurring expression products, including wild-type or mutant proteins, e.g., cDNA molecules or synthetic, chemically synthesized genes. My definition of human gene patents excludes patents that claim biotechnology methods and reagents of general applicability which are not directed to a specific genetic sequences, as well as patents claiming proteins.

V. Search methodology

I searched Lexis and Westlaw databases to identify any patent infringement suit involving a human gene patent, including declaratory judgment actions filed by a plaintiff

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[96] For example, one patent in the database is U.S. Patent No. 7,211,789, assigned to IBM, which is directed to methodology generally useful for manipulating molecules. Although the patent describes use of the invention on biological molecules like proteins and DNA, the invention is not DNA specific and has nothing to do with a gene.

[97] *Inverness Med. Switz. Gmbh v. Princeton Biomeditech Corp.*, 309 F.3d 1365, 1371 (Fed. Cir. 2002) (stating that being one's own lexicographer is an approved practice under U.S. patent law).

alleging a reasonable apprehension of being sued for infringement.[98] In cases where multiple lawsuits were filed involving the same parties, the same patent(s), and the same general allegation of infringement, I sometimes consolidated the lawsuits and treated them as a single "litigation."[99] Patent-related lawsuits that do not involve an allegation of infringement, such as appeals of interference decisions or disputes over inventorship, were not considered in this study. Most searches were conducted in April of 2007.

My primary searches were conducted in a Lexis databases which contains all U.S. utility and reissue patents.[100] I began by using a strategy based on the Jensen/Murray approach, searching for any patent that included the term "SEQ ID NO" in the claims, and with respect to which notice of litigation had been filed with the patent office.[101] This search was designed to identify any patent in the Jensen/Murray database with respect to which a complaint had been filed. The Lexis search failed to identify two litigations involving patents in the Jensen/Murray database, which I only discovered by performing an independent search of a Westlaw database.[102] In one case, this was because the Lexis database did not include the text of the patent, and so the SEQ ID NO language in the claims was not picked up by my query. In the other case, the patent litigation was missed because Lexis's records for the litigated patents did not include a notice of litigation. The first case clearly involved an error on the part of Lexis. Regarding the second case, it is unclear why the Lexis record contained no notice of litigation. There are three potential points where the error might have occurred: the District Court might have failed to comply with the requirement that it send notice to the patent office as required by law; the patent office might have either not received the notice, lost the notice, or failed to inform Lexis of the notice; or it could simply have been an error on the part of Lexis, similar to the omission of the patent text in the other case. [103]

I then conducted a second, more comprehensive search of the same Lexis patent databases, this time looking for any patent with respect to which a notice of litigation had been filed and the claims or abstract included any one of the many terms used in collecting patents for the Georgetown DNA patent database.[104] This search resulted in

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98 The filing of a declaratory judgment action is typically followed by the patent owner suing for infringement, and in any event the fact that the declaratory judgment plaintiff felt sufficiently threatened to bring suit is indicative of patent impact.

99 This would be the case, for example, when a patent owner responds to a declaratory judgment by filing an infringement lawsuit (e.g., Alzheimer's Institute of America), or when a defendant to an infringement suit retaliates by suing its antagonist for infringement of a patent relating to the same general subject matter (e.g.,the lawsuits filed by Oncormed and Myriad against each other).

100 Lexis File-names UTIL and REISS, respectively.

101 Under 35 USC ??, courts are required to provide notice to the US patent office within one month of any complaint being filed with respect to a US patent. Searched databases for any patent including the terms "SEQ ID NO" or "sequence ID" in the claims. I found two patents that incorrectly used "sequence ID" instead of "SEQ ID."

102 infra

103 I talked to a technical representative at Lexis, and she could not explain why notice of litigation was not present with these patents.

104 Searched claims and abstract for appearance of any of the following terms: antisense or cDNA or centromere or deoxyoligonucleotide or deoxyribonucleic or deoxyribonucleotide or DNA or exon or gene or genetic or genome or genomic or genotype or haplotype or intron or mtDNA or nucleic or nucleotide or oligonucleotide or oligodeoxynucleotide or oligoribonucleotide or plasmid or polymorphism or

many more hits, but again I found that certain patents that had been the subject of litigation did not include a notice of the litigation in the Lexis patent file. In particular, I observed a number of instances where a complaint was filed asserting multiple patents and some of those patents had the notice of litigation in the Lexis file but others did not.[105] Again, it is not clear whether this is because the courts did not notify the patent office of all the asserted patents, or if this reflects an error on the part of the patent office and/or Lexis. However, the omission is not fatal so long as at least one of the asserted patents bears the notice of litigation, since I can usually access the complaint via PACER or by other miscellaneous means) and from there identify other patents involved in the litigation.

More troubling were two litigations I identified where the Lexis records for all of the asserted patents failed to include a notice of litigation – I would have missed these litigations if I had not been able to identify them by other means. In one case I identified the litigation by means of an independent Westlaw search. The other case was Amgen v. Chugai, a case which resulted in a famous Federal Circuit decision which I was already familiar with.

The fact that certain patent entries in the Lexis database are missing specifications or do not provide notice of litigation means that I cannot assume that my Lexis queries identified all human gene patent litigations. Clearly they did not, as exemplified by the two cases I found by different means. With respect to the problem of omitted specifications, I believe that this is an error that occurs relatively infrequently, based on my own previous experience using the Lexis database on numerous occasions without ever seeing such an omission. In an attempt to assess the frequency at which Lexis patent records are deficient for failing to include notice of litigation, I queried the database for any patent having a patent number in the range of 5,300,000 to 6,300,000 bearing a notice of litigation in the Lexis database.[106] The search resulted in 10,674 hits. It has previously been estimated that about 1-2% of issued patent are litigated,[107] which closely approximates my finding that approximately 1.07 % of these million patents have been litigated, and suggests that although there are omissions in the Lexis database they probably occur relatively infrequently.[108]

I also conducted a search for any reported judicial decision involving a human gene patent, by querying the Lexis Combined Federal Court Cases database for any decision containing in the opinion one of the DNA Patent Database terms, and containing

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polynucleotide or polyribonucleotide or ribonucleotide or ribonucleic or "recombinant DNA" or RNA or mRNA or rRNA or siRNA or snRNA or tRNA or ribonucleoprotein or hnRNP or snRNP or SNP

[105] One example would be Regent of UC v Lilly, where only one of two asserted patents included Notice of Litigation in the Lexis database. 4,652,525 (No), 4,431,740 (Yes)

[106] This is approximately the range of the first million patents represented in the Murray and Jensen database, which extends from 5,324,638 to 6,919,077.

[107] Valuable patents, Lemley Allison, n. 7. Lemley, Rational Ignorance, 95 NW. U.L.Rev. 1495, 1501 (2001).

[108] It would be interesting at some point to more thoroughly assess the extent of the problems with the Lexis database.

within the opinion a sentence including the word "patent" and some form of the word "infringe."[109]

I supplemented my Lexis search by querying Westlaw's "Intellectual Property Docket Summaries" database, which contains docket header and intellectual property information from patent and trademark lawsuits filed in the U.S. District Courts beginning 2 January 2003. In one Westlaw query I searched for any of the 4271 patents appearing in the Jensen/Murray database with respect to which a complaint had been filed. The other query searched for any patent containing any of the DNA Patent Database terms in the abstract. Note that my Lexis searches queried the claims, not patent abstracts, and this was the approach taken by Murray and Jensen and by the curators of the DNA Patent Database database. Searching claims is preferable to searching abstracts, but unfortunately Westlaw only allows for searches of the patent number, patent classification, and abstract fields.[110] However, the list of search terms I employed is quite expansive, and it seems likely that most if not all human gene patents would include at least one of these terms in their abstract.

In all cases identified in the searches, the complaint, asserted patents and/or reported decision were analyzed to the extent necessary to determine the nature of the action and whether it involved a human gene patent.[111] This was necessary for a variety of reasons, including the fact that on a number of occasions I found that litigations that were identified in the database as patent infringement litigations actually were not. For example, I found interference appeals, inventorship disputes, and trade secret actions all erroneously characterized as infringement litigations in the commercial databases.[112] I have also found that it is impossible to determine whether a patent is a human gene patent without actually reading and analyzing the claims.

Although I make no representation that this combination of searches identified every human gene patent litigation, and I suspect I missed a few, I believe that I did identify the majority of human gene patents litigations, particularly those that resulted in a reported decision. The existence of a few more patents and litigations that were not uncovered here would probably not substantially alter the conclusions and policy implications that flow from the study.

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[109] [get name of Lexis database] The following were the search terms used. OPINION(antisense or cDNA or centromere or deoxyoligonucleotide or deoxyribonucleic or deoxyribonucleotide or DNA or exon or gene or genetic or genome or genomic or genotype or haplotype or intron or mtDNA or nucleic or nucleotide or oligonucleotide or oligodeoxynucleotide or oligoribonucleotide or plasmid or polymorphism or polynucleotide or polyribonucleotide or ribonucleotide or ribonucleic or "recombinant DNA" or RNA or mRNA or rRNA or siRNA or snRNA or tRNA or ribonucleoprotein or hnRNP or snRNP or SNP) and OPINION (patent w/s infring!)

[110] As noted by the Lemley and others, the patent classification system is problematic and I decided not to use it for searching for gene patents.

[111] Complaints, motion, unreported rulings, and the like were accessed primarily via PACER, but sometimes were obtained from other sources. PACER is a great resource for this type of research, but unfortunately some courts do not post their documents. In such cases I must rely on other means to obtain access to the desired information., such as press releases and SEC filings, or by obtaining documents directly from the litigating parties.

[112] Examples: PROCTOR v. TRANSKARYOTIC, ET AL, inventorship, Univ Mi Regents, et al v. Bristol Myers Squibb, Filed August 17, 2000, D.C. E.D. Michigan, Doc. No. 2:00cv73690, inventorship.

VI. Results broken down by context of alleged infringement

At the outset of this study, I anticipated that the sorts of activities that might lead to an allegation of infringement of a human gene patent would fall into four general categories: (1) recombinant production of human therapeutic proteins;[113] (2) research tools; (3) genetic testing products and services; and (4) gene therapy. The results of the study confirm that all human gene patent litigation has involved one of the first three categories of allegedly infringing activity – none involved gene therapy.[114] In this section I summarize the results of the study, broken down into the three categories of protein therapeutics, research tools and genetic testing.

A. Therapeutic Proteins

The biotechnology industry essentially arose out of the development of methodologies in the 1970s and early 1980s which allowed for the cloning of human genes, the insertion of those genes into bacterial or cell culture, and the over-expression of the gene to produce large quantities of recombinant human proteins for use as therapeutics.[115] These recombinant human protein therapeutics, often referred to as biologics, were the first important products of biotechnology, and continue to be its most lucrative. Thus, it should come as no surprise that the earliest human gene patent litigations all involved an allegation of infringement relating to the commercial production and sale of a recombinant therapeutic protein encoded by the patented gene. In particular, pioneering biotechnology products comprising recombinant human insulin,[116] human growth hormone (hGH),[117] tissue plasminogen activator (t-PA),[118] and erythropoietin (EPO)[119] have all been the subject of substantial patent litigation involving human gene patents.[120]

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[113] Recombinant therapeutic proteins are often referred to as biologics.

[114] The finding that no lawsuits have been filed alleging infringement of a human gene patents in the context of gene therapy is not surprising, since the technology has been disappointingly slow to mature and has yet to emerge from clinical testing is a viable non-experimental course of treatment.

[115] [BIO website should have info]

[116] *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559 (Fed. Cir. 1997)

[117] *Bio-Technology Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 38 USPQ2d 1321 (Fed.Cir.1996) and 267 F.3d 1325, 60 U.S.P.Q.2d 1430, C.A.Fed. (N.Y.), September 27, 2001), *Novo Nordisk v. Genentech*, 77 F.3d 1364 (Fed. Cir. 1996), *Genentech v. Eli Lilly & Co.*, 998 F.2d 931 (Fed. Cir. 1993), *Genentech, Inc. v. Regents of University of California*,143 F.3d 1446 (Fed. Cir. 1998),

[118] *Genentech, Inc. v. Wellcome Foundation Ltd.*, 29 F.3d 1555 (Fed. Cir. 1994).

[119] *Amgen v. Chugai*, 927 F.2d 1200 (Fed. Cir. 1991), *Amgen v. Roche*, 2007 WL 942104, *Amgen v. HMR*, 457 F.3d 1293 (Fed. Cir 2006), *Amgen, Inc. v. Genetics Institute, Inc.*, 98 F.3d 1328 (Fed. Cir. 2006), *Amgen, Inc. v. Elanex Pharmaceuticals, Inc.*, 1996 WL 84590 (W.D.Wash. 1996)

[120] Note that patent litigation involving recombinant therapeutic proteins typically involves the innovator biotechnology company asserting multiple patents relating to the product or the processes and regions used to produce the product. These include human gene patents, and also oftentimes other patents covering the product directly or other technology used in the production of the product. [Example is Amgen v. HMR]. See for examples Zymogenetics v. BMS (D.C. Delaware, Doc. No. 1:06cv500) and Zymogenetics v. Immunex (D.C.W.D. Washington, Doc. No. C02-561R), cases where biologic drugs Enbrel and Abatacept were alleged to infringe patents generically claiming certain dimerized polypeptide fusions.

To this day a substantial majority of human gene patent litigations involve an allegation of infringement based on the recombinant production of a therapeutic protein. In particular, recombinant products comprising interferon-α (IFN- α),[121] α-galactosidase A,[122] interferon-β (IFN-β),[123] insulin-like growth factor (IGF-1),[124] IGF binding protein-3 (IGFBP-3),[125] and follicle stimulating hormone (FSH)[126] have all been the subject of human gene patent infringement suits. A number of these cases are still pending, many have settled, while others have resulted in some of the seminal Federal Circuit decisions relating to biotechnology patents.[127] Note that these products are proteins, not polynucleotides, so they are not directly claimed by gene patents. However, the proteins are produced by recombinant expression of the corresponding human gene, and the lawsuits are all based on allegations that a human gene patent has been infringed by the reagents and/or methods used in the production process. Much of the patent litigation brought with respect to protein therapeutics involved patents that are not human gene patents, but rather patents directed to the protein product itself,[128] or to genetic methods and reagents of general applicability, i.e., methods and reagents not restricted to a specific gene.[129] Nevertheless, human gene patents have clearly played an important role in attempts by biotechnology companies to maintain market exclusivity for innovative products.

Human gene patent infringement litigations involving protein therapeutics tend to be vigorously contested, often resulting in full trials and appellate decisions. This is in direct contrast with human gene patent litigations relating to genetic testing and research tools, which tend to settle at an early stage.[130] Still, I was only able to identify one therapeutic protein with respect to which a human gene patent was enforced to a final, unappealable judgment that found the patent valid and infringed. That protein is EPO, one of the earliest biotechnology success stories and the first blockbuster product for Amgen, the world's largest biotechnology company.

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121 *Schering v. Amgen*, 222 F.3d 1347 (Fed. Cir. 2000), *Schering v. v. Interferon Sciences, Inc.* Docket #: CA 89-131 (D.C Del.).

122 *Genzyme v. TKT*, 346 F.3d 1094 (Fed. Cir. 2003)

123 *Biogen v. Berlex*, 318 F.3d 1132 (Fed. Cir. 2003)

124 Genentech v. Insmed (IGF-1 in prokaryotes) (cite)

125 Genentech v. Insmed (IGF-1 in prokaryotes) (cite)

126 *Ares-Serono, Inc. v. Organon Intern. B.V.*, 160 F.R.D. 1 (D.Mass.,1994).

127 For example, UC v. Lilly (written description), Amgen v. Chugai (enablement) and Genentech v. Wellcome (doctrine of equivalents).

128 For example, *Genentech v. Boehringer Mannheim*, 47 F. Supp.2d 91 (D. Mass. 1991) (patents claiming general methodology for expressing "quasi-synthetic" genes in microbes, methods of solubilizing the protein in pharmaceutical compositions, and general methods of purifying proteins); *Genentech v. Amgen*, 289 F.3d 761 (Fed. Cir. 2002 (patents claiming recombinant DNA technology of general applicability); and *Novo Nordisk Pharmaceuticals, Inc. v. Bio-Technology General Corp.*, 2004 WL 1739720 (D. Del. 2004)(patent claiming the recombinant protein)[get appellate decision].

129 For example, Genentech sued Amgen for allegedly infringing some patents directed to general used by Amgen in the production of Neupogen. [Amgen settled for $47 million, find cite]

130 infra

Amgen's first successful human gene patent enforcement effort involved its US patent No. 4,703,008, which includes claims directed to any "purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin," as well as any "procaryotic or eucaryotic host cell transformed or transfected with [the claimed DNA sequence] in a manner allowing the host cell to express erythropoietin." These claims are unusually broad, purporting to cover any DNA sequence encoding human EPO, including not only the commercially relevant cDNA, but also genomic DNA (i.e., the sequence including introns), and chemically synthesized DNA. [131] The court found that the claims were infringed by defendant Genetics Institute, presumably by its use of the native human erythropoietin cDNA sequence in the production of cells capable of expressing native human erythropoietin.[132] The court rejected challenges to the validity and enforceability of the infringed claims based on allegations of lack of priority, obviousness, failure to disclose best mode, and inequitable conduct in the prosecution of the patent.[133]

Note that while Amgen's claims are quite broad, they are potentially susceptible to circumvention in a variety of ways, and thus fall far short of precluding any substantial and beneficial use of the gene by others. For example, the claims would probably not prevent a competitor from using a modified version of the human erythropoietin gene to produce a non-naturally occurring, genetically engineered variant of erythropoietin. While early efforts of biotechnology were often directed to simply making a recombinant version of a naturally occurring protein, it has become increasingly common to make modified versions of human proteins with enhanced function relative to the natural protein. Amgen itself followed up its pioneering erythropoietin product with a second-generation modified version of the protein with superior therapeutic properties.[134]

In fact, Amgen's '008 patent included a claim 7 that sought to encompass such modified versions of the native erythropoietin gene, covering all possible DNA sequences that would encode any polypeptide having an amino acid sequence "sufficiently duplicative" of erythropoietin (EPO) to possess the property of increasing production of red blood cells. However, the Federal Circuit invalidated this claim in *Chugai* for lack of enablement, essentially for overbreadth relative to the patent's disclosure. Although an attempt to design around the claims by introducing trivial modifications into the native EPO sequence might well have been found to infringe the patents narrower but valid

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[131] US Patent No. 4,703,008, claim 2.asserted in 706 F.Supp. 94. Note that at the time of the invention chemical synthesis of the full length gene was probably not practically feasible, but would be today by companies such as DNA 2.0.

[132] The inference that GI expressed native human is supported by statements in the district court decision. For example, the court found that GI "had not produced any evidence disputing that it has infringed the claims of the '008 patent, and appears not to contest infringement in any of the post-trial memoranda." The court also warned that GI would not be able to avoid infringement under the Doctrine of Equivalents "by means of insignificant deletions, additions or substitutions of amino acids to the EPO protein which have no substantial effect on the biological activity of EPO," implying that GI had not made such alterations.

[133] The same patent was also successfully asserted against Elanex for activities relating to efforts to produce recombinant EPO to be marketed in Europe. *Amgen, Inc. v. Elanex Pharmaceuticals*, 1996 WL 84590.

[134] ARANESP

claims under the Doctrine of Equivalents, a second generation EPO with substantially modified function would probably have avoided both literal and equivalent infringement.

Amgen's success in cloning and recombinantly expressing EPO was a significant breakthrough because it allowed for the creation of cell lines that could be grown in culture to produce therapeutic quantities of human erythropoietin. However, its patent would probably not encompass the creation of functionally equivalent cells (i.e., cells that could be grown in culture to express high levels of EPO) by means that did not involve the use of an isolated EPO gene or the introduction of the EPO gene into a foreign host cell. At the time Amgen filed its patent application in 1983,[135] the only known technologies for overexpressing a human gene required isolation of the gene and/or introduction of the gene into a foreign cell, so Amgen's patent probably provided effective coverage for any practical method for producing a competing recombinant EPO. However, in the early 1990's technology known as "gene activation" was developed by a company called Transkaryotic Technologies (TKT). Gene activation provides an alternate technology for the production of a human cell line expressing large quantities of a desired protein which does not involve isolating the corresponding gene, or introducing the gene into a foreign host cell. Instead, gene activation entails modifying the regulatory region controlling the expression of a targeted gene to increase the expression levels of a gene in the cell in which the gene naturally reside. In other words, while the traditional technology involved the over-expression of an ***exogenous*** gene in a foreign host cell, gene activation allows for the over-expression of an ***endogenous*** gene in a native host cell.[136]

Amgen likely became aware of the vulnerability of its original EPO patents to circumvention by gene activation when that technology became known in the early 1990s, and responded by making strategic use (some might characterize it as misuse) of the current liberal continuation rules to secure patents literally encompassing gene activation.[137] In particular, in 1995 it filed two divisional applications claiming priority to the 1984 patent application which had already resulted in the 1987 issuance of the '008 patent (successfully asserted in Chugai). These applications resulted in the issuance of U.S. Patent Nos. 5618698 and 5756349, which essentially claim vertebrates cells that express a human EPO gene under the regulation of a non-human promoter, or that contain amplified DNA encoding human EPO, as well as processes for using these cells to produce EPO. These broad claims not only encompass the traditional methodology used by Amgen to express an exogenous human EPO gene in a mammalian cell, but also gene activation technology, which generally relies on the use of non-human viral promoters[138] and results in gene amplification.[139] Amgen's patent clearly does not enable the expression of erythropoietin by gene activation technology, since it was filed years before the development of that technology,[140] which might strike some as odd.

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135 US patent No. 4,703,008 claims priority to a 1983 application.

136 The distinction between the expression of exogenous and endogenous genes was to prove crucial in subsequent litigations, particularly Amgen v. HMR and Genzyme v. TKT.

137 4,703,008, asserted in Chugai, and 5,441,868.

138 *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, at 1299 (2006).

139 *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 339 F. Supp. 2d 202, at 282 (2004).

140 Id., at 290, n.110 ("it is undisputed that endogenous activation technology and homologous recombination were unknown to those skilled in the art when Amgen filed its patent application in 1983-84.").

However, the law is clear that a broad genus claim can satisfy the enablement requirement even if it encompasses non-enabled species, particularly when those species are only made possible by technology developed subsequent to the patent filing date.[141]

Amgen's strategic foresight paid off later when TKT and its partner HMS (referred to herein jointly as "TKT") sought to market a recombinant version of human EPO produced via gene activation technology. TKT's process likely would not have been found to infringe the '008 patent, because gene activation does not require the use of an isolated EPO gene, nor the introduction of the EPO gene into a foreign host cell by transformation or transfection, key elements of the claims found to be infringed in *Chugai*.[142] However, the Federal Circuit found both patents valid and infringed by TKT, whose processes nevertheless involve the use of non-human promoter and amplification of the EPO gene.[143]

Note the critical role that patents have played in providing Amgen with an intellectual property position with respect to its groundbreaking achievement in making recombinant EPO available as a practical therapeutic. Although the product is a protein, patent coverage for the molecule per se was unavailable because the protein had long been known and the native protein had previously been isolated and purified from natural sources, in particular human urine. Amgen was able to obtain patents that sought to distinguish and specifically claim recombinant EPO, and pharmaceutical compositions comprising recombinant EPO, but so far has been unsuccessful in attempts to assert these patents. For example, three such patents were asserted against TKT, one was found invalid, another not infringed, and a third might well be found invalid after a recent claim construction ruling by the Federal Circuit adverse to Amgen and a subsequent denial of certiorari by the Supreme Court.

To better appreciate the difficulty Amgen has had in attempting to protect EPO by patents directly covering the product, and the consequent importance of its gene patents, it is informative to review the specific setbacks Amgen has experienced. The Federal Circuit first held that U.S patent No. 5,547,933, which claims non-naturally occurring EPO "having glycosylation which differs from that of human urinary erythropoietin," invalid under 112, p2 as indefinite for failing to adequately define how one could determine the glycosylation of human urinary erythropoietin.[144] The court cited Amgen experiments which showed that the glycosylation of human urinary EPO varied from patient to patient and depended upon the specific purification process used, as well as the specific method used to assay for glycosylation, rendering Amgen's claims "insolubly ambiguous."[145]

Another patent asserted by Amgen, 5,621,080, claims isolated EPO that "is not isolated from human urine" and which comprises the 166 amino acid sequence of EPO as disclosed in the patent specification. Unfortunately for Amgen, subsequent studies showed that while the disclosed amino acid sequence was correct in that it corresponded to EPO as it was first expressed in the cell, prior to the secretion of the protein from a cell

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141 Chiron v. Genentech.

142 Likewise, another Amgen patent 5,441,868 was also inapplicable for requiring transformation or transfection of the EPO gene into a foreign host cell.

143 *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006) (Amgen IV). a final judgment since TKT apparently has not appealed to the Supreme Court.

144 *Amgen Inc. v. Hoechst Marion Roussel*, 314 F.3d 1313, at 1340-42

145 Id.

the terminal amino acid is removed, resulting in a final product of 165 amino acids in length. The claim was not literally infringed by TKT's 165 amino acid product. Furthermore, the Federal Circuit held that the product was not infringed under the doctrine of equivalents. [146] The claim had been amended during prosecution and the Federal Circuit, applying *Festo*, found that the 165 amino acid product was a foreseeable equivalent at the time of amendment and that the amendment was more than merely tangential to the alleged equivalent.[147]

The third Amgen product patent, 5,955,422, claims a pharmaceutical composition comprising a "therapeutically effective amount" of human erythropoietin "purified from mammalian cells grown in culture." The Federal Circuit has interpreted the term "therapeutically effective amount" to essentially encompass any purified EPO capable of eliciting a biological response – Amgen had argued for a narrower interpretation it apparently believed would help distinguish over the prior art.[148] Upon remand, the district court will have to decide whether the asserted claim is anticipated by prior art which describes purified forms of EPO allegedly able to elicit such a response, albeit arguably not able to elicit a true therapeutic effect, at least as Amgen would define the term. Amgen's attempt to define "therapeutically effective amount" more narrowly was thwarted by language in the specification which the Federal Circuit interpreted as requiring the broader definition of the term asserted by TKT.[149]

The Amgen EPO patent saga is far from over, and a new chapter might be just beginning. Roche has begun producing a pegylated version of EPO (peg-EPO) and importing it into the U.S., and Amgen has sued alleging infringement of a total of six patents, including the two human gene patents successfully asserted against TKT and another previously unasserted gene patent claiming methods of producing recombinant EPO from cells transfected or transformed with an EPO-encoding gene.[150] The extraterritorial production of the protein and the modification of the protein by peglation prior to importation into the US raise some interesting issues with respect to the susceptibility of human gene patents to circumvention by off-shoring production. In general, US patents are not infringed by activities occurring outside the US. For example, Roche's production and use of recombinant cells expressing endogenous erythropoietin might well constitute infringement of Amgen's 5,756,349 patent covering vertebrate cells if these activities were conducted in the US, but by off-shoring the activity this human gene patent should not be an issue (although Amgen has asserted it). However, the other two Amgen gene patents cover processes for expressing recombinant EPO,[151] and under 35 USC 271(g) the importation of product made outside the US by a patented process can constitute patent infringement, unless it has been "materially changed by subsequent processes" or become a "trivial and nonessential component of another product." It has been reported that the Roche product comprises the amino acid sequence of native human EPO, in which case infringement under 271(g) would appear likely with respect to the

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146 *Amgen Inc. v. Hoechst Marion Roussel,* 457 F.3d at 1313-16. (Supreme Court denied cert on this issue).

147 Id.

148 1300-02.

149 Id.

150 5,441,868

151 5,441,868 and 5618698.

two human gene patents found valid and infringed in HMR. However, Roche might be counting on the 271(g) exception for "materially changed" products. Clearly Amgen is concerned with this possibility – in its complaint, is specifically alleges that 'the addition of PEG to glycosylated human EPO does not materially change" the EPO. However, PEG is generally known to alter the therapeutic properties of proteins, for example by increasing their half-life, and Roche has specifically touted the superior characteristics resulting from pegylation of EPO. At some point liability might depend upon a court's perception of the materiality of the change. In any event, the case illustrates a recurring theme of this study, which is the limited ability of gene patents to block beneficial uses of human genes.

The Amgen EPO cases provide the only examples of final judicial determinations that I could identify where in a valid human gene patent has been infringed, but there have been cases where the parties have stipulated that an asserted human gene patent was valid and infringed as part of a settlement entered into subsequent to a district court decision, with the alleged infringer forgoing an opportunity to appeal. For example, Terrica and Insmed recently settled a lawsuit alleging that Insmed's IPLEX product, which comprises a combination of IGF-1 and IGFBP-3, infringed human gene patents relating to the IGF-1 and IGFBP-3 genes.[152] A district court ruled that the patents were valid and infringed by Insmed's product, and instead of appealing the decision Insmed agreed to stipulate that the patents were valid and infringed. Terrica alleged that IPLEX competed directly with its product Increlex, which comprises free IGF-1 but not IGFBP-3. Pursuant to the agreement, Insmed agreed to terminate marketing of the product for certain indications, but is allowed freedom to operate regarding other indications.

Let us consider the scope of the human gene patents that were at issue in *Genentech v. Insmed*. The patent claiming the IGF-1 gene, 6,331,414, is relatively narrow, being limited to processes for producing recombinant IGF-1 in prokaryotic cells. As noted by Terrica, the patent could have probably been designed around by producing the protein in a non-prokaryotic cell, such as the mammalian cells used by Amgen and its would-be competitors in the EPO market. For some reason, Insmed chose to use a prokaryotic expression system, perhaps to facilitate FDA approval by creating a product more similar to Terrica's pioneering product.

Terrica's IGFBP-3 gene patent, 5258287, is substantially broader and claims isolated DNA molecules encoding IGFBP-3, as well as DNA molecules sharing some degree of structural and functional similarity with native IGFBP-3, including both naturally occurring and non-natural genetic sequences. It also encompasses expression vectors including the sequence, any cell modified transformed with the sequence, and methods of producing the protein by expressing these cells. The broad coverage of sequence variants was accomplished by means of a hybridization claim, a standard form of polynucleotide claim that encompasses not only a single reference sequence, but also a huge number of related sequences sharing sufficient similarity to hybridize to the reference sequence.[153] In this case, the reference sequence was an actual IGFBP-3 encoding sequence disclosed in the patent specification. If the claims had been limited to

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[152] The patents are owned by Genentech, Insmed is the exclusive licensee.

[153] LAST paper

this particular sequence Insmed might well have been able to avoid it, but the court found that the variant sequence they used did hybridize to the reference sequence and hence infringed the patent. While this patent is relatively broad, it also probably could have been designed around, for example by use of gene activation technology. Alternatively, Terrica posited that the patent could have been designed around by using an alternate IGF binding protein such as IGFBP-5 to achieve the same function as IGFBP-3.

A similar settlement occurred in Bio-technology General Corp. v. Genentech, a case brought by Genentech to block Bio-technology General's from marketing a competing recombinant human growth hormone product. The claims of the patent asserted by Genentech appear to be relatively narrow, limited to certain specified method of expressing human growth hormone in microbes.[154] After the Federal Circuit reversed a district court determination that the patent was invalid and remanded on the issue of infringement, Bio-technology agreed to a stipulated final judgment and permanent injunction. Although it appears likely that Bio-technology would have been found liable for infringement in this case, the relatively narrow scope of claim coverage would have been susceptible to design around, for example by expressing the protein in insect, plant or mammalian cells, or even in microbes by means of alternate genetic engineering techniques. For example, in another Federal Circuit decision involving the same patent the court held that the claims were limited to direct expression of human growth hormone and were not infringed by a process that involved expression of the protein in the form of a fusion.[155] As described in more detail below, the technology for recombniantly expressing a human protein in bacteria as a fusion has been known since the early days of biotechnology, and often is a superior methodology than the direct expression claimed by this Genentech patent.[156]

There are several examples where a human gene patent has been asserted in the context of a therapeutic protein, and prior to any definitive determination on the merits of the case the alleged infringer has agreed to a settlement requiring substantial payment to the patent owner. In some cases, the settlement occurred at a point where it appears likely the patent owner would have ultimately prevailed. For example, in 1999 Genentech agreed to pay the University of California $200 million to settle a lawsuit involving a UC patent claiming certain DNA vectors encoding human growth hormone after a six-week trial that resulted in a deadlocked jury.[157] Eight of the nine jurors found that the university's patent no. 4,363,877 had been infringed, but a unanimous verdict was required, so the case was set for retrial at the point when the parties settled.[158] At the time, the settlement was described as the largest patent settlement ever in the context of biotechnology.[159] Pursuant to the settlement Genentech was able to stay on the market with its human growth hormore product.

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154 4601980

155 infra

156 Novo v Genentech

157 http://www.secinfo.com/d9N9s.5d.8.htm

158 http://www.nature.com/nature/journal/v402/n6760/full/402335b0.html. see Nature 399, 512; 1999

159 Id.

In other cases, the alleged infringer agrees to make substantial settlement payments even though it appears to have a good chance of prevailing on the merits. For example, in Biogen v. Berlex the parties settled the case while it was on appeal to the Federal Circuit. The case involved a very narrow human gene patent limited to certain methods of expressing IFN-beta in chinese hamster ovary (CHO) cells.[160] Pursuant to the settlement, the alleged infringer Biogen agreed to pay Berlex $20 million upfront and an additional $55 million if the appellate court remanded the case to the District Court for any reason. Ultimately, the Federal Circuit's decision was generally favorable to Biogen, holding that Biogen did not literally infringe but remanding the case to the district court for a determination under the doctrine of equivalents.[161] Under the settlement, Biogen was able to stay on the market with its product, and the $75 million might have been considered a small price to pay to avoid the expense and uncertainty of pursuing the litigation.

In a dispute between Ares-Serono and Organon, Ares-Serono alleged that Organon's importation of recombinant follicle stimulating hormone (FSH) infringed its US Patent No. 4923805, which claimed vectors comprising a genetic sequence encoding FSH and methods of producing recombinant FSH in mammalian cells containing such a vector. After the district court rejected Organon's motion for summary judgment and held that the evidence raised genuine issue of material fact as to whether alleged infringers' importation of hormone into United States was sufficiently significant to be infringing,[162] the parties settled under terms granting Organon a non-exclusive license to use the patented technology.[163] Ares-Serono and Organon both ultimately entered the US market with recombinant FSH products.[164]

In some cases, a human gene patent owner and an alleged infringer marketing a therapeutic protein have settled early in the litigation, prior to any substantive rulings. For example, Novo Nordisk and Genentech settled a litigation involving Genentech's alleged infringement of a relatively narrow human gene patent[165] covering certain methods of expressing recombinant human growth hormone immediately subsequent to Genentech filing an answer to the complaint.[166] Genentech remained on the market with its recombinant human growth hormone.

More often than not, human gene patent cases that do not settle are ultimately decided against the patent owner, with the asserted claims adjudged invalid and/or not infringed. For example, asserted human gene patent claims have been found invalid in cases where the patent owner sought broad claim coverage exceeding the scope of a relatively limited disclosure. As discussed above, in *Amgen v. Chugai* the Federal Circuit

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160 infra

161 The parties had not even briefed the issue of equivalent infringement, believing that Berlex was totally foreclosed from asserting infringement under the doctrine of equivalents by the Federal Circuit's en banc *Festo* decision. However, the Supreme Court's reversal of Festo compelled the Federal Circuit to at least provide Berlex with the opportunity to argue for equivalent infringement.

162 862 F.Supp. 603, 615 (D. Mass. 1994).

163 http://www.market-research-report.com/datamonitor/lsa_deals.pdf.

164 http://www.shire.com/shire/uploads/reports/12003AR.pdf.

165 5,618,697

166 **Novo** Nordisk of North America, Inc., et al v. **Genentech,** Inc., et al, Filed Oct. 6, 1997, D.C. New Jersey (Trenton), Doc. No. 97-4848.

held that claims covering functional variants of the disclosed human EPO gene were invalid for failing to adequately enable the full scope of the claim. In *UC v. Eli Lilly*, the Federal Circuit invalidated claims purporting to encompass the cDNA encoding human insulin for failure to comply with the written description requirement. The court found that the patent specification's disclosure of the rat insulin cDNA did not adequately demonstrate possession of human or other mammalian insulin cDNAs.

In a number of cases an alleged infringer have been able to escape liability by successfully arguing that its processes do not infringe the asserted patent, i.e., the patent has been successfully designed around. For example, TKT was able to successfully avoid Genzyme's patent relating to the recombinant expression of human α-galactosidase A by employing a, alternate, later-developed technology to express the same gene.[167] At the time Genzyme filed its patent application, the only practical technologies available for expressing a human gene in mammalian cell culture involved removing the human gene from a cell in which it is naturally expressed, introducing the gene into a foreign host cell, and then expressing the gene in the foreign host cell.[168] TKT used "gene activation" to express the gene, a technology that was apparently developed around the time Genzyme filed its patent application but was not public knowledge at that time.[169] The traditional technology and the later developed gene activation technology both resulted in the production of large amounts of the desired protein in cultured mammalian cells, but the traditional technology involved the expression of an "exogenous" gene, while with gene activation the expressed gene is "endogenous" to the cultured cell. The Federal Circuit held that Genzyme's claims were limited to methods of expressing exogenous genes, and that TKT's process for expressing an enodgenous α-galactosidase A gene did not infringe Genzyme's patent.[170]

In a similar manner, Biogen was able to avoid literal infringement of Berlex's patent covering the recombinant expression of human interferon in Chinese hamster ovary (CHO) cells.[171] The patent describes genetic constructs and expression methodologies employing what the court referred to as "linked co-transformation." In contrast, the Biogen process involved "unlinked co-transformation." The court construed the claims as limited to linked co-transformation, and hence not literally infringed by the Biogen's process.[172] The court did leave open the possibility for a finding of infringement under the Doctrine of Equivalants, but the parties settled prior to any determination regarding equivalence.

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167 *Genzyme v. TKT*, 346 F.3d 1094 (Fed. Cir 2003).

168 Supra discussion of *Amgen v. HMR*.

169 Genzyme's patent had a filing date of Oct 24, 1990. The gene activation technology employed by TKT is claimed in TKT patents having 1991 priority dates (5,641,670, 5,968,502, and 5,733,761), and in more general terms in a 5,272,071 which claims priority to December 22, 1989. None of these patent applications would have published prior to 1991.

170 Under the trade name Replagal. Although they market Replagal in Europe and other parts of the world, they failed to get FDA approval and do not sell the drug in the US. They were kept off the US market by the Orphan Drug act, presumably could not show either superior safety or efficacy. *TKT to End Efforts to Seek U.S. Approval of Replagal*, http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/01-12-2004/0002087878&EDATE (Jan. 12, 2003).

171 [Describe CHO cells]

172 As discussed above, pursuant to an earlier settlement agreement, the parties did not pursue the case at the district court level, so the question of equivalent infringement was never decided.

There have been a number of cases where a patent claim directed to methods or systems for expressing a human gene have been avoided by expressing the protein as a fusion protein. Essentially, a fusion protein is a genetically modified, non-naturally occurring protein that is formed by fusing together two protein sequences. This is accomplished by engineering an artificial gene encoding the fusion protein, typically by fusing the two coding sequences together in a single gene and expressing the gene in a host cell. Adding a fusion sequence to the protein can have a number of practical benefits that facilitate the expression and purification of the desired protein, particularly when a human gene is expressed in a bacterial cell. In many cases the additional sequence is eventually cleaved off to produce the desired protein for use as a therapeutic, i.e., the fusion protein is an intermediate in the production of a desired non-fusion protein.

For example, in Regent of UC v. Eli Lilly,[173] the court held that UC's claim to vectors containing the human insulin gene did not encompass insulin fusion genes, and thus was not infringed by Lilly's process which involved production of a protein fusion. Not only did the use of protein fusion technology circumvent the patent, it also probably provided a better vehicle for expressing and purifying the desired protein. This is an example of an adaptation of technology that not only circumvents a patent but provides substantial technical advantages, and might well have been employed even if patent avoidance were not a consideration. Note that UC was unable to successfully claim fusion proteins because it was required during prosecution of the patent to amend the claim to include the closed "consisting essentially of" language instead of the broader "comprising" language normally desired by a patentee seeking to avoid trivial design around. Although the amendment might well have been necessary to secure issuance of the patent, it also resulted in a claim that was extremely easy to design around using fusion technology, which was well known at the time the patent issued and generally applicable to protein expression. This is an example of a situation where a patent that might appear on it face to claim an important human gene, but in fact is so limited in scope that it should not block practically desirable uses of the gene.

Similarly, in Novo Nordisk v. Genentech the Federal Circuit ruled that Genentech's patented method for producing recombinant human growth hormone was limited to direct expression of the protein, and was not infringed by Novo Nordisk's method which involved the production of a cleavable fusion product.[174]

The trend in biotechnology is towards the development of second-generation protein therapeutic variants comprising structural changes relative to the naturally occurring protein, i.e., non-naturally occurring proteins. This is often accomplished by modifying the sequence of a native gene. These modifications have not only resulted in superior therapeutic efficacy, but have also in many cases successfully designed around human gene patents.

An early example of this can be seen in Genentech v. Burroughs Wellcome, wherein the Federal Circuit determined that a patent broadly claiming the "human tissue plasiminogen activator gene" was limited to the native gene and naturally occurring

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173 *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997).

174 *Novo Nordisk of N. Am., Inc. v. Genentech, Inc.*, 77 F.3d 1364 (Fed. Cir. 1996).

variants thereof. The allegedly infringing product was a non-naturally occurring variant of human tissue plasiminogen activator (tPA) that had been modified by the removal of substantial portions of the native protein, and by changes to the protein's amino acid sequence that substantially modified the protein's glycosylation pattern. These modifications were reflected in the genetic sequence used to encode the protein. In view of the substantial structural changes in the encoded protein, which resulted in significant alteration in function compared to the native protein, including a 10-fold increase in half-life, the court held that the non-naturally occurring gene sequence used by Wellcome did not infringe Genetech's gene patent either directly or under the doctrine of equivalents.

More recently, Amgen avoided a Schering patent purporting to cover any genetic sequence encoding human interferon alpha (IFN-α), a therapeutically relevant cytokine.[175] Instead of employing a gene sequence encoding a native IFN-α, Amgen developed a consensus IFN- α sequence based on genetic variations that were known to exist in naturally occurring subtypes of IFN- α.[176] Some of these subtypes were not even known at the time the patent was filed. Note that while this consensus sequence is based on naturally occurring sequences, it is a synthetic gene sequence that probably does not occur in nature. The court construed the patent claims to be limited to certain naturally occurring subtypes of IFN-α that were specifically known at the time the patent was filed, and hence not infringed by Amgen's synthetic product. Patent considerations aside, the consensus product is purported to have distinct, improved therapeutic utility relative to naturally occurring subtypes.[177]

Schering had previously asserted the same patent against Interferon Sciences for its inclusion of IFN- αb in a topical gel called Alferon that was undergoing clinical trials for treatment of viral skin diseases like genital herpes and possibly some cancers.[178] Schering dropped its suit after Interferon Sciences agreed to avoid the patent by substituting IFN- αa for IFN- αb. At the time Interferon Sciences stated that the substation was not expected to alter the product's effectiveness, but would necessitate more tests to obtain FDA approval.[179] The suit was terminated early prior to ny substantive ruling by the court.

B. Research Tools

The term "research tool" is used often in patent policy debates, and generally refers to instruments, reagents, methods and information "the main commercial value of which is in furthering research."[180] Research tool status is often associated with so-called "upstream" technologies which are useful in early-stage research that ultimately may lead to "downstream" commercial products. It has been argued that excessive patenting of upstream technologies might unduly impede the development of the downstream

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175 *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347 (Fed. Cir. 2000).

176 Most proteins come in a variety of subtypes. [cite]

177 [cite?, maybe mentioned in litigation, briefs filed by Amgen.]

178 *Schering v. v. Interferon Sciences, Inc.*, Docket #: CA 89-131 (D.C Del.).

179 Schering -Plough Drops Suit, AP News, available at http://query.nytimes.com/gst/fullpage.html?res=9D0CE4D91238F932A15750C0A967958260

180 Reaping the Benefits at page 51.

products desired by society.[181] The use of human genes as research tools has resulted in much less human gene patent litigation than human therapeutic proteins, but I did identify seven litigations that occurred in this context.[182]

Typically, the gene is being used as a tool for studying the protein encoded by the gene, often in the context of drug discovery. Early stage drug discovery typically involves testing a large number of candidate molecules for biological or pharmacological effect in the hope of identifying a lead compound, which hopefully will form the basis for identifying an actual drug. Drugs typically function by specifically binding to and interacting with a protein target, and human genes are useful in this regard because they can be used to express a target human protein for use in drug screening studies. In some cases, the human gene is expressed to produce purified protein for use in in vitro screening assays. Other times, cell-based assays are used to assess the affect of test compounds on cells recombinantly expressing a cloned human gene. In other cases a human gene can be introduced into a transgenic animal, such as a mouse, allowing for drug screening in a living mammalian system. All of these types of research tool usages of human genes are represented in the patent litigations identified in this study.

The seven research tool litigations identified alleged the use of the patented human gene either as a component of a research tool, or in the production of a research tool.[183] Three of the cases allege the sale of a research tool product, where the actual user of the research tool is a customer of the alleged infringor. In another three cases the party accused of infringement was alleged to have directly used the patented research tool, either in its own drug discovery program, or as a service performed for its clients in their own discovery efforts, e.g., by contract research organizations (CROs).[184] Finally, in one case the allegation of patent infringement occurred in the context of a litigation primarily alleging misappropriation of trade secrets[185] – early on the patent owner filed a declaration agreeing not to sue for patent infringement after the alleged infringer filed counterclaims asking that the patent be found invalid, unenforceable and not infringed.[186]

In New England Medical Center Hospitals, Inc., et al v. Peptrotech, one of the litigations involving the sale of a research tool, the alleged infringement involved a research tool company's recombinant expression of the gene encoding IL-1B in a microbe to produce the protein.[187] The protein product was sold, presumably to drug companies who would use it in drug discovery efforts directed towards this important human cytokine.[188] The asserted claim did not cover the gene per se, but was limited to methods of recombinantly expressing the gene in a microbe. This case is notable as the

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[181] In fact, there have been attempts to ban the patenting of research tools, albeit as of yet there has been little indication of success. The primary opponents of restrictions on the patenting of research tools are universitities, leading developers and patenters of this sort of technology.

[182] New England Medical, Incyte. MDS Pan Lab the gene pante wa

[183] Cross-filing of patent infringement lawsuits by OncorMed an Myriad is considered a single dispute.

[184] http://en.wikipedia.org/wiki/Contract_Research_Organization.

[185] Cistron Biotechnology v. Immunex Corp. (Docket #: CIV93-4322) (NJ)

[186] http://www.secinfo.com/dRqWm.94Ga.htm

[187] Interleukin 1-B.

[188] *New England Medical Center Hospitals, Inc., et al v. Peptrotech*; (See FTC inquiry into Amgen Immunex merger for discussion of importance as drug discovery target)

only case in the research tool context where a human gene patent has been successfully asserted to a final judgment for the patentee.[189]

The real interested party in New England Medical Center was the medical center's exclusive licensee Cistron Biotechnologies, a small company using the patented interleukin-1 gene in a drug discovery program specifically targeting interleukin-1. The defendant Peptrotech was using the patented process to produce interleukin-1 for commercial sale, and presumably some was purchased by other laboratories for use in their own research efforts targeting interleukin-1, in direct competition with Cistron. Cistron's interleukin-1 drug discovery efforts were clearly substantial – in fact, when Cistron was acquired by Celltech in 2000, the related SEC filing attributes the entire value of the company to its cash holdings and intellectual property surrounding antibody therapeutics targeted to interleukin-1.[190] This intellectual property, which ultimately formed the entirety of the non-cash value of the company, was presumably the fruit of its research conducted under the asserted patent.

The second case involving sale of a research tool, Elan v. Mayo, was brought by a biotechnology company heavily engaged in drug discovery research targeting Alzheimer's disease and alleged infringement of its patent claiming transgenic rodents, particularly mice, genetically engineered to include a gene encoding a human APP polypeptide comprising the so-called "Swedish mutation." This mutation has been linked with the onset of Alzheimer's disease, and these transgenic mice provide researchers with a potentially powerful tool for studying the disease and hopefully developing a drug.[191] . The alleged infringement involved Mayo's production and sale of the patented mice to pharmaceutical companies at reported prices of up to $850,000 for a breeding group.[192] The district court initially found the claims at issue invalid on a motion for summary judgment, but the Federal Circuit reversed and the parties settled while the case was pending in the district court on remand. Pursuant to the settlement, Mayo was granted a license to use the patented technology. Note that Elan's claim is limited to transgenic rodents incorporating a mutant human gene. Important technology, but the patent in no way restricts the use or study of the gene outside the claimed embodiment.

The third litigation involving sale of a research tool, Incyte v. Invitrogen, is the only case that came up in this study that involved the sale of a cloned human gene per se, as opposed to the sale of a product incorporating the gene (the transgenic mouse at issue in Elan), or the use of the gene in the production of a product or the performance of a service. [193] Notably, however, this lawsuit clearly appears to have only been filed in

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189 Based on Peprotech's infringing sales of $300,000, the court awarded $2.7 million, which included lost profits based on Cistron's higher profit margin, attorneys' fees, and interest. (from Fish and Richardson website).

190 In 2000 Celltech acquired cistron biotechnology for $18 million. Of that, $8.75 million was directly attributed to intellectual property encompassing anti-interleukin (IL-1) antibodies as treatments for chronic inflammatory disorders and about $9.25 million for Cistron's cash reserves. [http://www.secinfo.com/dX73y.57.htm]

191 Elan v. Mayo

192 Nature, Vol. 405, 29 June 2000, at 989. The price underscores illustrates the perceived high commercial value of these mice. Lawrence Osborns, *Fuzzy Little Test Tubes*, The New York Times Magazine, July 30, 2000 http://www.nytimes.com/library/magazine/home/ 20000730magmouse.html.

193 Incyte Genomics Inc, et al v. Invitrogen Corp

retaliation for a lawsuit filed by Invitrogen against Incyte one month earlier.[194] In any event, Incyte v. Invitrogen settled quickly prior to any substantive action and resulted in Incyte granting a nonexclusive license to Invitrogen.

In one of the research tool litigations, Synaptic Pharmaceutical Corporation v. MDS Panlabs, Inc., the company accused of infringement was a CRO allegedly using the patented gene in a cell-based drug screening assay.[195] The defendant company was performing the allegedly infringing assays as a service for its customers, who were presumably using the results in their own drug discovery efforts. Note that the initial complaint asserted multiple patents, including one human gene patent (5639652). Subsequently, Synaptic filed a first amended complaint that omits any reference to the previously asserted human gene patent, and the human gene patent never reappeared in the litigation, so this is a human gene patent litigation in a purely formal sense. In any event, after a ruling at the district court level on various summary judgment motions that appears to have been generally adverse to the patent owner, the parties settled on terms reportedly favorable to MDS Panlabs which allowed it to continue its allegedly infringing activities.[196]

Two research tool cases involved the use of an allegedly patented research tool by a company in its own internal drug discovery program.[197] The first of these, Ligand Pharmaceuticals v. La Jolla Research, the alleged infringement involved a biotechnology company using a gene encoding retinoic acid receptor in the recombinant production of the protein for the company's own drug discovery efforts targeting that protein. The receptor is a promising target for anticancer drugs.[198] The patent, 5171671, appears quite broad, claiming "substantially pure DNA encoding retinoic acid receptor," as well as vectors containing the DNA, cells transformed with the DNA, and methods for recombinantly expressing the protein. Ligand Pharmaceuticals, the patent owner, was engaged in a substantial drug development program targeting the same protein target. The case settled at an early stage prior to any substantive rulings, with the defendant

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[194] It appears that the lawsuit against Invitrogen was filed solely as a defensive move. On October 17, 2001, Invitrogen filed a lawsuit against Incyte, alleging that in conducting its genomic operations Incyte infringed Invitrogen patents relating to the creation and use of a modified reverse transcriptase enzyme. [United States District Court, D. Delaware.No.CIV.A.01-692-SLR.] Incyte responded by filing a lawsuit against Invitrogen on November 21, 2001, alleging that Invitrogen infringed a number of Incyte's human gene patents. [D.C. S.D. California, Doc. No. 3:01cv2141] The alleged infringement involved Invitrogen's sale of embodiments of these genes as clones for use as research tools. At about the same time, Incyte settled with Invitrogen, granting Invitrogen a non-exclusive license, and Invitrogen and Incyte stayed their case. Once the stay was lifted, the parties soon settled.

[195] *Synaptic Pharmaceutical Corporation v. MDS Panlabs, Inc., et al*, Filed Jun. 5, 2000, D.C. New Jersey (Newark), Doc. No. 00cv2728 (HAA); *Synaptic Pharmaceuticals Corp. v. MDS Panlabs, Inc.*, 265 F.Supp. 2d 452 (D.N.J.,2002.). .

[196] *Synaptic Pharmaceuticals, Inc. v. MDS Panlabs, Inc.* (D. N.J.) http://www.foleyhoag.com/engagements.asp?pID=000320865101 ("We represented MDS Pharma Services in a patent infringement action directed to the importation of data generated abroad from binding assays using cloned human receptors. The case was favorably settled after we obtained summary judgment for our client on the principal infringement claim.")

[197] *Ligand Pharmaceuticals, Inc., et al v. La Jolla Cancer Research Foundation, et al*, Filed Dec. 10, 1993, D.C. S.D. California, Doc. No. 93-1895IEG (CM) and Alzheimer's Institute of America, Inc. v. Mayo Clinic et al, 2:03CV02645, U.S. District Court Kansas, 12/18/2003.

[198] http://cancerres.aacrjournals.org/cgi/content/abstract/57/1/162

agreeing to discontinue commercial drug discovery efforts involving the patented gene, although the settlement did explicitly permit the defendant to continue using the patented gene in conjunction with basic research activities.

More recently, the case of Alzheimer's Institute of America v. Mayo Clinic involves an allegation that the Mayo Clinic, which purports to be a non-profit research institute, is conducting commercial drug discovery research in collaboration with Myriad Genetics, a private company.[199] The human gene patent at issue in this case, 5455169, broadly claims any isolated nucleic acid encoding the "Swedish mutation" of human amyloid precursor protein (APP) (i.e., the same mutation at issue in Elan v. Mayo), as well as vectors and immortalized mammalian cell lines comprising the mutant gene. A district court has characterized the litigation as primarily a contract dispute ordered the parties to arbitrate the matter; in the meantime, the court has stayed the case.

C. Genetic testing

The seven remaining human gene patent litigations identified in the study all fall within the category of genetic testing. In four of the seven, the alleged infringement involved commercial testing for a mutation in a single gene known to be associated with either a genetic disease, or a predisposition to disease, i.e., BRCA1, and the genes associated with TPMT-deficiency and Long QT syndrome. In a fifth litigation, the allegedly infringing test was not directed towards a particular human genes, but rather to a set of probes useful in detecting a chromosomal aberration known be associated with leukemia, wherein the aberration involves the fusing of two gene which normally reside on different chromosomes. The final two litigations involved the same patent, which claims a stretch of non-protein encoding genomic DNA useful in genetic identification for forensic and paternity testing applications.

Two of the litigations involved Myriad Genetics and patents relating to the BRCA1 gene, mutations of which have been shown to correlate with a predisposition for certain forms of cancer. The patents claim, inter alia, the wild-type gene and specific mutations, including fragments, probes capable of detecting the mutations, and methods for identifying the mutations, and are widely considered to effectively cover the current genetic testing methodologies that would be used to screen women for susceptibility to breast cancer based on certain mutations of the chain.[200] In one case, Myriad and OncorMed (a competing genetics diagnostic company) sued one another for allegedly infringing each others BRCA1 patents.[201] The parties eventually settled their dispute, with OncorMed licensing its patent to Myriad for some amount of cash and agreeing to exit the BRCA1 testing market, leaving Myriad with a dominant patent position in the BRCA1 testing business.[202] The case settled prior to any substantive legal rulings regarding patent validity or infringement.

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[199] Document 34, page 3

[200] Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health (2006), pages 63-68.

[201] The Oncormed patent covers consensus sequence, so not a human gene patent under definition of this study. This is biotechnology, product of judgment, and could provide improved function over natural sequence. "an isolated consensus DNA sequence of the BRCA1 coding sequence."

[202] [cite to settlement agreement]Reaping the Benefits of Genomic and Proteomic Research: Intellectual Property Rights, Innovation, and Public Health (2006), pages 63-68.

The second BRCA1 lawsuit was filed by Myriad against the University of Pennsylvania for allegedly providing commercial BRCA1 genetic testing service, reportedly for a price of $1900.[203] The case was quickly dismissed for Myriad's failure to serve process on the defendant.[204] However, Myriad's decision to drop the case was apparently premised on a university agreeing to withdraw from the commercial testing market. The university subsequently reported that its decision to stop offering the test was a result of Myriad's decision to enforce its patents.[205]

The finding that Myriad has only on two occasions sought to enforce its BRCA patents in court, and that both cases were dismissed relatively early on, might come as a surprise to some. There has been a great deal of commentary decrying the chilling effect of gene patents on accessibility to health care, particularly in the US, and particularly with respect to genetic testing services, and Myriad and its BRCA patents are generally cited as the primary anecdotal evidence for this perceived problem.[206] Clearly, the chilling effect is based on an unwillingness to challenge the patents; the courts have not played a direct role, and since no lawsuit has gone so far as to result in a substantive ruling it is hard to predict the actual power of the patents should someone decide to challenge them.

In DNA Sciences v. Genedx, the allegedly infringing activity involved commercial genetic testing for Long QT syndrome, a genetic disease sometimes referred to as Sudden Arrhythmic Death Syndrome (SADS)).[207] DNA Sciences asserted three patents claiming, inter alia, DNA sequences corresponding to certain genetic mutations associated with the syndrome, nucleic acid probes that would hybridize to a DNA having any one of several specific mutations which according to the patent are associated with the syndrome, and methods for diagnosing for the syndrome by testing for the specified mutations. As with the Myraid BRCA1 patents, DNA Sciences' patent protection would appear to effectively encompass any practical method of testing for these mutations. The parties settled the lawsuit less than three months after the complaint was filed, prior to the filing of an answer, which resulted in the dismissal of the lawsuit without prejudice. The lawsuit reportedly involved Genedx agreeing to exit the long QT syndrome testing market, at a time when no one else was providing the test commercially, including DNA Sciences.[208] DNA Sciences was acquired in 2005 by Genaissance Pharmaceuticals, which currently provides the *FAMILION*™ genetic test to detect theses mutations.[209]

In the most recently filed genetic testing litigation, Prometheus Labs v. Quest diagnostics, Prometheus is asserting patents covering mutant forms of the TPMT gene, as

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[203] Myriad Genetics, Inc. v. University of Pennsylvania, Filed Nov. 19, 1998, D.C. Utah, Doc. No. 2:98cv829

[204] Cite

[205] Reynolds, Tom, *NCI-Myriad Agreement Offers BRCA Testing at Reduced Cost*, 92 J. of the National Cancer Inst. (April 19, 2000) *available at* http://jnci.oxfordjournals.org/cgi/content/full/92/8/596.

[206] [Kieff article]

[207] [cite]

[208] Conversation with Alice Lara at the SADS Founation. A check of their website on April 6, 2007, revealed that the company is not offering testing for this disease. The company continues to offer genetic testing for a host of other genetic diseases.

[209] http://www.sads.org/Genetics/Clinical%20Testing.htm

well as reagents and methods for identifying the mutations.[210] The mutations are associated with TPMT-deficiency, a potentially serious genetic condition which results in an inability to tolerate thiopurine drugs.[211] Although the complaint does not specifically identify the nature of the alleged infringement, it can be inferred that Quest is being sued for providing commercial genetic testing for TPMT deficiency.[212] Prometheus licensed the technology from DNA Sciences, the plaintiff in the Long QT Syndrome litigation.[213] Quest diagnostics has moved for summary judgment of noninfringement, and the parties have commenced discovery. According to quest diagnostics website, the company continues to offer genetic testing for TPMT-deficiency.

The fifth genetics testing case, Ventana v. Vysis, was filed by the exclusive licensee of patents claiming DNA probes specifically useful for detecting a chromosomal aberration. The aberration involves the fusion of portions of the BCR gene from chromosome 22 and the ABL gene from chromosome 9, resulting in leukemia. The plaintiff and defendant made competing products for detecting the fusion event, which involved probes able to specifically bind to portions of the two genes. Note that the patents would only be infringed by products including probes that specifically bind portions of both genes, and would in no way restrict any uses of the individual genes. Early in the litigation, prior to discovery or any substantive ruling by the court, the parties requested and were granted a stay of the case pending the resolution of interference dispute involving the two asserted patents. While the stay was pending the parties settled and the case was dismissed with prejudice, and shortly thereafter it was announced that final judgment has been entered against Ventana in the interference with respect to at least some of the asserted claims.[214]

The sixth genetics testing case, Promega v. Lifeprobes arguably does not involve human genes, since the patents do not cover protein encoding sequences, but rather specific genomic sequences useful in genetic identification, essentially "DNA fingerprints" useful in forensics and paternity testing.[215] Thus, for example, these patents would not be classified as human gene patents in the Murray/Jensen study. Nevertheless, although some would characterize the patented sequences as "junk DNA," they are actually quite useful in genetic identity testing because they include variable number of

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[210] *Prometheus Labs, Inc. v. Quest Diagnostics*, U.S. District Court S.D. of Calif., 02/23/2006.

[211] Important examples of these drugs include 6-mercaptopurine and azathioprine, two drugs used in a range of indications, from childhood leukemia to autoimmune diseases. The FDA has recommended that individuals be tested for this genetic condition before being put on a regimen that includes these drugs. An unrecognized TPMT-deficiency can result in potentially fatal drug toxicity in patients treated with thiopurines.

[212] Important examples of these drugs include 6-mercaptopurine and azathioprine, two drugs used in a range of indications, from childhood leukemia to autoimmune diseases. The FDA has recommended that individuals be tested for this genetic condition before being put on a regimen that includes these drugs. An unrecognized TPMT-deficiency can result in potentially fatal drug toxicity in patients treated with thiopurines.

[213] Prometheus Investor Relations News Release (Oct. 15, 2002) http://phx.corporate-ir.net/phoenix.zhtml?c=130685&p=irol-newsArticle&ID=465184&highlight=; http://phx.corporate-ir.net/phoenix.zhtml?c=130685&p=irol-newsArticle&ID=464952&highlight=

[214] (O.G. February 22, 2005) (O.G. February 22, 2005)

[215] *Promega Corp. v. Lifecodes Corp.*, 53 U.S.P.Q.2D 1463, 1999 U.S. Dist. LEXIS 21094, (D.Utah 1999),

tandem repeat (VNTR) sequences. Essentially, these regions have a sequence that is repeated multiple times, and the number of repeats varies between individuals. VNTR regions reside throughout the human genome, and by measuring the number of repeats at a number of different VNTR regions it is possible to identify a specific individual with a high degree of certainty. The importance of these sequences is underscored by the fact that this is the only genetic testing patent litigation that was litigated to completion – no other genetic testing case even proceeded to a substantive legal decision prior to settling. The defendant Lifecodes was found liable for willful infringement, resulting in monetary damages and an injunction.

The seventh genetics testing case involved the same patent at issue in Promega v. Lifeprobes, and was brought by the original patent owners Genmark and the University of Utah against Lifeprobes.[216] Shortly after the complaint was filed and prior to the filing of an answer the parties settled, pursuant to which defendant Lifeprobes obtained an exclusive license to the patent.[217] In an unusual twist, Lifeprobes was subsequently sued years later for infringing the same patent by Promega, its exclusive licensee.[218]

VII. Conclusion: assessing the impact of human gene litigation

Criticism of human gene patents is based in large part on an assumption that these patents have a negative impact on biomedical research, public health, and perhaps even human dignity and personal autonomy. Moreover, the magnitude of this negative impact must be perceived as substantial to warrant the drastic legislative response embodied in the GRAA. However, the actual enforcement history of human gene patents does not appear to bear out these fears, nor does it seem to justify a bar to patentability specifically targeting genes or DNA.

Not surprisingly, none of the fears regarding patent holders asserting ownership in other peoples bodies, or suing people for patent infringement based on the presence of patented genes in their bodies, have materialized. While there are many who would maintain that the mere existence of patents relating to human genes is immoral and offensive, these patents have not been asserted in any manner that would directly impact human dignity or personal autonomy. Of course, some might argue that a patent that delays or even adds to the cost of genetic testing or lifesaving drugs is an affront to human dignity. But such concerns are by no means specific to gene patents, but apply to patents in general, particularly those claiming drugs or general molecular biology methods and reagents used in drug development and genetic testing.[219]

As a means of assessing the impact of these patents, it would be instructive to calculate the rate at which human gene patents are litigated and compare it with the rate for patents in general. Unfortunately, because of the manner in which I have defined human gene patents and the nature of the search methodology, I have no practical way of

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216 Genmark v. Lifecodes (Docket #91-c-0707B) UT.

217 [Lifeprobe's SEC filing]

218 Promgea v. Lifeprobes, discussed supra.

219 Examples of methods that impact drug and diagnostic availability include Roche's PCR patents, Columbia's co-transformation patents, and Genentech's Cabilly patents.

determining the total number of human gene patents.[220] However, Jensen and Murray specifically identified a total of 4270 patents as satisfying their definition of a human gene patent, which provides a denominator for a calculation of litigation rate. Furthermore, their dataset forms the basis for the frequent assertion that 20% of human genes are patented, so it is interesting to consider to what extent these patents have been the subject of actual judicial enforcement.

In view of the angst brought about by the Murray and Jensen article, it might come as a surprise to some to learn that my study identified only six litigations alleging infringement of a patent appearing in the Jensen and Murray database,[221] involving a total of seventeen patents with claims reciting twelve distinct human genes.[222] Only one of the litigations, *Genzyme v. TKT*, resulted in a substantive court decision, and in that case the patent was found not to be infringed. One of the litigations, *Prometheus*, was only filed recently and there have been no substantive rulings as of this date.[223] The four remaining litigations settled at an early stage, prior to any substantive decision by the court.[224] Not one of the 4270 patents in the dataset has ever been found valid and infringed, or resulted in preliminary injunction.

In addition, more than ½ of the litigated patents (9 of 17), representing ¾ of the claimed human genes (9 of 12), were asserted in a single litigation, *Incyte v. Invitrogen*. As noted above, this lawsuit was apparently only filed as a form of retaliation after Invitrogen sued Incyte for patent infringement, and the parties quickly settled under terms granting Invitrogen a non-exclusive license to the gene patents. This case would appear to have had little if any impact on research or public health. If anything, one might argue that any impact was positive, since Incyte only brought the lawsuit in an attempt to secure its own freedom to operate and the result was a license for Invitrogen.[225]

Four of the six cases involved genetic testing targeting a total of three single gene mutations associated with disease - BRCA1, TPMT and Long QT Syndrome. These

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[220] My search strategy was very broad and would pick up many nonhuman gene patents, and I was only able to identify cases involving human gene patents by actually reading the cases and asserted patents.

[221] 5843725 appears in the database and was asserted Zymogenetics v. Immunex and Zymogenetics v. Bristol-Myers Squibb. However, that patent does not meet the definition of human gene patent provided by Jensen and Murray or myself, and is rather directed to dimerized polypeptide fusions, a type of non-naturally occurring genetic construct allegedly used in two otherwise unrelated drugs, Enbrel® and Orencia®. In one case, the human gene patent was removed from the first amended complaint and was never actually part of the patent litigation, Synapatic v. MDS 5639652 appeared in initial Synaptic complaint, but removed from first amended complaint]. .

[222] DNA Sciences v. Genedx [6207383, 6,432,644], Myriad v. Penn, Myriad v. Oncormed and Oncormed v. Myriad [5753441, 5747282, 5709999, 5693473 5654155], Prometheus [5856095] Incyte v. Invitrogen [6001598, 5962263, 5925542, 5853997, 5840535, 5817497, 5776753, 5637462, 5633149], Genzyme v. TKT [5356804]. There were also lawsuits filed in connection with 5843725, which appears in Murray and Jensen's database due to limitations of their automated search method, but which contains no claims directed to a specific human gene, but rather is directed to general methodology for "the expression of growth factor receptor analogs and biologically active dimerized polypeptide fusions." Zymogenetics v. Immunex and Zymogenetics v. Bristol-Myers Squibb.

[223] Prometheus

[224] DNA Sciences v. Genedx [6207383, 6,432,644], Myriad v. Penn and Myriad v. Oncormed [5753441, 5747282, 5709999, 5693473], Oncormed v. Myriad [5654155] Prometheus [5856095] Incyte v. Invitrogen

[225] infra

litigations have presumably had some impact on the availability of these tests, or at least their cost. In particular, defendants in the BRCA1 and Long QT Syndrome cases reportedly exited the market in response to the lawsuits. In the case of BRCA1, the patent owner Myriad was providing the testing service, so while the decision of the alleged infringers to exit the market denied consumers the benefit of market competition, particularly with respect to the cost of testing, it did not prevent patients from being tested for mutations in the BRCA1 gene. In the case involving Long QT Syndrome, on the other hand, the patent owner DNA Sciences was reportedly not providing its own commercial testing services at the time of the lawsuit, so Genedx's exit from the market appears to have deprived patients of access to commercial genetic testing for this condition. Research laboratory-based test were probably still available. However, shortly thereafter DNA Sciences was acquired by Pharmassaince, which began offering the test by 2005. The TPMT-deficiency case involving Prometheus is at its early stages – at the time this article is being written both Prometheus and the defendant Quest Diagnostics are advertising the availability of TPMT-deficiency testing on their websites.

In total, only about 0.4% of the Murray/Jensen human gene patent patents have ever been the subject of infringement litigation. If we exclude the patents asserted in the retaliatory lawsuit filed by Incyte, less than 0.2% of the Jensen & Murray patents have been asserted, claiming a total of four human genes. In contrast, it has been reported elsewhere that about 1-2% of issued patents are litigated, and it has been estimated 6% of biotechnology patents are the subject of litigation.[226] Of course, most of the patent in the Murray/Jensen dataset are still in force, so it is possible that some of the patents will be the subject of future lawsuits. But as described earlier, I found that 1.07% of a random sample of 1,000,000 patents issued in the same time frame as the patents in the Murray & Jensen database have already been the subject of lawsuit, very close to the previously estimated 1-2% for patents in general.[227]

Most of the human gene patents litigations I identified as occurring in the context of research tools and protein therapeutics involved proteins that did not appear in the Jensen and Murray dataset.[228] Most of these litigations were asserted in the context of therapeutic proteins, usually in a dispute between innovator biotechnology company patent owners and firms attempting to market a competing product. In these litigations, human gene patents are essentially playing a role analogous to that of drug patents in the conventional pharmaceutical context.

Human gene patents are clearly having an impact on the availability of protein therapeutics, but overall impact is probably a positive one. Convincing arguments have been made that patents play a critical (some would argue necessary) role in the development of drugs, due in large part to the need for innovator companies to recoup the huge expenses associated with drug development, and especially in gaining FDA approval. These arguments should have even more force in the case of recombinant protein therapeutics, which are generally more expensive to develop and bring to market than conventional drugs. I would argue that the use of human gene patents to provide

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[226] Josh Lerner, Patenting in the Shadow of Competitors, 38 J.L. & Econ. 463 (1995) (presenting study showing that 6% of biotechnology patents were involved in litigation).

[227] Supra, and [cite]

[228] The reason for this is discussed supra.

market exclusivity for pioneering therapeutic protein products has not been so detrimental to the public health that it would warrant a ban on gene patents; if anything, the use of these patents to incentivize the development of this increasingly important class of drugs would support an argument in favor of allowing gene patents.

In contrast, there have been substantially fewer lawsuits filed in the context of research tools and genetic testing. In only two of these cases, *New England Medical Center v. Peptrotech* and *Promega v. Lifecodes*, has a court found a human gene patent to be valid and infringed. Both cases probably had a relatively minimal impact on public health.

For example, in *New England* the infringement involved Peprotech's use of a patented method of expressing the IL-1B gene in microbes to produce the IL-1B protein, which it then sold as a research tool. However, given that the protein and gene sequences were public knowledge, a research laboratory with competency in molecular biology could have without undue effort cloned the gene itself and produced its own protein, or even bought the gene off the shelf.[229] Alternatively, the protein could have been expressed in an organism other than a microbe, such as an insect, plant or mammalian cell, which would avoid the patent (at least literally) and at the same time quite likely result in a product that more closely resemble that natural human protein. While purchasing the protein from Peptrotech was apparently more cost effective for its customers than producing the protein internally, removal of the Peptrotech product from the market would not necessarily block these laboratories from continuing to pursue drugs targeting the protein. In any event, the patent did not prevent the development of drugs targeting IL-1B, as evidenced by the 2001 FDA approval of Amgen's IL-1 inhibitor Kineret, and the fact that Immunex and Regeneron had competing IL-1 inhibitors in clinical trials by 2002.[230]

The outcome of *Promega v. Lifeprobes* likewise probably had little impact on biomedical research or public health. For one thing, the infringing activity involved genetic identification technology, not health care. The particular patented genomic sequences at issue were valuable primarily because they had become standards in established identification testing protocols which had been adopted by the FBI and others. The human genome is full of regions containing variations of potential use in genetic identification; indeed, the asserted patent purports to provide a powerful methodology for finding such sequences. Anyone willing to invest in identifying alternate sequences for genetic identification could have done so, although it might have been difficult to compete with Promega if customers regarded the patented Promega sequences as standards and were thus effectively locked into using them.

Furthermore, it does not appear that Promega's lawsuit against LifeProbes substantially restricted third-party access to the probes. For example, in the damages section of the *Promega* decision the court found that all of LifeProbes sales would have been made by Promega in the absence of infringement. If Lifeprobes were selling at a substantially lower price than Promega would have, then presumably they would have made sales to customers who would not have purchased from Promega. The court's

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229 DNA 2.0

230 http://www.ftc.gov/os/caselist/c4056.shtm

decision implies that customers did not substantially benefit from Lifeprobe's presence in the market, even in terms of lower price as the result of competition.

New England and *Promega* are the exception; for the most part genetic testing and research tool patent cases tend to settle and to do so at an early stage in the litigation. The mere filing of a lawsuit is rare and suggestive of impact, but this inference of impact is attenuated in cases that settle, particularly those that settle early and prior to any substantive ruling. A final judgment of infringement typically results in the court imposing damages and/or an injunction, which might substantially albeit indirectly impact the public by preventing the infringer from using the technology in its research or product development. The patent owner's success in court might also dissuade others from challenging the patent. In cases that settle, on the other hand, the alleged infringer has voluntarily agreed to the terms of the settlement. The settlement terms will vary on a case-by-case basis course, but in many instances a settlement will allow the alleged infringer to continue using the contested technology, albeit perhaps with the requirement of paying some royalties or licensing fee. But even in cases where the settlement involves the alleged infringer agreeing to forgo use of the patented technology, the decision to settle, particularly at an early stage in the litigation, is evidence that use of the technology was not viewed as especially valuable.[231]

Of course, a patent can have impact even in cases where the patent is never asserted. If researchers agree to license the patent, paying some royalty to the patent owner, this royalty payment ultimately increases the cost of research, which might impact society in the form of reduced output or increased cost for the ultimate product. Alternatively, researchers might choose to simply avoid using the technology to avoid the possibility of an infringement lawsuit, which again could negatively impact society by resulting in the avoidance of certain research projects or the utilization of second-best technologies, again ultimately resulting in reduced output and or higher prices.

It is difficult to directly assess the above described impact that does not involve the filing of a lawsuit, since the terms licensing agreements are often not publicly available, and the only way to assess the extent to which patented technologies are avoided is by the imperfect tool of surveys.[232] Lemley has posited that patents are only licensed at about three times the rate they are litigated, and if that holds true for human gene patents one can speculate that the rate at which human gene patents are the subject of licensing fees is like litigation relatively infrequent.[233] A low rate of licensing, and more generally a low rate of commercial relevance, might explain why Incyte, the assignee of the most human gene patents is letting many of its patents lapse for failure to pay maintenance fees It might also account for a recently noted drop off in the rate at which patent applications direct to genes are being filed.[234]

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[231] Cite to Valuable Patents paper for proposition that when the stakes are high, even a slim chance of success will motivate a company to expand the money on a patent litigation. For an example of this, consider how a large proportion of the biologic and disputes are fully litigated, consistent with the high commercial value of biologics compared to research tools and genetic testing services.

[232] Walsh and Cohen, Cho

[233] [cite]

[234] Michael Hopkins, DNA patenting: the end of an era?, Nature Biotechnology Vol 25:185-87. (2007).

I would suggest that a litigation frequency provides an indirect measure of non-litigation impacts. Professor Lemley has suggested that it is relatively rare for patents to be licensed at a substantial level without some lawsuit being filed. Using the same logic, it also seems unlikely that widespread avoidance of an important patented technology would occur without some lawsuit being filed, be it an infringement suit or a declaratory judgment action. Thus, a finding of modest litigation impact of human gene patents is suggestive of modest non-litigation impact.

While avoidance of patented technologies by researchers based on fear of patent infringement liability is clearly a real effect, it might not be based on a rational fear. After learning of a patent, a researcher, research institution, or company might decide to avoid the technology based on a flawed perception of the likelihood of lawsuit. To the extent action is based on a misperception of risk, the impact is not caused so much by patents but as by the misperception. For example, it academic researchers face little or no real threat of lawsuit based on patent infringement but nevertheless avoid the use of certain patented genes and other technologies in their research, it is this misperception rather than patents per se that is having the impact.

The relatively modest impact of human gene patents in the context of genetic testing and research tools, at least as measured by rate of enforcement and litigation outcome, does not to my mind justify the GRAA's sweeping prohibition on the patenting of DNA and DNA-related inventions. The ban would encompass too many important inventions involving DNA and other "nucleotide sequences" that have nothing to do with genes, or even biology. If any legislation is deemed necessary, it would be more appropriate to specifically protect research and genetic testing from inappropriate restrictions based on gene patents. In fact, this is what a bill introduced in Congress in 2002 would have done, providing limited exemptions for patent infringement liability where the alleged infringement involves the use of "genetic sequence information" in genetic testing or basic non-commercial research.[235]

In my view, not only is the GRAA overly broad, for example, in failing to distinguish between natural and non-naturally occurring nucleotides sequences or between genetic and non-genetic uses and function of DNA, its narrow focus on polynucleotides would probably fail to address the more pressing problems associated with US patents laws current expansive definition of patentable subject matter. Although genes are important, gene patents have had a relatively minor impact compared to other patents claiming fundamental biological principles, which generally do not claim DNA or genes. Examples include Ariad's NF-kB patent, the WARF's embryonic stem cell patents, Metabolite's patent broadly claiming virtually any practical use of the discovery of a correlation between homocysteine and B vitamins, Classen's patent claiming the use of the discovery of a correlation between vaccination schedule and risk of developing an immune disorder in vaccination protocols,[236] and JN MacRi's patent broadly claiming the diagnostic application of a relationship between a woman's maternal serum level of free beta human chorionic gonadotropin and gestational age and the woman's risk of carrying

[235] H.R. 3967, the Genomic Research and Diagnostic Accessibility Act of 2002.

[236] Docket No. WDQ-04-2607, (D. Maryland).

a fetus with Down syndrome.[237] The focus on gene and gene patents appears to be a manifestation of a general phenomonen often referred to as "genetic exceptionalism," i.e., a tendency of legislators and the public to seek gene-specific policy decisions based on an unwarranted perception that genes and genetics raise concerns that are fundamentally different and more compelling than other biological materials and information.[238] Instead of focusing solely on genes and DNA, legislators and policy advocates would do better to address the broader problem of patents that broadly claim any practical application of fundamental biological discoveries. Gene patents make up only a small subset of this problematic class of patents, and to date the most problematic patents have for the most part not claimed genes or gene-related inventions.

The push to ban the patenting of human genes, or DNA in general, is implicitly based on an assumption that for this particular category of technology, the overall cost of patents exceeds any positive benefit. However, many of the attacks on gene patents fail to adequately take into account fair the positive benefits of human gene patents. Any analysis of the patent system that focuses solely on the negative attributes of patent will surely lead to a conclusion that patents are a detriment to society, but the analysis is flawed for failing to account for the substantial benefits to innovation. Clearly human gene patents have played some positive role in incentivizing the development of life-saving protein therapeutics, and I think it is wrong to dismiss out of hand the possibility that they also can provide a meaningful incentive for the development, improvement and commercialization of research tools and genetic testing. Without more compelling evidence of an overwhelming negative impact in contexts that are critical to the public good, there is no adequate justification for rushing into a radical legislative fix that might have substantial unintended negative consequences.

A number of observations can be drawn from the results of this survey of human gene patent litigation. For example, consider the role of universities and academic research. Basic research appears to never be the subject of a patent infringement lawsuit, at least in the context of human gene patents, and probably in general. On the other hand, the vast majority of asserted human gene patents arose out of university research, especially in the context of research tools and genetic testing. Furthermore, the data provides no evidence of a patent thicket effect of human gene patents, nor do patent trolls appear to be a problem. These and other conclusion gleaned from this and ancillary studies will be the subject of my talk at IPSC 2007 and of a follow-up paper.

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[237] *JN MacRi Technologies, LLC et al*, Filed March 5, 2004, D.C. E.D. New York, Doc. No. 2:04cv953.

[238] Another example is a genetics discrimination bill also being considered by Congress at this time. Cf. TIBs 24:6 251 argues that compulsory licensing of genetic technologies is unwarranted owing to the minor role these technologies play in most health care systems.