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

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THE IMPACT OF HUMAN GENE PATENTS ON INNOVATION AND ACCESS: A SURVEY OF HUMAN GENE PATENT LITIGATION

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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]

The editorial alleges that certain unspecified parties have used gene patents to secure "ownership" of diseases and entire genomes, and argues that by issuing patents on genes the United States Patent and Trademark Office ("USPTO") has misinterpreted Supreme Court precedent.[2] Mr. 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.[3]

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[1] Michael Crichton, Op-Ed., *Patenting Life*, N.Y. TIMES, Feb. 13, 2007, at A2.

[2] Crichton, *Patenting Life*, *supra* note 1.

[3] *See, e.g.*, NATIONAL ACADEMIES OF SCIENCE, BOARD ON SCIENCE, TECHNOLOGY, AND ECONOMIC POLICY (STEP), REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH 125-27 (Stephen Merrill & Anne-Marie Mazza eds., National Academic Press 2006) [hereinafter REAPING THE BENEFITS]; The Institute for Science, Law & Technology, *Nobel Laureate Opposes Gene Patents*, http://www.whoownsyourbody.org/sulston.html (last visited Jan. 30, 2007); Letter from Bruce Alberts, President, National Academy of Sciences to Todd Dickinson, Assistant Sec'y of Commerce (Mar. 22, 2000), *available at* http://www.uspto.gov/web/offices/com/sol/comments/utilguide/nas.pdf; Press Release, College of American Pathologists, Gene Patents Put America's Healthcare at Risk, says CPA (June 28, 2006), *available at* http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=media (follow "News Release Index" hyperlink); American College of Medical Genetics, Position Statement on Gene Patents and Accessibility of Gene Testing (Aug. 2, 1999), *available at* http://genetics.faseb.org/genetics/acmg/pol-34.htm.

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 and Dave Weldon, M.D. 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."[4] 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 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 importance of the proposed ban, bear in mind that U.S. law currently contains no subject matter-specific proscription on patentability.[5] 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.[6] The extreme and unprecedented nature of the GRAA, were the bill to pass, prompts a number of policy questions. For example, does objective evidence exist supporting the

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[4] H.R. 977, 110th Cong. (2007).

[5] Christopher M. Holman, *Patent Border Wars: Defining the Boundary Between Scientific Discoveries and Patentable Inventions,* 25 TRENDS IN BIOTECHNOLOGY 539, 541 (2007) (noting that U.S. law permits the government to block the patenting of an invention in certain rare situations where publication of a description of the invention would endanger national security, and that there are substantial limitations on the remedies available for infringement of certain disfavored classes of patent, particularly patents claiming medical procedures or business methods).

[6] Helen Dewar, *Human Cloning Ban Sidetracked; Senate Vote Deals Amendment Second Setback in a Week*, WASHINGTON POST, June 19, 2002, at A4; Holman, *supra* note 5, at 539. *See also* Sander Rabin, *The Human Use of Humanoid Beings: Chimeras and Patent Law*, 24 NATURE BIOTECHNOLOGY 517, 517-19 (2006); Dennis Crouch, *USPTO: Still No Patent on Life Containing Human Cells*, PATENTLY-O, Feb. 23, 2005, *available at* http://www.patentlyo.com/patent/2005/02/uspto_still_no_.html. *But see* S. 681, 110th Cong. § 1 (2007) (introducing legislation that would ban the patenting of certain tax planning methods). The USPTO has implemented a policy of refusing to grant patent claims that would encompass a human being. *See* MANUAL OF PATENT EXAMINING PROCEDURE § 2105 (2007) (opining that human beings are not patentable subject matter under 35 U.S.C. § 101 (2006)). Since 2004, Congress has included in general appropriations legislation the so-called Weldon Amendment, which provides that none of the funds appropriated to the USPTO in that year can be used to issue patents directed to or encompassing a human organism. However, it has been noted that the amendment has had little if any impact on USPTO practice because, *inter alia*, it fails to define "human" and did not amend the patent statute so as to provide a basis for rejecting such a claim. *See* Margo A. Bagley, *A Global Controversy: The Role of Morality in Biotechnology Patent Law*, 327-30 (Univ. of Va. Law School Pub. Law and Legal Theory Working Paper Series, Working Paper No. 57, 2007), *available at* http://law.bepress.com/cgi/viewcontent.cgi?article=1097&context=uvalwps. For example, the provision has not been interpreted by the USPTO to include human cloning patents. *Id.* at 327-29.

assumption that gene patents, and particularly patents claiming human genes, have been detrimental to the public interest? More specifically, have gene patents been asserted in a manner that restricts personal autonomy, offends human dignity, impedes biomedical research, or harms public health? If problems truly exist, is the GRAA a proportionate response, or might there be more sound alternatives to a blanket prohibition on the patenting of polynucleotides? What might be the unintended consequences of the proposed ban?

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, the genome possesses a singularly important, perhaps even sacred status as the blueprint of life.[7] 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.[8] 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 disease should retain control over the mutations associated with their disease.[9] Clearly, some of the concerns arise from widespread misunderstanding of the nature of the patent grant. For example, some have suggested that a gene patent permits the patent owner to do things with other people's genes,[10] or "that a person whose body includes a patented gene could be [found] guilty of patent infringement."[11] Some have even suggested that patents on human genes constitute a form of slavery.[12]

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[7] *See e.g.*, Brian Gargano, *The Quagmire of DNA Patents: Are DNA Sequences More Than Chemical Compositions of Matter?*, 2005 SYRACUSE SCI. & TECH. L. REP. 3, 16 (2005); Carl T. Hall, *Biotech Industry Battles Move to Ban Patents*, S.F. CHRON., May 16, 1995, at D1(discussing the "Joint Appeal Against Human and Animal Patenting" a document signed by "[a]bout 200 individuals from 80 religious organizations . . ." that "paints the whole idea of patenting life as akin to heresy."); David B. Resnik, *DNA Patents and Human Dignity*, 29 J.L. MED. & ETHICS 152, 157 (2001).

[8] *See e.g.*, Gargano, *supra* note 7, at 16; Hall, *supra* note 7; Resnik, *supra* note 7, at 157. *See also*, Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001) [hereinafter Utility Examination Guidelines]; Timothy R. Holbrook, *The Expressive Impact of Patents*, 84 WASH. U. L. REV. 573, 588 (2006) (arguing that patents on human genes can result in expressive harms to a person's identity, particularly in the context of genes linked to sexual orientation).

[9] Reaping the Benefits, *supra* note 3, at 64-65 (reporting a dispute between patient families and a hospital over the patenting of the gene associated with Canavan Disease); Debra L. Greenfield, Greenburg v. Miami Children's Hospital: *Unjust Enrichment and the Patenting of Human Genetic Material*, 15 ANNALS HEALTH L. 213, 213-14 (2006).

[10] *See* 153 CONG. REC. E315-16 (daily ed. Feb. 9, 2007) (statement of Rep. Becerra) (asserting that "who we are is owned by someone else . . ." and that "we have absolutely no say in what those entities do with our genes.") [hereinafter Becerra Statement].

[11] Utility Examination Guidelines, *supra* note 8, at 1093.

[12] Gargano, *supra* note 7, at 21; Greenfield, *supra* note 9, at 213; Resnik, *supra* note 7, at 157.

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 pursue follow-on research subsequent to the initial discovery of a gene.[13] Some fear that these patents, by inhibiting biomedical research, will substantially delay, or even prevent, the development of potentially life saving cures.[14] Another concern is 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.[15]

Both moral and utilitarian concerns figure prominently in Congressman Becerra's statement accompanying the introduction of GRAA in Congress.[16] He begins by appealing to morality, citing the impact of human genes on personal autonomy and warning that "one-fifth of the blueprint that makes up you – me – our children – all of us – who we are is owned by someone else. And we have absolutely no say in what those patent holders do with our genes. This cannot be what Watson and Crick intended [sic]."[17] However, the statement quickly shifts its 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 test in progress because of gene patents."[18] 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 . . . ."[19] He also implies that gene patents

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[13] Michael Heller & Rebecca Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 701 (1998); Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCIENCE 239, 239-40 (2004); *Cf.* Lori Andrews et al., *When Patents Threaten Science*, 314 SCIENCE 1395, 1395-96 (2006).

[14] Crichton, *supra* note 1; Becerra Statement, *supra* note 10, at E316.

[15] *See* Timothy Caulfield et al., *Evidence and Anecdotes: An Analysis of Human Gene Patenting Controversies*, 24 NATURE BIOTECHNOLOGY 1091, 1091-94 (2006); *see also* American College of Medical Genetics, *supra* note 3; Bryan William-Jones, *History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 HEALTH L. J. 123, 144 (2002).

[16] Becerra Statement, *supra* note 10, at E316.

[17] *Id*. at E316. Watson and Crick are credited with discovering the double helix structure of DNA and were awarded a Nobel prize in connection with this important scientific breakthrough.

[18] *Id*.

[19] *Id*.

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.[20]

Generally speaking, published statements criticizing human gene patents tend to provide little documented evidence of specific instances where such fears have actually manifested themselves.[21] 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 genes residing naturally in the human body, and patent claims reciting human genetic sequence vary dramatically in scope on a claim-by-claim basis.[22] 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.[23] In fact, although critics such as 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.

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.[24] 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.[25] 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.[26] A dispute between Miami Children's Hospital and patient families over patent rights relating to genetic mutations associated with Canavan disease is the other widely cited horror story of alleged harm from patenting human genes, but this was a dispute over control of the patents, and did not involve an attempt by the patent owner to enforce its patents in court.[27] In fact, it appears that the disputed patents have never been asserted in

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[20] *Id*.

[21] For example, no references are provided to support the shocking statistics cited in the Becerra Satement, *see supra*, note 10 at E316.

[22] *See infra* Sections IV-VI.

[23] *See, e.g.,* Wil S. Hylton, *Who Owns This Body?*, ESQUIRE, June 1, 2001 ("It might be in your body, but it doesn't belong to you.").

[24] Caulfield, *supra* note 15, at 1091.

[25] *Id*. *See also* William-Jones, *supra* note 15, at 123.

[26] *See* Caulfield, *supra* note 15, at 1092-93. There have been reports of adverse effects of patents claiming non-human genes, particularly genes of pathogenic microorganisms and viruses. *See, e.g.,* Becerra Statement, *supra* note 10.

[27] REAPING THE BENEFITS, *supra* note 3, at 64-65; Greenfield, *supra* note 9.

court.[28] Even the Myriad example is based primarily on anecdotal reports of laboratories voluntarily curtailing their genetic testing services involving the BRCA gene due to fears of patent liability, fears which are based on subjective assessments of risk by laboratory directors.[29] In fact, Myriad has rarely asserted its patents in court, and those lawsuits settled early before any substantive ruling on the merits.[30] The mere threat of a lawsuit clearly has the potential to substantially impede follow-on research and access; however, voluntary acquiescence to a threat of lawsuit is different than actual judicial enforcement, and this distinction is relevant to policy discussions.

The paucity of documented examples in which 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 the 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, objectively validating the tangible impact of these patents.[31] Likewise, in the biomedical sector courts have found patents on fundamental biological pathways and correlations infringed and not invalid, raising substantial public policy concerns.[32] In contrast, the case against gene patents is attenuated to the extent it relies 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 attempts to inform the debate regarding gene patents by identifying and analyzing instances in which a human gene patent has been the subject of a lawsuit alleging infringement. Section II begins by discussing the nature of the patent grant, particularly as manifested in the context human gene patents, and seeks to dispel any perception that a patent claim reciting a human genetic sequence is equivalent to "ownership" of a human gene. Section III explains the rationale for focusing this study on the small subset of issued human gene patents which have been asserted in court, and why litigation serves as a useful (albeit by no means exclusive) measure of patent impact. Section IV explores the challenges attendant to any attempt to provide a unitary definition for the term "human gene patent," and formulates a working definition of the term for use in this article. Section V provides a description of the search methodology used to identify all human gene patent litigations, and discusses

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[28] The search for human gene patent litigation which forms the basis for this article failed to identify an instance where the Canavan disease gene patents were ever asserted in court.

[29] Jon F. Merz et al., *Diagnostic Testing Fails the Test*, 415 NATURE 577, 577-79 (2002).

[30] *See infra* Section VI.

[31] *See, e.g.,* Microsoft v. AT&T, 127 S. Ct. 1746 (2007); eBay Inc. v. MercExchange, L.L.C., 126 S. Ct. 1837 (2006); Eolas Techs., Inc. v. Microsoft, 399 F.3d 1325 (Fed. Cir. 2005); Amazon.com, Inc. v. Barnesandnoble.com, Inc., 239 F.3d 1343 (Fed. Cir. 2001).

[32] Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings, 370 F.3d 1354, 1361 (Fed. Cir. 2004) (claim infringed by doctors correlating patient homocysteine and vitamin B levels); Ariad Pharm., Inc. v. Eli Lilly & Co., No. 02-11280-RWZ, 2007 U.S. Dist. LEXIS 49076, *5 (D. Mass. July 6, 2007) (claim infringed by use of drug that represses Nuclear Factor Kappa B pathway).

some of the difficulties encountered and limitations of the databases and search strategies employed. Section VI describes and discusses the human gene patent litigations identified. These litigations are broken out into three categories based on the nature of the allegedly infringing activity: production of protein therapeutics (i.e., biologics), research tools, and genetic testing. Particular emphasis is placed on assessing the impact of the litigations, in terms not only of litigation frequency, but also the nature of the allegedly infringing act, the overall context surrounding the litigation, the vigor with which the dispute is litigated, and the outcome of the litigation. Finally, Section VII concludes with some observations on the implications of the study, particularly as they relate to the GRAA and to the direction of future policy in this area.

One of the primary objectives of this article is to "put a face" on human gene patents and human gene patent litigation. It is not surprising that human gene patents, when considered in the abstract, raise an almost visceral opposition among many, particularly in an environment where these patents are characterized as conferring ownership on a person's genes and body. However, a more reasoned and appropriate response to human gene patents can only come out of a richer and more nuanced understanding of the nature of specific patents falling within this category. For example, one patent that would be considered by many as a "human gene patent" has claims limited to Chinese hamster ovary (CHO) cells that have been recombinantly engineered to include a genetic construct that encodes the therapeutically relevant human protein interferon-β.[33] Such a patent falls short of conferring ownership on a human gene; it restricts only a very small fraction of the potential uses of the claimed gene and is demonstrably susceptible to avoidance by design-around.[34] Not only that, it could very well incentivize the development of a life-saving drug. For the most part, specific examples of human gene patents and human gene patent litigation will probably provoke far less consternation than the abstract concept, although as discussed below there are some human gene patents that clearly do raise public policy concerns and might warrant some intervention, especially in the context of genetic testing.[35]

II. THE CRUCIAL DISTINCTION BETWEEN OWNING A GENE PATENT AND OWNING A GENE

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 is equivalent to "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. Statements by Rep. Becerra, for example, evidence

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[33] U.S. Patent No. 4,431,740 (filed June 8, 1982). *See also infra* Section VI (discussing patent in the context of Biogen v. Berlex, 318 F.3d 1132 (Fed. Cir. 2003)).

[34] *See infra* Section VI.

[35] *See infra* Section VI.

confusion on this point by asserting that owners of gene patents can do whatever they want with the genes in our bodies, and that we have "absolutely no say" in the matter.[36] 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.[37] In particular, 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 U.S.[38]

Importantly, a patent in no way expands the patent owner's ability to do what it wants with the patented subject matter. Researchers and others are generally 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 general rule. To be sure, a variety of legal restrictions limit 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.[39] Congress is currently considering legislation that would ban certain uses of an individual's genetic information.[40] 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 human-derived genetic sequence.[41] These patents should generally pose no impediment to use of the recited gene in other contexts. For example, a patent with claims limited to expression of a

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[36] Becerra Statement, *supra* note 10, at E316.

[37] F. Scott Kieff, *Perusing Property Rights in DNA*, *in* PERSPECTIVES ON PROPERTIES OF THE HUMAN GENOME PROJECT 127 (F. Scott Kieff ed., 2003).

[38] 35 U.S.C. § 271 (2006). For a discussion of this distinction between the rights conferred by a patent versus what most people think of as "ownership," and the implications for policy decisions regarding genetic-based patents, see Kieff, *supra* note 37, at 127-30.

[39] FDA Center for Biologics Evaluation and Research,, Cellular & Gene Therapy, http://www.fda.gov/cber/gene.htm (last visited Jan. 30, 2008).

[40] Genetic Information Nondiscrimination Act of 2007, H.R. 493, 110th Cong. (2007) (prohibiting discrimination on the basis of genetic information with respect to health insurance and employment).

[41] The term "human-derived" is used because many of the patented genetic constructs are chemically distinct from actual human genes, but were originally derived from human genes and are functionally and structurally related to actual genes, e.g., cDNA. *See* ALBERTS ET AL., *infra* note 67.

human gene in certain recombinant mammalian cell culture systems does not restrict research on the gene or other commercial uses of the gene, including expression of the identical gene in an alternate mammalian cell culture.[42] Likewise, a patent limited to a hybridization microarray employing a defined set of genetic sequences does not restrict the use of those sequences in other contexts.[43] 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.[44] These are just a few of the many examples of gene patents which have been characterized as "claiming the gene,"[45] which some have extrapolated to outright "ownership" of the genes.[46] 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.[47] 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. While in some cases a broad patent claim might encompass many non-natural uses of a genetic sequence, it is a mistake to conflate this with the concept of ownership in the context of genes.

III. THE RATIONALE FOR FOCUSING ON LITIGATED PATENTS

While the literature includes numerous empirical studies of gene patents, often focusing on human gene patents,[48] I am not aware of any that have 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 put a face on human gene patent litigation in order to facilitate a more informed policy debate. Many of the concerns that

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[42] *See* U.S. Patent No. 5,356,804 (filed Oct. 24, 1990); *see also* Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1105-06 (Fed. Cir. 2003) (finding the '804 patent was not infringed by a mammalian cell culture produced using an alternate, later developed technology).

[43] For a discussion of such a patent, see Jensen & Murray, *supra* note 13, at 239.

[44] *See, e.g.*, U.S. Patent No. 6,673,562 (filed Jan. 6, 2004); U.S. Patent No. 5,851,795 (filed Dec. 22, 1998); U.S. Patent No. 5,844,095 (filed Dec. 1, 1998).

[45] Jensen & Murray, *supra* note 13, at 239-40 (characterizing these patents as claiming the gene).

[46] Becerra Statement, *supra* note 10, at E316; Crichton, *supra* note 1.

[47] The point that patents do not confer ownership on genes has been made by the USPTO. Utility Examination Guidelines, *supra* note 8, at 1093 ("Patents do not confer ownership of genes, genetic information or sequences.").

[48] *See* Jensen & Murray, *supra* note 13, at 239-40.

have been expressed arise out of a tendency by many to consider gene patents in the abstract. However, any serious assessment of the impact of human gene patents should only proceed from a more sophisticated understanding of the phenomenon that can only be gained by considering the specific details of human gene patent claims and their enforcement pattern.

Of course, one might argue that by focusing solely on litigated patents this 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 expensive infringement lawsuit.[49] 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, 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 threat of human gene patents by polling laboratory directors for their subjective assessment of liability risk.[50]

John Allison and colleagues recently argued convincingly that patent litigation (i.e., the filing of an infringement-related lawsuit) is a good indicator of patent value.[51] They 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.[52]

In this article, 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 have an impact are likely valuable and valuable patents are likely having an impact. But this article focuses 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, if patent infringement lawsuits are rarely filed in connection with human gene patents, then perhaps these patents are not having as much

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[49] Merz et al., *supra* note 29, at 577-79.

[50] *See, e.g.,* Elizabeth A. Rowe, *The Experimental Use Exception To Patent Infringement: Do Universities Deserve Special Treatment?*, 57 HASTINGS L.J. 921, 942-45 (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). This is not to say that subjective assessment of risk is not relevant, since it can inform decisions and result in a laboratory deciding to refrain from certain important activities. Still, it is worthwhile to assess the extent to which such fears can be objectively validated. If the actual level of risk is less than the subjective perception, perhaps an awareness of actual risk can shift the perception and embolden laboratories to continue activities they might otherwise terminate out of an exaggerated perception of risk.

[51] *See generally*, John R. Allison et al., *Valuable Patents*, 92 GEO. L. J. 435 (2004).

[52] *Id*. at 435, 441-43.

impact as has been feared, and do not warrant immediate, exceptional or extreme countermeasures, as exemplified by the GRAA.

This article does not assume that litigation is the sole measure of patent impact, far from it. For example, a patent used to extract licensing fees clearly has some impact. But, as noted by Allison and his co-authors, 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.[53] 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.[54] 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.[55] Biotechnology companies and universities are not shy about litigating over patents in general.[56] If non-litigated gene patents for some reason pose unique obstacles to biomedical progress, perhaps this represents a market failure which should be addressed, but at this point it seems far from clear that legislation imposing a broad ban on gene patenting is the most appropriate response.

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.[57] A huge number of patents exist purporting to cover many of the tools, reagents and protocols used in research laboratories throughout the U.S. every day, including human gene patents.[58] Studies have shown that these patents have had a relatively minor 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 let the existence of patents dictate research agendas.[59] These

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[53] *Id*. at 442 ("we are skeptical that there is a large class of extremely valuable but never-litigated patents.").

[54] *Id*.

[55] *Id.*

[56] Mark A. Lemley & Carl Shapiro, *Probablistic Patents*, 19 J. ECON. PERSPECTIVES 75, 79 (2005) (litigation rates vary by industry and are particularly high in biotechnology). This author's unpublished study on university patent litigation identified numerous instances where universities have actively litigated over their patent rights.

[57] An exception to this general rule exists for drug patents listed in the Orange Book pursuant to the Hatch-Waxman Act. *See* Christopher M. Holman, *Do Reverse Payment Settlements Violate The Antitrust Laws*?, 23 SANTA CLARA COMPUTER & HIGH TECH. L.J. 489, 513-14 (2007).

[58] *See generally* John P. Walsh et al., *Effects of Research Tool Patents and Licensing on Biomedical Innovation*, *in* PATENTS IN THE KNOWLEDGE-BASED ECONOMY 285-340 (Wesley M. Cohen & Stephen A. Merrill eds., 2003); John P. Walsh et al., *Working Through the Patent Problem*, 299 SCIENCE 1021, 1021 (2003); John P. Walsh & Wei Hong, *Secrecy is Increasing in Step with Competition*, 422 NATURE 801, 801-802 (2003); John P. Walsh et al., *View from the Bench: Patents and Material Transfers*, 309 SCIENCE 2002, 2002-03 (2005) [hereinafter Walsh et al., View from the Bench].

[59] Walsh et al., *View from the Bench*, *supra* note 58, at 2003.

researchers are behaving rationally, because in fact, basic research activities have rarely, if ever, been the subject of a patent infringement lawsuit.[60] Regardless of the number and breadth of claims 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 in fear of otherwise being sued for infringement. A patent that is ignored and never asserted should have no direct impact on biomedical research or the public interest.[61]

An important advantage of focusing on patent litigation, as opposed to the mere issuance of patents by the USPTO, 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. Such a scenario in which the patent functions to deny patients access to important medical technology, were it ever to occur, 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 the patent owner's unique proprietary protein expression system would be much less problematic, particularly if alternate technologies for producing a functionally equivalent product are readily available. In fact, the patent in such a scenario might be serving a positive role in incentivizing the necessary investment in the research and development of life-saving therapeutics. In short, while critics might decry the large number of patents claiming human genes, any potential for negative impact is attenuated to the extent these patents are not asserted in a manner contrary to the public interest.

My decision to focus solely on litigated *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 many of the patents of most relevance to agricultural and veterinary

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[60] I am currently conducting a study focused on university patent litigation, in connection with which I conducted a rigorous search to identify all university patent litigations. I was unable to find a single case, subsequent to the Federal Circuit's 2002 *Madey* decision wherein a university was sued for patent infringement based solely on use of patented technology in basic, non-commercial research. Madey v. Duke Univ., 307 F.3d 1351, 1361-62 (Fed. Cir. 2002) (finding university research generally does not fall within research use exemption). Even *Madey* is better characterized as an employment dispute rather than a lawsuit filed against a university for conducting basic research. *See* Chris Holman, *Clearing a Path Through the Patent Thicket*, 125 CELL 629, 632 (2006).

[61] This is aside from the psychic injury apparently brought about in some by the mere knowledge that such patents exist. The patent might be of some tangible benefit to the inventor, to the extent it is perceived as evidence of productivity, or to the patent owner, who might use the patent as the basis for securing investment funding. *See, e.g.*, Christopher M. Holman, *Biotechnology's Prescription for Patent Reform*, 5 J. MARSHALL REV. INTELL. PROP. L. 318, 327-29 (2006).

biotechnology. Patents claiming genetic sequences of important human pathogens, such as the hepatitis C virus and HIV, have raised substantial policy concerns, and some have been the subject of litigation.[62] However, human gene patents have been the primary focus of the controversy surrounding gene patents and provide a useful demarcation to limit the scope of the present study.[63]

IV. DEFINING THE TERM "HUMAN GENE PATENT"

As a preliminary to discussing human gene patents, we should stop to consider exactly what is meant by the 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.[64] In fact, many patents routinely referred to as "gene patents" actually claim molecular constructs that do not exist in nature, but that instead merely correspond to, or are derived from, naturally occurring genes.[65]

In classical genetics, the word "gene" was used to refer to the fundamental unit of inheritance.[66] 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.[67] Today, the term "gene" is often defined as genetic material that encodes a protein.[68] 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, as of July 16, 2007, *Wikipedia* defined 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,

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[62] Chiron Corp. v. LabCorp et al., No. 03-03707 (N.D. Cal. Aug. 7, 2003) (U.S. Patent No. 6,531,276, claiming method of detecting human immunodeficiency virus (HIV)); Chiron Corp. v. National Genetics Institute et al., No. 03-01521 (N.D. Cal. April 9, 2003) (U.S. Patent No. 6,074,816, claiming reagent for detecting hepatitis C virus (HCV)).

[63] For example, although the bill to ban gene patents is not limited to humans, or even to genes for that matter (encompassing any nucleotide sequence), the ire of individuals such as Congressman Becerra and Michael Crichton seems particularly directed at "human gene patents" and the ownership of human genes. *See supra* Section I. The seminal Jensen & Murray study 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. Jensen & Murray, *supra* note 13, at 239.

[64] *See e.g.*, Helen Pearson, *Genetics: What Is a Gene?*, 441 NATURE 398, 398 (2006) ("The idea of genes as beads on a DNA string is fast fading. Protein-coding sequences have no clear beginning or end and RNA is a key part of the information package . . . ."); Elizabeth Pennisi, *DNA Study Forces Rethink of What It Means to Be a Gene*, 316 SCIENCE 1556, 1556-57 (2007).

[65] Examples include the patents claiming cDNA discussed *infra* in this section.

[66] Pearson, *supra* note 64, at 399.

[67] *Id.*; BRUCE ALBERTS ET AL., THE MOLECULAR BIOLOGY OF THE CELL 254-55, 595 (2d ed. 1998).

[68] Jensen & Murray, *supra* note 13, at 240 n.2 (defining the term as "a set of cotranscribed protein-encoding exons"). *See also infra* Section IV.

> transcribed regions dictating the sequence of the RNA product, and/or other functional sequence regions.[69]

This *Wikipedia* definition seems as good as any I have come across, and highlights many of the issues glossed over in much of the current debate over gene patents.[70] For example, instead of defining a gene as DNA encoding a protein, it defines it as a *nucleic acid* that encodes a functional RNA.[71] 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

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[69] Wikipedia.org, Gene, http://en.wikipedia.org/wiki/Gene#_note-Pearson_2006 (last visited July 16, 2007). For those who might question my citation to Wikipedia, see Jim Giles, *Special Report: Internet Encyclopaedias Go Head to Head*, 438 NATURE 900, 900 (2005) (reporting investigation by NATURE that concluded that *Wikipedia* comes close to ENCYCLOPEDIA BRITANNICA in terms of the accuracy of its science entries). In contrast, ENCYCLOPEDIA BRITANNICA ONLINE defines a gene as a "unit of hereditary information that occupies a fixed position (locus) on a chromosome. Genes achieve their effects by directing the synthesis of proteins." http://www.britannica.com/eb/article-9036352/gene (last visited Jan. 22, 2008). The ENCYCLOPEDIA BRITANNICA ONLINE definition is outdated for focusing solely on protein synthesis, implicitly excluding genes that encode functional RNA, and thus is less comprehensive and less accurate than the Wikipedia definition. Wikipedia definitions are constantly evolving, and as of January 15, 2008, its definition of gene has been substantially revised relative to the version I accessed in July, 2007. This revision reflects the continuing evolution of the scientific community's understanding of the word gene, as described infra in this section. I opted to focus my discussion on the July, 2007, version of the Wikipedia definition of gene, which has the virtue of relative brevity while including the important features that are generally understood to define genes.

[70] Perhaps more importantly for those considering policy, the converse is also true. The term DNA is used in a variety of non-genetic and non-biological applications, such as nanotechnology and DNA computers. *See, e.g.*, Constantin Pistol & Chris Dwyer, *Scalable, Low-Cost, Hierarchical Assembly of Programmable DNA Nanostructures* 18 NANOTECHNOLOGY 125305, 125305 (2007) ("demonstrating a method for the assembly of fully programmable, large molecular weight DNA complexes."); Paul W. K. Rothemund, *Folding DNA to Create Nanoscale Shapes and Patterns*, 440 NATURE 297 (2006); William A. Shih et al., *A 1.7-kilobase Single-Stranded DNA that Folds into a Nanoscale Octahedron*, 427 NATURE 618 (2004); Chris Dwyer, Assistant Prof., Duke University, Website, http://www.ee.duke.edu/~dwyer/ (last visited Jan. 15, 2008) (describing DNA self-assembly for computer system fabrication and hybrid DNA/silicon semiconductor processing); Paul W.K. Rothemund, Senior Research Fellow, California Inst. of Tech., Website, http://www.dna.caltech.edu/~pwkr/ (last visited Jan. 15, 2007) (describing methods of making nanoscale shapes and patterns using DNA); William Shih, Assistant Prof., Harvard Med. Sch., Website, http://research2.dfci.harvard.edu/shih/ (last visited Jan. 15, 2008) (describing the lab's efforts using DNA to create mechanically-functional motifs).

[71] The terms "polynucleotide" and "nucleic acid" are generally used interchangeably, particularly in the patent context, and are used interchangeably in this article. *See, e.g.*, U.S. Patent Application No. 2003/0083480 ("The terms 'polynucleotide,' 'nucleotide sequence,' and 'nucleic acid' are used to refer to a polymer of nucleotides"). DNA and RNA are important examples of polynucleotides that serve as the primary genetic molecules in living organisms. ALBERTS ET. AL., *supra* note 67, at 95-106.

nucleic acid.[72] The definition would also encompass messenger RNA ("mRNA"), the nucleic acid that serves as an intermediate in the expression of a protein from the corresponding gene.[73]

More relevant to a discussion of human gene patents, the Wikipedia definition focuses on the production of a *functional RNA* rather than an encoded *protein*.[74] RNA production is an intermediate step in the expression of a gene-encoded protein, so this definition encompasses the traditional notion of a gene as a protein-encoding genetic sequence.[75] The definition also includes the production of RNA that is not subsequently translated into protein, so it is substantially broader than more traditional definitions limited to protein-encoding genes.[76] It has long been recognized that certain RNA molecules function directly, rather than as intermediates in protein expression.[77] Important examples would include transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs), RNA molecules involved in the biochemical processes required to translate an mRNA into the corresponding protein.[78] 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.[79] 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.[80] 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.[81] The Wikipedia definition of "gene" also includes regulatory regions that are not themselves transcribed into RNA, but that regulate transcription, such as promoter and enhancer regions.[82]

The Wikipedia definition would also seem to encompass artificial, non-naturally occurring nucleic acid sequences that encode a functional RNA

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[72] For a definition of retrovirus, see Wikipedia.org, Retrovirus, http://en.wikipedia.org/wiki/Retrovirus (last visited Jan. 30, 2008).

[73] Wikipedia.org, RNA, http://en.wikipedia.org/wiki/RNA (last visited Jan. 30, 2008).

[74] Wikipedia.org, Gene, http://en.wikipedia.org/wiki/Gene#_note-Pearson_2006 (last visited July 16, 2007).

[75] *Id.*

[76] *Id.*

[77] Wikipedia.org, RNA, http://en.wikipedia.org/wiki/RNA (last visited Jan. 15, 2008); ALBERTS ET. AL., *supra* note 67, at 101-06.

[78] The term "translation" refers to the biochemical processes which take the sequence information embedded in an mRNA sequence and translating that into the encoded protein.

[79] Pearson, *supra* note 64, at 400.

[80] *Id*.

[81] *Id*.

[82] Wikipedia.org, Gene, http://en.wikipedia.org/wiki/Gene#_note-Pearson_2006 (last visited July 16, 2007). For a description of promoter and enhancer regions, see ALBERTS ET AL., *supra* note 67, at 203-205, 564-69.

product.[83] For example, it would appear to encompass complementary DNA (cDNA) molecules, i.e., non-naturally occurring DNA molecules that are created in the laboratory and which correspond in sequence to a protein-encoding mRNA.[84] 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.[85] As a consequence, most 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 and hence generally cannot express human genes directly.[86] cDNA molecules, although they do not occur in nature, encode directly for native proteins and are often classified as genes.[87] In fact, some of the earliest reported judicial decisions involving "gene" patents actually involved claims directed to cDNA, not naturally occurring genes.[88] 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.[89]

I now turn to the critical task of defining the term "human gene patent" for the purpose of this article. Some of the misperceptions and undue fear surrounding gene patents likely stems from the failure of much of the published commentary on gene patents to explicitly define the term, or even to provide a specific example of a gene patent.[90] As a starting point, I again refer to *Wikipedia*, which defines "gene patents" as "patents on specific sequences of genes, their usage, and often their chemical composition."[91] This is for the most part a reasonable definition, at least for a lay audience.[92] *Wikipedia's* definition

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[83] Wikipedia.org, Gene, http://en.wikipedia.org/wiki/Gene#_note-Pearson_2006 (last visited July 16, 2007).

[84] ALBERTS ET. AL., *supra* note 67, at 260-62.

[85] *Id.* at 102, 487.

[86] *Id.* at 102.

[87] For example, many of the human gene patents identified by Jensen & Murray claim cDNA molecules, not naturally genomic genes as they occur in the human genome. *See* Jensen & Murray, *supra* note 13, at 239-40. *See also*, the patents asserted in Incyte Genomics Inc. v. Invitrogen Corp., Civ. No. 01-2141 (S.D. Cal.), discussed *infra* Section VI.

[88] *See, e.g.*, Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1562 (Fed. Cir. 1997); *In re* Deuel, 51 F.3d 1552, 1553 (Fed. Cir. 1995); *In re* Bell, 991 F.2d 781 (Fed. Cir. 1993).

[89] Wikipedia.org, Gene, http://en.wikipedia.org/wiki/Gene#_note-Pearson_2006 (last visited July 16, 2007); *see, also* Linda A. Castle et al., *Discovery and Directed Evolution of a Glyphosate Tolerance Gene,* 304 SCIENCE 1151 (2004) (describing creation of a novel, non-naturally-occurring gene that breaks down glyphosate (ROUNDUP®) and thereby confers glyphosate resistance on plants expressing the gene).

[90] This problem is alluded to in Jensen & Murray, *supra* note 13, at 239.

[91] Wikepedia.org, Gene Patents, http://en.wikipedia.org/wiki/Gene_patents (visited Jan 30, 2008).

[92] The above reference to "specific sequences of genes . . . and often their chemical composition;" however, 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

includes "usages" of genes, which comports with the GRAA's proposal to ban the patenting of the "functions and correlations" of "nucleotide sequences."[93] Note that the term "usages" might 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 itself 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.[94] 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.[95] Citing to this precedent, the USPTO 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.[96] In general, 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.[97]

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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. The GRAA also used the term "nucleotide sequence," but it seems clear that the intent is to cover polynucleotides, i.e, the actual molecules rather than information *per se*.

[93] Wikepedia.org, Gene Patents, http://en.wikipedia.org/wiki/Gene_patents (visited Jan 30, 2008); *see* H.R. 977, *supra* note 4.

[94] Utility Examination Guidelines, *supra* note 8, at 1092. *But see* U.S. Patent No. 6, 421,613 (filed July 16, 2002) (claiming a data structure supporting computer access to data representing a specified genetic sequence).

[95] Utility Examination Guidelines, *supra* note 8, at 1093. For example, in 1873 Louis Pasteur received U.S. Patent No. 141,072, claiming "yeast, free from organic germs of disease, as an article of manufacture." U.S. Patent No. 141,072 (filed July 15, 1873). 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. *See e.g.,* In re Bergstrom, 427 F.2d 1394, 1397 (C.C.P.A. 1970); Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95, 103 (S.D.N.Y. 1911). Purified native proteins are also routinely patented. *See, e.g.,* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1202-04, 1219 (Fed. Cir 1991) (alleging infringement of U.S. Patent No. 4,677,195, which claims purified erythropoietin); Scripps Clinic & Research Found. v. Genentech, Inc., 927 F.2d 1565, 1568, 1581-82 (Fed. Cir. 1991) (alleging infringement of U.S. Reissue Patent No. 32,011, which claims purified Factor VIII:C).

[96] The point that patents do not confer ownership on genes has been made by the USPTO. Utility Examination Guidelines, *supra* note 8, at 1093.

[97] *Id*. *See*, Fiers v. Revel, 984 F.2d 1164, 1169 (Fed. Cir. 1993); Amgen v. Chugai, 927 F.2d 1200, 1206 (Fed. Cir. 1991); Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568 (Fed. Cir. 1997); *In re* Deuel, 51 F.3d 1552, 1557-58 (Fed Cir. 1995). *See also* Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?*, 17 BERKELEY TECH. L.J. 1155, 1174-82 (2002). 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

Some previous studies of human gene patenting have apparently classified any patent that discloses a human gene as a human gene patent.[98] 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. 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 human gene patent since it provides no basis on which to exclude any use of a human gene and in no sense confers ownership of the gene.[99]

Another complication in defining human gene patents is that patent claims reciting human genetic sequences vary widely in scope, and can claim either products or processes. 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,[100] a gene fragment,[101] a regulatory region,[102] or a genomic region of unknown function, i.e., so-called "junk DNA."[103] Many product claims broadly encompass any polynucleotide encoding a naturally occurring protein, or even any polynucleotide claiming any variant of a naturally occurring protein.[104] Note that such a claim would probably not cover the native gene including introns, at least 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.[105] These and many other sorts of claims are all commonly referred to as human gene patents.

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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. *See* Brief for Amicus Curia Affymetrix, Inc. in Support of Appellee, 2, 18, In re Fisher, 421 F.3d 1365 (Fed. Cir. 2005) (No. 04-1465).

[98] Jensen & Murray, *supra* note 13, at 239.

[99] *See, e.g.*, U.S. Patent No. 7,238,376 (filed July 3, 2007) (specification discloses sequence fragments from BRCA gene, while claims are limited to a method of treatment using black tea extract); U.S. Patent No. 7,238,469 (filed July 3, 2007) (specification discloses mouse gene sequence fragments, while claims are limited to a method of administering carbon monoxide during an organ transplant operation).

[100] U.S. Patent No. 5,616,483 (filed Apr. 1, 1997) (genomic DNA sequences encoding human BSSL/CEL).

[101] U.S. Patent No. 6,204,020 (filed Mar. 20, 2001).

[102] U.S. Patent No. 6,534,268 (filed Mar. 18, 2003).

[103] U.S. Patent No. 4,963,663 (filed Feb. 8, 1989) (asserted in Promega Corp. v. Lifecodes Corp., No. 2:93-CV-0184C, 1999 U.S. Dist. LEXIS 21094 (D. Utah Oct. 27, 1999)) (discussed *infra* Section VI.).

[104] 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, 57-74 (2004). *See, e.g.*, U.S. Patent No. 5,215,892 (filed Oct. 22, 1990).

[105] The claims encompass an astronomical number of different polynucleotides, a consequence of the redundancy of the genetic code. *See* Holman, *supra* note 104, at 58-61.

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.[106] In many cases a patent will claim only a single variant, such as the predominant wild-type sequence,[107] or perhaps one or more specific polymorphic forms, such as specific BRCA mutations associated with a predisposition towards cancer.[108] Some claims are drafted in a manner that attempts to encompass any variant of a gene, including as yet undiscovered variations.[109] In some cases, these patents broadly claim any recombinant or isolated form of naturally occurring gene sequence; these are probably the closest thing to a patent claiming a gene *per se*, since on their face they would appear to cover any biotechnological product or process making or using the claimed sequence.[110] In many cases, 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.[111] These claims

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[106] *See* REAPING THE BENEFITS, *supra* note 3, at 62-63.

[107] *See, e.g.*, U.S. Patent No. 5,747,282 (filed June 7, 1995) (Claim 1: An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.).

[108] *See, e.g.*, U.S. Patent No. 5,693,473 (filed June 7, 1995) (Claim 1: An isolated DNA comprising an altered BRCA1 DNA having at least one of the alterations set forth in Tables 12A, 14, 18 or 19 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO:1.).

[109] 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. *See* Holman, *supra* note 104, at 60. *See also*, U.S. Patent No. 5,258,287 (filed Mar. 22, 1988). Claim 1:

> An isolated DNA molecule comprising a sequence that hybridizes, under stringent conditions of 50% formamide with 0.75M NaCl and 0.075M sodium citrate, at 42.degree. C., to the portion of the DNA sequence of FIG. 3 coding for mature BP53 or the preprotein for BP53 and which encodes a BP53 protein that binds to IGF-I or IGF-II, excluding BP28, PP 12, and HEP-G2.

Id; U.S. Patent No. 4,703,008 (filed Nov. 30, 1984). Claim 7:

> A purified and isolated DNA sequence consisting essentially of a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession of the biological property of causing bone marrow cells to increase production of reticulocytes and red blood cells, and to increase hemoglobin synthesis or iron uptake.

Id.

[110] *See, e.g.*, U.S. Patent No. 6,001,598 (filed Jan. 20, 1999) (Claim 1: An isolated and purified polynucleotide sequence encoding the human DnaJ-like protein comprising the amino acid sequence of SEQ ID NO:3.).

[111] Numerous examples of such patents that have been litigated are discussed *infra* Section VI.

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 and claim-by-claim 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.[112] Other claims recite polymerase chain reaction (PCR) primers that could be used to amplify the sequence,[113] or some fragment of the sequence.[114] Although these claims do not necessarily cover the genetic sequence directly, they can be extremely effective in covering reagents necessary 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.[115]

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.[116] This runs counter to the conventional wisdom that product claims are generally more powerful than process claims. For example, a claim purporting to encompass any method for identifying the presence of a specified mutation could be difficult, if not impossible, to design around.[117]

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[112] U.S. Patent No. 5,693,473 (filed June 7, 1995). Claim 5:

> A nucleic acid probe specifically hybridizable to human altered BRCA1 DNA and not to wild-type BRCA1 DNA, said altered BRCA1 DNA having one of the alterations set forth in Tables 12A or 14 with the proviso that the alteration is not a deletion of four nucleotides corresponding to base numbers 4184-4187 in SEQ. ID. NO: 1.

Id.

[113] U.S. Patent No. 5,747,282 (filed June 7, 1995). Claim 16:

> A pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene.

Id.

[114] *Id.* (Claim 5: An isolated DNA having at least 15 nucleotides of the DNA of claim 1.).

[115] *See* discussion *infra* in Section VI.

[116] U.S. Patent No. 5,753,441 (filed Jan. 5, 1996). Claim 1:

> A method for screening germline of a human subject for an alteration of a BRCA1 gene which comprises comparing germline sequence of a BRCA1 gene or BRCA1 RNA from a tissue sample from said subject or a sequence of BRCA1 cDNA made from mRNA from said sample with germline sequences of wild-type BRCA1 gene, wild-type BRCA1 RNA or wild-type BRCA1 cDNA, wherein a difference in the sequence of the BRCA1 gene, BRCA1 RNA or BRCA1 cDNA of the subject from wild-type indicates an alteration in the BRCA1 gene in said subject.

Id.

[117] U.S. Patent No. 6,432,644 (filed Nov. 22, 1999). Claim 1:

> A method for diagnosing the presence of a polymorphism in human KCNE1 (the coding region of which is bases 193-579 of SEQ ID NO:3) which causes long QT syndrome wherein said method is performed by means which identify the presence of

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, one of the most influential and informative empirical studies of human gene patenting formed the basis for a 2003 article by Kyle Jensen and Fiona Murray in the prestigious journal *Science*.[118] This study has been widely cited in arguments against gene patents, and is presumably the basis for the assertions by Michael Crichton and Xavier 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) Jensen and Murray defined the term "gene" as "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."[119] Note that their definition of "human gene" is relatively conservative and much narrower than, for example, the *Wikipedia* definition, because it excludes approximately 98% of the human genome that is not thought to encode for proteins, for example, regulatory sequences, transcribed sequences that encode RNA not translated into proteins, and the vast stretches of genomic DNA having no known function, sometimes referred to as "junk" DNA.[120] The Jensen and Murray definition would encompass human genes residing in the genome, and also cDNA molecules produced in a laboratory but corresponding in sequence to human mRNA molecules and proteins.[121]

On the other hand, their definition of "patented" is fairly expansive, and encompasses any patent whose claims reference a human gene sequence, regardless of how limited the scope of the claim.[122] 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,[123] or a hybridization array comprising multiple human gene sequences,[124] or molecules encoding a genetically engineered, non-naturally occurring variant of a human protein.[125]

> said polymorphism, wherein said polymorphism is one which results in the presence of a KCNE1 polypeptide of SEQ ID NO:4 with an altered amino acid, said altered amino acid being selected from the group consisting of: a) a Leu at residue 74.

Id.

[118] Jensen & Murray, *supra* note 13, at 239.

[119] *Id.* at 240.

[120] *Id*.

[121] *Id.*

[122] *Id.*

[123] U.S. Patent No. 5,376,367 (Nov. 22, 1991) (Claim 1: A fusion protein comprising MGF linked to IL-3, wherein MGF and IL-3 are linked via a C-terminal to N-terminal fusion.) (included in Jensen & Murray dataset). Fusion proteins are described in more detail *infra* Section VI.

[124] Jensen & Murray, *supra* note 13, at 239.

[125] U.S. Patent No. 5,444,153 (filed Oct. 11, 1991). Claim 1:

> A plasminogen activator inhibitor type 2 variant in which the 66-98 amino acid residue region of SEQ ID NO: 2 has been altered to eliminate at least one protease sensitive site, which variant maintains biological activity of plasminogen activator

These sorts of claims would encompass only a minute fraction of the potential uses of the human gene, but the Jensen and Murray criterion does not attempt to assess the scope or practical significance of the claims. Although this methodology is perfectly reasonable and suited for what was essentially an automated data-mining survey, gene patent critics such as Crichton and 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 in which the "SEQ ID NO." term is used in conjunction with a specific genetic sequence corresponding to a known human gene.[126] Their search identified 4,270 patents reciting 4,382 human genes, and based on this result they concluded that approximately one fifth of human genes were claimed in U.S. patents.[127]

While their search strategy has the significant advantage of being amenable to automation, permitting them to query the entire set of relevant issued patents, like most search strategies (including those employed in this current study) there are certain limitations, and when disregarded these limitations can render their conclusions susceptible to misinterpretation. Jensen and Murray explicitly noted some of these limitations.[128] 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.[129] But any patent claiming a genetic sequence in this matter would not be identified by their query, unless, as is often the case, the patent also explicitly claims a specific exemplary nucleotide sequence encoding the protein, for example, the specific cDNA isolated by the inventor.[130] A more significant limitation stems from the fact that many human gene patents, particularly older ones, do not use the "SEQ ID NO."

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inhibitor type 2 of SEQ ID NO: 2 amino acids up to 65 and from 99 of plasminogen activator inhibitor type 2 in frame.

Id. ('153 patent was included in Jensen & Murray dataset).

[126] Jensen & Murray, *supra* note 13, at 239.

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

[128] Jensen & Murray, *supra* note 13, at 239 ("we do not consider claims on genes defined through amino acid sequence") and in Supporting Online Material: caveats and notes, *available at* http://www.sciencemag.org/cgi/content/full/310/5746/239/DC1 (last visited Jan. 30, 2008).

[129] Holman, *supra* note 104, at 58-74. The reason for this is that it 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 broader patent protection. *Id.*

[130] *See, e.g.*, U.S. Patent No. 7,196,172 (filed July 14, 2006) (Claim 11: An isolated *polynucleotide* molecule encoding a first *polypeptide* and a second *polypeptide* as shown in claim 1.) ('172 patent was included in Jensen & Murray dataset, emphasis added).

format, and therefore cannot be identified by this search strategy.[131] The use of SEQ ID NO. began in 1990, many years after people began filing patents on genetic sequences.[132] As a result, the oldest patent in the Jensen and Murray dataset was issued in 1993.[133] To this day, patents are allowed to issue with claims that reference genetic sequences without using SEQ ID NO., e.g., claims that identify a gene by its common name rather than explicitly reciting a genetic sequence.[134] In fact, a majority of the litigated human gene patents I identified in this study did not appear in the Jensen and Murray dataset.[135]

An alternative approach to defining and identifying gene patents was used in generating the DNA Patent Database, an online database of DNA patents compiled and administered by the Kennedy Institute of Ethics at Georgetown University.[136] Although the database is identified as a DNA patent database, as opposed to a gene patent database, the focus on DNA and nucleic acids reflects an underlying interest in patents relating to genes.[137] The DNA Patent Database was compiled based on a two stage automated search of the Delphion patent

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[131] *See, e.g.*, Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 15562, (Fed. Cir. 1997) (asserting U.S. Patent No. 4,431,740 (filed June 8, 1982) and U.S. Patent No. 4,652,525 (filed June 28, 1983)).

[132] 37 C.F.R. § 1.821-.825 (2007). *See also*, MANUAL OF PATENT EXAMINING PROCEDURE, *supra* note 6, at § 2420.

[133] U.S. patent No. 5,215,892 (filed Oct. 22, 1990) (issued June 1, 1993). Claim 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.

Id. Jensen & Murray provided me with a database identifying all of the patents identified in their study.

[134] *See, e.g.*, U.S. Patent Nos. 4,703,008 (filed Nov. 30, 1984) (discussed in Amgen, Inc. v. Chugai Pharm. Co., 808 F. Supp. 894, 896 (Fed. Cir. 1991)); U.S. Patent 4,431,740 (filed June 8, 1982) (discussed in *Regents of the Univ. of Cal.*, 119 F.3d at 1562 (Fed. Cir. 1997)); U.S. Patent No. 4,766,075 (filed Apr. 7, 1983) (discussed in Genentech v. Wellcome Found. Ltd., 29 F.3d 1555, 1557 (Fed. Cir. 1994)); U.S. Patent No. 6,025,126 (filed Oct. 28, 1991) (asserted in Ventana Med. Sys., Inc. v. Vysis, Inc,, 2003 WL 23820077 (N.D. Ill. July 15, 2003); U.S. Patent No. 6,414,133 (filed Oct. 13, 1998) (asserted in Ventana Med. Sys., Inc. v. Vysis, Inc,, 2003 WL 23820077 (N.D. Ill. July 15, 2003).

[135] *See infra* Section VI.

[136] DNA Patent Database, http://dnapatents.georgetown.edu/ (last visited Jan. 30, 2008). The center identifies itself as "the world's oldest and most comprehensive academic bioethics center." The Kennedy Institute of Ethics, http://kennedyinstitute.georgetown.edu/index.htm (last visited Jan. 30, 2008).

[137] 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." DNA Patent Database, *About the DPD*, http://dnapatents.georgetown.edu/aboutdpd.htm. (last visited Jan. 30, 2008).

database, and continues to be updated on an ongoing basis.[138] 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.[139] 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.[140]

As of August 24, 2007, the DNA Patent Database included 44,972 patents, roughly 10 times more patents than identified by Jensen and Murray, which in part reflects the highly inclusive nature of the DNA Patent Database search strategy.[141] 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.[142] 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 majority, are not what one would normally consider gene patents.

Cognizant of the limitations of previous attempts to define gene patents, I decided to act as my own lexicographer and for the purpose of this survey to define a "human gene patent" as any patent with a claim directed to a product or

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[138] *See* DNA Patent Database, *Delphion Search Algorithm*, http://dnapatents.georgetown.edu/SearchAlgorithm-Delphion-20030512.htm (last visited Jan. 30, 2007) [hereinafter Delphion Search Algorithim].

[139] MANUAL OF PATENT EXAMINING PROCEDURE, *supra* note 6, at § 902 (describing U.S. Patent Classification System).

[140] *See* Delphion Search Algorithm, *supra* note 138. 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, and SNP.

Id.

[141] *See* DNA Patent Database, *supra* note 138. The Jensen & Murray dataset was compiled several years earlier than my 2007 search of the DNA Patent Database, which would account for a portion of the discrepancy in count. *See* Jensen & Murray, *supra* note 13.

[142] *See* DNA Patent Database, *supra* note 138. For example, one patent in the Patent Database is U.S. Patent No. 7,211,789, assigned to IBM, which is directed to methodology generally useful for manipulating molecules. U.S. Patent No. 7,211,789 (filed October 14, 2004). 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.

process that includes a single, specific human genetic sequence.[143] The sequence can be naturally occurring, or a synthetic sequence created by biotechnology albeit 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 by Jensen and Murray. For example, the definition encompasses any DNA sequence that occurs naturally in the human genome, regardless of whether it encodes a protein. My definition of a gene 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.[144] My definition also includes polymorphisms and mutant forms of genomic DNA sequence, regardless of the frequency at which it occurs, non-DNA polynucletides 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 that are not directed to a specific genetic sequences, as well as patents claiming only proteins.[145]

V. SEARCH METHODOLOGY

I searched both Lexis and Westlaw databases to identify any patent infringement suit involving a human gene patent,[146] including declaratory judgment actions filed by a plaintiff alleging a reasonable apprehension of being sued for infringement.[147] In cases where multiple lawsuits were filed involving the same parties, the same patent(s), and the same general allegation of infringement, I generally consolidated the lawsuits and treated them as a single

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[143] *See generally* 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).

[144] *See*, *e.g.,* Promega Corp. v. Lifecodes Corp., No. 2:93-CV-0184C, 1999 U.S. Dist. LEXIS 21094 (D. Utah Oct. 27, 1999). Discussed *infra* Section VI.

[145] My own search results, not reported in this article, indicate that most litigated biotechnology patents are not human gene patents. *See also infra* Section VII, where I note that it appears that human gene patents are litigated at a substantially lower rate than biotechnology patents in general.

[146] Most searches were conducted in April of 2007.

[147] 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. I found no instance where a declaratory judgment action was filed and the patent did not respond by filing an infringement suit.

"litigation."[148] 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.

My primary searches were conducted in a combination of Lexis databases that purport to contain all U.S. utility and reissue patents.[149] 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.[150] 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 on a Westlaw database. 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 search 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.[151]

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 abstracts included any one of the many terms used in the Georgetown DNA patent database search query.[152] This

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[148] This would be the case, for example, when a patent owner responds to a declaratory judgment by filing an infringement lawsuit, as in *Alzheimer's Inst. of Am., Inc. v. Mayo Clinic*, Civ. No.03-02645 (D. Kan.), discussed *infra* Section VI, 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. *See, eg.,* the lawsuits filed by Oncormed and Myriad against each other, discussed *infra* Section VI.

[149] *See* http://www.lexisnexis.com. (the databases used were Lexis File-names UTIL and REISS, respectively).

[150] Under 35 U.S.C. § 290 (2007), 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. I 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.").

[151] 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. I talked to a technical representative at Lexis, and she could not explain why notice of litigation was not indicated on these patent records.

[152] 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 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.

search resulted in 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 but not all of the corresponding Lexis patent records included a notice of litigation.[153] 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, such an omission is not fatal as long as at least one of the asserted patents bears the notice of litigation, since I can usually access the complaint via the Public Access to Court Electronic Records system ("PACER"), or sometimes by other means, and the complaint identifies other patents involved in the litigation.[154]

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 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.[155] The search resulted in 11,302 hits.[156] It has previously been estimated that about 1-2% of issued patent are litigated,[157] which closely approximates my finding that approximately 1.1% of these million patents have been litigated, and suggests that although there are omissions in the Lexis database they probably occur relatively infrequently.

To further explore the source of the omitted notices of litigation in the Lexis database, I queried the Derwent LitAlert database for sixty-four patents I knew to have been the subject of litigation.[158] LitAlert purports to identify all patents that have been the subject of an infringement suit. In fact, I found that overall LitAlert did a worse job of identifying litigated patents than the Lexis patent database. Of the sixty-four patents, fourteen were not identified as litigated in the Lexis database, and twenty were not identified in LitAlert. Eleven of the

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See, Delphion Search Algorithm, *supra* note 138

[153] One example of such as case is *Regents of the Univ. of Cal. v. Eli Lilly & Co*, where only one of two asserted patents included a "Notice of Litigation" in the Lexis database (U.S. Patent No. 4,652,525 (filed June 28, 1983) (no notice of litigation included) and U.S. Patent No. 4,431,740 (filed June 8, 1982) (notice of litigation included)). 119 F.3d at 15562.

[154] Public Access to Court Electronic Records, https://pacer.login.uscourts.gov/cgi-bin/login.pl.

[155] 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. *See* Jensen & Murray, *supra* note 13, at 239-40.

[156] Search conducted January 23, 2008.

[157] Allison et al., *supra* note 51, at 435; *see also*, Mark A. Lemley, *Rational Ignorance at the Patent Office*, 95 NW. U.L. REV. 1495, 1501 (2001).

[158] Derwent Litalert is available through the Westlaw website, http://www.westlaw.com.

patents were identified as litigated in Lexis but not LitAlert, while ten were identified as litigated in Litalert but not Lexis. Both databases are derived from records of litigation reported to the USPTO, so the fact that both databases are missing the notice of litigation for patents that were accurately identified in the other database indicates that the problem, at least in these instance, originates with the databases themselves and cannot be attributed to a failure of courts to notify the PTO or the PTO to record the litigation.

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 query terms, and containing within the opinion a sentence including the word "patent" and some form of the word "infringe."[159]

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 January 2, 2003.[160] In one Westlaw query, I searched for any of the 4,271 patents appearing in the Jensen and 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 query 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. Searching claims is preferable to searching abstracts, but unfortunately Westlaw only allows for searches of the patent number, patent classification, and abstract fields. 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.[161] This was necessary for a variety of reasons, including the fact that on a number of

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[159] 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!).

[160] Intellectual Property Docket Summaries, IP-DOCK-SUM, http://courtexpress.westlaw.com.

[161] Complaints, motions, unreported rulings, and the like were accessed primarily via the PACER system, *supra* note 154, 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 electronic format. 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.

occasions I found that litigations identified in the database as patent infringement litigations actually were not. For example, I discovered interference appeals, inventorship disputes, and trade secret actions all erroneously characterized as infringement litigations in the commercial databases.[162] 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.

I make no representation that this combination of searches identified every litigation involving a human gene patent, and I may well have missed a few; however, I believe that I did identify the majority of human gene patents litigations, particularly those that resulted in a reported decision. Any litigation that is substantial and not dismissed at an early stage would normally be expected to result in some district court decision addressing, for example, a motion to dismiss, a motion for summary judgment, motions to compel discovery or for protective orders, and the like. 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, particularly since any missed litigation was probably not vigorously contested (as evidenced by the lack of any published document in the Lexis Combined Federal Court Cases database).

VI. PUTTING A FACE ON HUMAN GENE PATENT LITIGATION

At the outset of this study, I anticipated that the sorts of activities and products 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; (2) research tools; (3) genetic testing products and services; and (4) gene therapy.[163] 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.[164] This section summarizes the results of the study, broken down into the three categories of therapeutic proteins, 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 that allowed for the cloning of human genes, the introduction of those genes into bacterial or cell culture, and

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[162] *See, e.g.*, Regents of the Univ. of Mich. v. Bristol Myers Squibb, 301 F. Supp. 2d 633, 634 (E.D. Mich. 2003) (inventorship dispute).

[163] Gene therapy could include treatment with RNA, such as products based on RNA-mediated interference. *See, e.g*, Dinah W.Y. Sah, *Therapeutic Potential of RNA Interference for Neurological Disorders*, 79 LIFE SCIENCES 1773, 1774 (2006).

[164] 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 generally yet to emerge from clinical testing as a viable non-experimental course of treatment.

the over-expression of the gene to produce large quantities of recombinant human proteins for use as therapeutics.[165] These recombinant human protein therapeutics, often referred to as biologics, were the first important products of biotechnology, and continue to be its most lucrative and medically significant. Thus, it should come as no surprise that the earliest human gene patent litigations involved allegations of infringement relating to the commercial production and sale of a recombinant therapeutic protein encoded by a patented gene. In particular, pioneering biotechnology products comprising recombinant human insulin,[166] human growth hormone (hGH),[167] tissue plasminogen activator (t-PA),[168] and erythropoietin (EPO)[169] have all been the subject of substantial patent litigation involving human gene patents.

To this day, a 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),[170] α-galactosidase A,[171] interferon-β (IFN-β),[172] insulin-like growth factor (IGF-I),[173] IGF binding protein-3 (IGFBP-3),[174] and follicle stimulating hormone (FSH)[175] 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.[176]

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[165] Sonia Wallman, *A Short History of Biotechnology*, *available at* http://biotech.nhctc.edu/BT220/Section_1_0_0.html (last visited Jan. 30, 2008).

[166] *Regents of the Univ. of Cal.*, 119 F.3d at 1563.

[167] Bio-Tech. Gen. Corp. v. Genentech, Inc., 267 F.3d 1325, 1327 (Fed. Cir. 2001); Bio-Tech. Gen. Corp. v. Genentech, Inc., 80 F.3d 1553, 1556 (Fed.Cir.1996); Novo Nordisk of N. Am. v. Genentech, 77 F.3d 1364, 1365 (Fed. Cir. 1996); Genentech v. Eli Lilly & Co., 998 F.2d 931, 935 (Fed. Cir. 1993); Novo Nordisk of N. Am., Inc. v. Genentech, Inc., No. 97-4848 (D.N.J. Jan. 12, 1999).

[168] *See* Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555, 1557 (Fed. Cir. 1994).

[169] *See, e.g.,* Amgen, Inc. v. Hoechst Marion Roussel, Inc. 457 F.3d 1293, 1295 (Fed. Cir. 2006); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1203 (Fed. Cir. 1991); Amgen, Inc. v. F. Hoffmann La Roche Ltd., 494 F.Supp.2d 54, 58 (D. Mass. 2007); Amgen, Inc. v. Elanex Pharm., Inc., 1996 WL 84590, *1 (W.D. Wash. Feb. 6, 1996).

[170] Schering Corp. v. Amgen, Inc., 222 F.3d 1347, 1348 (Fed. Cir. 2000).

[171] Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1096 (Fed. Cir. 2003).

[172] Biogen, Inc. v. Berlex Lab., Inc., 318 F.3d 1132, 1133 (Fed. Cir. 2003).

[173] Genentech, Inc. v. Insmed, Inc., 436 F. Supp. 2d 1080, 1082 (N.D. Cal. 2006).

[174] *Id*. at 1087.

[175] Ares-Serono, Inc. v. Organon Int'l B.V., 160 F.R.D. 1, 2-3 (D. Mass. 1994).

[176] *See, generally*, Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559 (Fed. Cir. 1997) (widely criticized for its application of the written description requirement to invalidate claims relating to insulin gene that appeared in the application as filed); Genentech, Inc. v. Wellcome Found. Ltd., 29 F.3d 1555 (Fed. Cir. 1994) (applying the doctrine of equivalents to patent claiming genes encoding human tissue plasminogen activator); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir. 1991) (applying the enablement requirement to invalidate claim broadly reciting functional equivalents of gene encoding human erythropoietin).

Note that the actual therapeutic products are proteins, not polynucleotides, so gene patents do not directly claim the products themselves. 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, i.e., recombinant cells and organisms. Much of the patent litigation brought with respect to protein therapeutics involve the assertion of patents that are not human gene patents, but rather patents directed to the protein product itself,[177] or to genetic methods and reagents of general applicability, in other word, methods and reagents not restricted to a specific gene.[178] Nevertheless, human gene patents have clearly played an important role in attempts by biotechnology companies to secure and maintain market exclusivity for innovative biologic 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 stark contrast with human gene patent litigations relating to genetic testing and research tools, which tend to settle at an early stage.[179] 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, the first blockbuster product for Amgen, sold under the trade name EPOGEN.[180]

Amgen's first successful enforcement of an EPO gene patent involved its U.S. 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."[181] 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

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[177] *See, e.g.*, Amgen, Inc. v. Hoechst Marion Roussel, Inc. 457 F.3d 1293, 1299 (Fed. Cir. 2006) (three patents asserted claiming the protein product); Novo Nordisk Pharm, Inc. v. Bio-Tech. Gen. Corp., 424 F.3d 1347, 1349 (Fed. Cir. 2005) (asserted patent claims the recombinant protein).

[178] *See, e.g.*, Genentech v. Amgen, 289 F.3d 761, 765 (Fed. Cir. 2002) (patents claiming recombinant DNA technology of general applicability); Complaint for Patent Infringement, Zymogenetics v. BMS, Civ. No. 06-500 (D. Del. Aug. 14, 2006) (alleging that biologic drug Enbrel infringes patents generically claiming certain dimerized polypeptide fusions); Zymogenetics v. Immunex, Civ. No. 02-561 (W.D. Wash. 2002) (alleging that biologic drug Abatacept infringes patents generically claiming certain dimerized polypeptide fusions); Genentech v. Boehringer Mannheim, 47 F. Supp. 2d 91, 105 (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).

[179] *See generally* this section.

[180] Amgen, Inc. v. Chugai Pharm. Co., 706 F. Supp. 94, 94 (D. Mass. 1989). Amgen was one of the first and continues to be one of the most successful biotechnology companies in the world. *See* About Amgen, http://www.amgen.com/about/company_history.html (last visited Jan. 30, 2008).

[181] U.S. Patent No. 4,703,008 (filed Nov. 30, 1984).

sequence including introns), and chemically synthesized DNA.[182] 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.[183] 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.[184]

Note that while Amgen's claims are quite broad, they are potentially susceptible to circumvention by a variety of means, 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.[185] 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.[186]

In fact, Amgen's '008 patent included a claim 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 EPO to possess the property of increasing production of red blood cells.[187] However, in *Chugai* the Federal Circuit invalidated this claim for lack of enablement, essentially finding that the breadth

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[182] *Id*. (the specification discloses cDNA sequences and explicitly "comprehends" genomic and "manufactured" DNA sequences).

[183] The inference that GI expressed native human is supported by statements in an order issued by the district court finding 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," and warning 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. Amgen, Inc., v. Chugai Pharm. Co., No. 87-2617-Y, 1989 WL 169006, at *61, *57 (D. Mass. Dec. 11, 1989).

[184] The same patent was also successfully asserted against Elanex for activities relating to its attempt to produce recombinant EPO to be marketed in Europe. Amgen, Inc. v. Elanex Pharm., Inc., No. C93-1483D, 1996 WL 84590, *6 (W.D. Wash. Feb. 6, 1996).

[185] *See Chugai*, 1989 WL 169006, at *57 (noting the district court's warning that GI would not be able to avoid the doctrine of equivalents by "insignificant" changes, thus implying that significant changes would avoid equivalent infringement.) For a case where substantial changes to an encoded protein resulted in a finding of noninfringement under the doctrine of equivalents see *Genentech v. Wellcome Found.* 29 F.3d. at 1569.

[186] For example, Amgen itself followed up its pioneering EPO product with darbepoietin alfa (marketed under the tradename Aranesp), a second-generation modified variant of the naturally-occurring protein with amino acid substitutions and two additional glycosylation sites, which results in longer half-life and less frequent administration. *See* http://www.ons.org/publications/journals/CJON/Volume7/Issue5/pdf/599.pdf.

[187] U.S. Patent No. 4,703,008 (filed Nov. 30, 1984).

of claim coverage exceeded that which would be commensurate with the patent's disclosure.[188] Although an attempt to design around the patent by introducing trivial modifications into the native EPO sequence might well have been found to infringe the patent's narrower (but valid) claims under the doctrine of equivalents, a second-generation EPO with substantially modified function would probably have avoided both literal and equivalent infringement.[189]

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 this important human protein. 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 protein) 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 1984, the only practical technologies available for over-expressing 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.[190] However, in the early 1990s technology known as "gene activation" was commercially developed by a company called Transkaryotic Technologies (TKT).[191] Gene activation provides an alternate technology for the production of a human cell line expressing large quantities of a desired human protein that does not involve isolating the corresponding gene, or introducing the gene into a foreign host cell.[192] Instead, gene activation entails modifying the regulatory region controlling the expression of a targeted gene to increase the expression levels of the gene in the cell in which the gene naturally resides.[193] 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.[194]

Amgen likely became aware of the vulnerability of its original EPO patents[195] to circumvention by gene activation when that technology became

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[188] Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212-14. (Fed. Cir. 1991).

[189] *See supra* note 183.

[190] U.S. Patent No. 4,703,008 (filed Nov. 30, 1984) (claiming priority to an application filed in 1983).

[191] The fundamentals of gene activation was described in U.S. Patent No. 5,272,071 (filed May 28, 1992) which pre-dates TKT's gene activation patents. However, TKT obtained its own patents and is the company primarily associated with efforts to commercialize the technology. *See*, *e.g.*, U.S. Patent No. 5,733,761 (filed May 26, 1995) and U.S. Patent No. 5,641,670 (filed May 13, 1994).

[192] *Id.*

[193] *Id*.

[194] The distinction between the expression of exogenous and endogenous genes was to prove crucial in subsequent litigations, particularly Amgen, Inc. v. Hoechst Marion Roussel, Inc. 457 F.3d 1293 (Fed. Cir. 2006) and Genzyme Corp. v. Transkaryotic Therapies, Inc., 346 F.3d 1094 (Fed. Cir. 2003), discussed *infra* in this section.

[195] U.S. Patent No. 4,703,008 (filed Nov. 30, 1984) (claiming isolated DNA sequences and cells "transformed or transfected" with EPO encoding DNA); U.S. Patent No. 5,441,868 (filed Oct. 23,

known in the early 1990s, and responded by making strategic use (which some might characterize as misuse) of the USPTO's liberal continuation rules to secure patents literally encompassing gene activation.[196] In particular, in 1995 it filed two continuation applications claiming priority to the 1984 patent application which had already resulted in the 1987 issuance of the '008 patent (successfully asserted in *Amgen v. Chugai*). These applications resulted in the issuance of U.S. Patent Nos. 5,618,698 and 5,756,349, which essentially claim vertebrate 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.[197] 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[198] and results in gene amplification.[199] Amgen's patent specification clearly does not enable the expression of erythropoietin by gene activation technology, since it was filed years before the development of that technology,[200] which might strike some as odd. 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.[201]

Amgen's strategic foresight paid off later when TKT and its partner Hoechst Marrion Roussel (together "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 does it entail 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*.[202] However, in *Amgen v. Hoechst Marion Roussel, Inc.* the Federal Circuit found

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1987) (claiming methods of expressing EPO in cells "transformed or transfected" with EPO encoding DNA).

[196] Mark A. Lemley & Kimberley A. Moore, *Ending Abuse of Patent Continuations*, 84 B.U. L. REV. 63, 64 (2004) (describing and critiquing continuation practice).

[197] U.S. Patent No. 5,618,698 (filed June 6, 1995); U.S. Patent No. 5,756,349 (filed June 6, 1995).

[198] Amgen, Inc. v. Hoechst Marion Roussel, Inc., 457 F.3d 1293, 1299 (Fed. Cir. 2006).

[199] Amgen, Inc. v. Hoechst Marion Roussel, Inc., 339 F. Supp. 2d 202, 282 (D. Mass. 2004).

[200] *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.").

[201] Christopher M. Holman, *Is Lilly Written Description a Paper Tiger?: A Comprehensive Assessment of the Impact of Eli Lilly and Its Progeny in the Courts and PTO*, 17 ALB. L.J. SCI. & TECH. 1, 6-11 (2007). *See also* In re Vickers, 141 F.2d 522, 525, (C.C.P.A. 1944) ("[an applicant] is generally allowed claims, when the art permits, which cover more than the specific embodiment shown.").

[202] Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1219 (Fed. Cir 1991). Likewise, another Amgen patent, only encompassed processes employing cells transformed or transfected with EPO-encoding DNA. U.S. Patent No. 5,441,868 (filed Oct. 23, 1987).

both patents valid and infringed by TKT, whose processes nevertheless involved the use of a non-human promoter and "amplification" of the EPO gene.[203]

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 protein *per se* was unavailable because the native protein had previously been isolated and purified from natural sources, specifically human urine.[204] Amgen was able to obtain patents that sought to distinguish and specifically claim recombinant EPO, and pharmaceutical compositions comprising recombinant EPO, but until very recently has been unsuccessful in its attempts to assert these patents.[205] 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.[206]

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 EPO gene patents, it is interesting to review some of 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 35 U.S.C. § 112, second paragraph, as indefinite for failing to adequately define how one could determine the glycosylation of human urinary erythropoietin. The court cited Amgen's own experiments which showed that the glycosylation of human urinary EPO varied from patient to patient and depended upon the specific process used to purify the protein, as well as the specific method used to assay for glycosylation, thus rendering Amgen's claims "insolubly ambiguous."[207]

Another patent asserted by Amgen, U.S Patent No. 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.[208] Unfortunately for Amgen, subsequent studies showed that the disclosed 166 amino acid sequence corresponded to EPO as it was first expressed in the cell,

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[203] 457 F.3d at 1317 (Fed. Cir. 2006) (Amgen IV) (a final judgment since TKT apparently has no pending appeal to the Supreme Court).

[204] Amgen, Inc. v. Chugai Pharm. Co., 706 F. Supp. 94, 96 (D. Mass. 1989).

[205] During the editing of this article, a jury found that Amgen's U.S. Patent No. 5, 547,933, claiming non-naturally occurring forms of EPO, is valid and will be infringed by Hoffmann-LaRoche's PEG-EPO product, discussed *infra* in this section. Jury Verdict, Amgen v. Hoffmann-LaRoche, Civ. No. 05-12237 (D. Mass 2005). A check of the case's docket via Pacer on Jan. 24, 2007 indicates that the parties have not settled and continue to pursue a host of post-trial motions. Hoffmann LaRoche will almost certainly appeal the jury decision if not overturned by the district court judge (assuming the parties fail to reach a settlement).

[206] *Hoechst Marion Roussel, Inc.*, 457 F.3d at 1293, *cert. denied,* 127 S.Ct. 2270 (2007).

[207] Amgen, Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1340-42 (Fed. Cir. 2003).

[208] U.S Patent No. 5,621,080 (filed June 6, 1995).

but that prior to the secretion of the protein from a cell a terminal amino acid is removed, resulting in a final secreted product with a length of only 165 amino acids.[209] The claim was thus not literally infringed by TKT's 165 amino acid product (corresponding to the secreted product). Furthermore, the Federal Circuit held that TKT's product did not infringe under the doctrine of equivalents.[210] 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.[211]

The third Amgen product patent, U.S. Patent No. 5,955,422, claims a pharmaceutical composition comprising a "therapeutically effective amount" of human erythropoietin "purified from mammalian cells grown in culture."[212] 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 that it apparently believed would help distinguish over the prior art.[213] Upon remand, the district court will have to decide whether the asserted claim is anticipated by prior art that 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 "therapeutic effect"). Amgen's attempt to define "therapeutically effective amount" more narrowly, in order to avert possible invalidation by anticipation, was thwarted by language in the specification which the Federal Circuit interpreted as requiring the broader definition of the term asserted by TKT.[214]

The Amgen EPO patent saga is far from over, and in fact a new chapter is currently unfolding. Hoffmann-LaRoche ("Roche") has begun producing a PEGylated[215] version of EPO (PEG-EPO) and importing it into the U.S. Amgen has sued alleging infringement of a total of six patents,[216] including the two human gene patents successfully asserted against TKT and another previously

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[209] *Hoechst Marion Roussel, Inc.,* 457 F.3d at 1296.

[210] *Id.* at 1313-16 (The Supreme Court denied certiorari on this issue, 127 S.Ct. 2270 (2007)).

[211] *Id.*

[212] U.S. Patent No. 5,955,422 (filed Aug. 2, 1993)

[213] *Hoechst Marion Roussel, Inc.*, 457 F.3d at 1300-02.

[214] *Id.*

[215] Wikipedia.org, Polyethylene Glycol, http://en.wikipedia.org/wiki/Polyethylene_glycol (last visited Jan. 30, 2008):

> PEGylation is the act of covalently coupling a [polyethylene glycol] structure to another larger molecule, for example, a therapeutic protein, (which is then referred to as PEGylated) . . . . When attached to various protein medications, polyethylene glycol allows a slowed clearance of the carried protein from the blood. This makes for a longer acting medicinal effect and reduces toxicity, and it allows longer dosing intervals.

Id.

[216] Amgen, Inc. v. F. Hoffmann-La Roche Ltd., No. 05-12237-WGY, 2007 WL 1893058 (D. Mass. July 3, 2007).

unasserted human gene patent claiming methods of producing recombinant EPO from cells transfected or transformed with an EPO-encoding gene.[217]

The extraterritorial production of the protein and modification of the protein by PEGylation prior to importation into the U.S. raise some interesting issues with respect to the susceptibility of human gene patents to circumvention by off-shore production. In general, U.S. patents are not infringed by activities occurring outside the U.S. However, the importation of product made outside the U.S. 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."[218] Roche's product reportedly comprises the amino acid sequence of native human EPO, in which case infringement under 271(g) would appear likely with respect to two patents claiming methods of producing the recombinant protein by expression of the EPO gene, found valid and infringed in *Amgen v. Hoechst Marion Roussel, Inc.*[219] However, Roche seeks to avoid liability by means of the 271(g) exception for "materially changed" products, arguing that PEGylation results in such a material change. 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.[220] However, a jury recently rejected Roche's argument, finding that Roche's extraterritorial production of EPO and subsequent importation of the PEGylated product will infringe Amgen's two gene patents claiming the production process.[221] The case could eventually provide the Federal Circuit with an interesting opportunity to decide on the applicability of the "materially changed" proviso of 271(g) to chemically-modified, second-generation protein therapeutics. The case also provides yet another example of the limited ability of most gene patents to effectively block all beneficial uses of a claimed gene, a theme that recurs throughout this study.

The Amgen EPO cases provide the only examples of final, unappealable judicial determinations that I was able to identify where a human gene patent has been found infringed and not invalid.[222] However, there have been cases where litigating parties have stipulated that an asserted human gene patent was infringed and not invalid as part of a settlement entered into subsequent to a district court decision, pursuant to which the alleged infringer forgoes an opportunity to appeal. For example, Tercica and Insmed recently settled a

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[217] U.S. Patent No. 5,441,868 (filed Oct. 23, 1987).
[218] 35 U.S.C. § 271(g).
[219] U.S. Patent No. 5,441,868 (filed Oct. 23, 1987); U.S. Patent No. 5,618,698 (filed June 6, 1995).
[220] U.S. Patent No. 6,583,272 (filed June 27, 2000).
[221] Jury Verdict, Amgen, Inc. v. F. Hoffmann-La Roche, Ltd., No. 05-12237 (D. Mass. Nov. 8, 2005) (finding claims of U.S. Patent Nos. 5,441,868 and 5,618,698 valid and infringed).
[222] Amgen, Inc. v. Hoechst Marion Roussel, Inc., 457 F.3d 1293, 1299 (Fed. Cir. 2006); Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200 (Fed. Cir 1991); Amgen, Inc. v. Chugai Pharm. Co., 808 F.Supp. 894 (Fed. Cir. 1991); Amgen, Inc. v. Hoechst Marion Roussel, Inc., 339 F. Supp. 2d 202, 282 (D. Mass. 2004); Amgen, Inc., v. Chugai Pharm. Co., No. 87-2617-Y, 1989 WL 169006 (D. Mass. Dec. 11, 1989).

lawsuit[223] alleging that Insmed's product IPLEX,[224] which comprises a combination of the proteins IGF-I and IGFBP-3, infringed Tercica's patents[225] relating to the IGF-I and IGFBP-3 genes. A district court found some of the asserted claims not invalid and infringed by Insmed's product,[226] and instead of appealing the decision Insmed agreed to stipulate that the patents were infringed and not invalid.[227]

Tercica alleged that IPLEX competed directly with its product, Increlex, which comprises free IGF-I, but does not include IGFBP-3.[228] Pursuant to the settlement, Insmed agreed to terminate marketing of IPLEX for certain indications, but is allowed freedom to operate regarding other indications.[229]

Consider for a moment the scope of the human gene patents that were at issue in *Genentech Inc., v. Insmed Inc.* The patent claiming the IGF-I gene (U.S. Patent No. 6,331,414) is relatively narrow, limited to processes for producing recombinant IGF-I in prokaryotic cells.[230] As noted by Tercica, 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.[231] Instead, Insmed chose to use a prokaryotic expression system, apparently because it was easier than attempting to design

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[223] *Genetech, Inc. v. Insmed Inc.*, 436 F. Supp. 2d 1080 (N.D. Cal. 2006).

[224] Press Release, Tercica, *Litigation Settlement Reached Between Tercica, Genentech and Insmed* (Mar. 6, 2007), *available at* http://trca.client.shareholder.com/releasedetail.cfm?ReleaseID=232741; *Insmed Settles All Litigation Over Iplex, Will Stop Selling Drug for Growth Treatment*, LIFE SCIENCES LAW & INDUSTRY REPORT, March 7, 2007, at 5.

[225] The patents are assigned to Genentech, and exclusively licensed to Tercica. *Genentech, Inc.*, 436 F. Supp. 2d at 1083; Consent Judgment and Permanent Injunction, Genentech, Inc. v. Insmed Inc., No. 04-05429 (N.D. Cal. Mar. 6, 2007).

[226] *Genentech, Inc.*, 436 F. Supp. 2d 1080; Jury verdict, Genentech, Inc. v. Insmed Inc., Civ. No. 04-05429 (N.D. Cal. Mar. 6, 2007).

[227] Consent Judgment and Permanent Injunction, Genentech, Inc. v. Insmed Inc., Civ. No. 04-05429 (N.D. Cal. Mar. 6, 2007).

[228] *Genentech*, 436 F. Supp. 2d at 1082. Plaintiffs' Combined Reply to Plaintiff's Motions for (a) Permanent Injunction; (b) Enhanced Damages; and (c) Exceptional Case, and Opposition to Defendants' Motions for Judgment as a Matter of Law or, Alternatively, a New Trial at 11, Genentech v. Insmed Inc., Civ. No. 04-05429 (N.D. Cal. Mar. 6, 2007). [hereinafter Plaintiffs' Combined Reply].

[229] Press Release, Tercica, *supra* note 224.

[230] U.S. Patent No. 6,331,414 (filed June 5, 1995). Claim 1:

> A process for producing human IGF-I comprising preparing a replicable expression vector capable of expressing the DNA sequence encoding human IGF-I in a prokaryotic host cell, transforming a prokaryotic host cell culture with said vector to obtain a recombinant host cell, culturing said recombinant host cell culture under conditions permitting expression of said human IGF-I-encoding DNA sequence to produce human IGF-I, and recovering said human IGF-I.

Id.

[231] Plaintiffs' Combined Reply, *supra* note 228, at 8.

around the patent, and perhaps to facilitate FDA approval by creating a product more similar to Tercica's pioneering product.[232]

Tercica's IGFBP-3 gene patent (U.S. Patent No. 5,258,287) is substantially broader than its IGF-I patent, 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.[233] It also encompasses expression vectors including the sequence, any modified cell transformed with the sequence, and methods of producing the protein by expressing these cells.[234] 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.[235] In this case, the reference sequence was an actual IGFBP-3 encoding sequence disclosed in the patent specification.[236] If the claims had been limited to this particular sequence Insmed might have been able to avoid it, but the court found that the variant sequence it used did hybridize to the reference sequence and, hence, infringed the patent.[237] While this patent is relatively broad, it also probably could have been designed around, for example, by use of gene activation technology. Alternatively, Tercica posited that one could have designed around the patent by using an alternate IGF binding protein such as IGFBP-5 to achieve the same function as IGFBP-3.[238]

A similar settlement occurred in *Bio-Technology General Corp. v. Genentech, Inc.,* a case brought by Genentech to block Bio-Technology General's attempt to market a competing recombinant human growth hormone product.[239] The claims of the patent asserted by Genentech appear to be relatively narrow, limited to certain specified methods of expressing human growth hormone in microbes.[240] After the Federal Circuit reversed a district

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[232] *Id.* at 14.

[233] *See* U.S. Patent No. 5,258,287 (filed Mar. 22, 1988). Claim 1:

> An isolated DNA molecule comprising a sequence that hybridizes, under stringent conditions of 50% formamide with 0.75M NaCl and 0.075M sodium citrate, at 42.degree. C., to the portion of the DNA sequence of FIG. 3 coding for mature BP53 or the preprotein for BP53 and which encodes a BP53 protein that binds to IGF-I or IGF-II, excluding BP28, PP12, and HEP-G2.

Id.

[234] *Id.* at Claims 7, 8, and 17.

[235] *See generally* Holman, *supra* note 104, at 58-68 (explaining how "hybridization" claims such as this provide broad protection for variants sharing some degree of structural and functional similarity with a reference DNA molecule).

[236] Genentech, Inc. v. Insmed, Inc., 436 F. Supp. 2d 1080, 1087 (N.D. Cal. 2006).

[237] *Id.* at 1092.

[238] Plaintiffs' Combined Reply, *supra* note 228, at 8.

[239] Bio-Technology Gen. Corp. v. Genentech, Inc., 80 F.3d 1553, 1557 (Fed. Cir. 1996).

[240] *See* U.S. Patent No. 4,601,980 (filed Mar. 9, 1982). Claim 1:

court determination that the patent was invalid and remanded on the issue of infringement,[241] Bio-Technology agreed to a stipulated final judgment and permanent injunction.[242] 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 protein.[243] As described in more detail below, the technology for recombinantly expressing a human protein in bacteria as a fusion has been known and used since the early days of biotechnology, and often is a superior methodology than the direct expression claimed by this Genentech patent.

There are several examples where a human gene patent has been asserted in the context of the production 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 when it appeared likely that the patent owner would have ultimately prevailed. For example, in 1999, after a six-week trial that resulted in a deadlocked jury, Genentech agreed to pay the University of California $200 million to settle a lawsuit involving a U.C. patent, claiming certain DNA vectors encoding human growth hormone.[244] "[E]ight of the nine jurors found that the university's patent had been infringed," but the jurisdiction's rules required a unanimous verdict, so the case was set for retrial, though the parties eventually settled.[245] At the time, the settlement was described

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> A method of producing human growth hormone which comprises: (a) disposing a culture of bacterial transformants comprising plasmids which, in a transformant bacterium, will express a gene for human growth hormone unaccompanied by the leader sequence of human growth hormone or other extraneous protein bound thereto within a fermenter vessel comprising aeration and agitation means in an aqueous, nutriment-containing fermentation broth; (b) growing up the culture under aeration and agitation while supplying additional nutriments as required to maintain vigorous growth; (c) separating the resulting cellular mass from the fermentation broth; (d) lysing the cells to free the contents thereof; (e) separating cellular debris from supernatant; and (f) isolating and purifying human growth hormone contained in the supernatant.

Id.

[241] Bio-Technology Gen. Corp. v. Genentech, Inc., 267 F.3d 1325 (Fed. Cir. 1996).

[242] Stipulation and Final Judgment and Permanent Injunction against BTG, Bio-Technology Gen. Corp. v. Genentech, Inc., No. 95-00110 (S.D.N.Y. Mar. 5, 2002).

[243] Novo Nordisk of N. Am., Inc. v. Genentech, Inc., 77 F.3d 1364, 1371 (Fed. Cir. 1996).

[244] Genentech, Inc. v. Regents of Univ. of Cal., 143 F.3d 1446 (Fed. Cir. 1998) (involving U.S. Patent No. 4,363,877 (filed Apr. 19, 1978)); *see also* Genentech, Inc., Annual Report, Settlement Agreement (Form 10-K405, EX-99) (Feb. 8, 2000), *available at* http://www.secinfo.com/d9N9s.5d.8.htm.

[245] Rex Dalton & Quirin Schiermeier, *Genentech Pays $200M Over Growth Hormone 'Theft*,*'* 402 NATURE 335, 335 (1999).

as the largest patent settlement ever in the context of biotechnology.[246] According to the settlement, Genentech was able to stay on the market with its human growth hormone product.[247]

In other cases, the alleged infringer agreed to make substantial settlement payments, even though it appeared to have a good chance of prevailing on the merits. For example, in 2002, Biogen settled a lawsuit with Berlex Laboratories while the case was on appeal to the Federal Circuit.[248] The case involved very narrow human gene patents limited to certain methods of expressing IFN-β in Chinese hamster ovary (CHO) cells.[249] Pursuant to the settlement, the alleged infringer, Biogen, agreed to pay Berlex $20 million upfront and an additional $55 million if the Federal Circuit reversed the district court's ruling granting summary judgment in Biogen's favor.[250] Ultimately, the Federal Circuit's decision was generally favorable to Biogen, holding that Biogen did not literally infringe and remanding the case to the district court for a determination under the doctrine of equivalents.[251] The settlement allowed Biogen 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 *Ares-Serono, Inc. v. Organon, International B.V.*, Ares-Serono alleged that Organon's importation of recombinant follicle stimulating hormone ("FSH") infringed its patent, which claimed vectors comprising a genetic sequence encoding FSH and methods of producing recombinant FSH in mammalian cells containing such a vector.[252] After the district court rejected Organon's motion

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[246] *Id.*

[247] Genentech, Inc., Annual Report, Settlement Agreement *supra* note 244.

[248] Biogen, Inc., Annual Report (Form 10-K, Exhibit 13), Financials, at 10-11 (Mar. 14, 2003), *available at* http://sec.edgar-online.com/2003/03/14/0000950135-03-001769/Section34.asp.

[249] Biogen, Inc. v. Berlex Laboratories, Inc., 318 F.3d 1132 (Fed. Cir. 2003); U.S. Patent No. 5,795,779 (filed Aug. 12, 1994). Claim 1:

> A CHO cell culture composition comprising (a) CHO cells transformed with DNA encoding human IFN-.beta., or progeny thereof, and (b) medium comprising IFN-.beta. produced by expression of said DNA, said culture composition directly resulting from secretion of said IFN-.beta. from said CHO cells and wherein the amount of said IFN-.beta. is 150,000-600,000 IU/ml of medium.

Id.; U.S. Patent No. 5,376,567 (filed Jan. 9, 1992). Claim 1:

> A DNA construct for expression in a Chinese hamster ovary cell comprising a human interferon gene and a dihydrofolate reductase gene, said construct being effective for transcription and translation of said interferon gene in a Chinese hamster ovary cell into which it has been introduced or in progeny cells thereof.

Id.

[250] Biogen, Inc., Annual Report, *supra* note 248, at 10-11.

[251] *Biogen*, 318 F.3d at 1411. 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. *Id.* 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. *Id.*

[252] Ares-Serono, Inc. v. Organon Int'l, 862 F. Supp. 603, 605 (D. Mass. 1994); *see* U.S. Patent No. 4,923,805 (filed Jan. 30, 1985) (Claim 1: A method for producing biologically active,

for summary judgment and held that the evidence raised a genuine issue of material fact as to whether the alleged infringers' importation of hormone into the U.S. was sufficiently significant to be infringing,[253] the parties settled under terms granting Organon a non-exclusive license to use the patented technology.[254] Ares-Serono and Organon both ultimately entered the U.S. market with recombinant FSH products.[255]

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, in *Novo Nordisk of North America v. Genentech, Inc.*, the parties settled a litigation involving Genentech's alleged infringement of a relatively narrow human gene patent covering certain methods of expressing recombinant human growth hormone.[256] The settlement occurred shortly after Genentech filed an answer to the amended complaint.[257] Genentech remained on the market with its recombinant human growth hormone product.[258]

More often than not, human gene patent cases brought in the context of protein therapeutics that do not settle are ultimately decided against the patent owner, with the asserted claims adjudged invalid and/or no infringement found. 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 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.[259] Likewise, in *Regents of the University of California v. Eli Lilly & Co.*, the Federal Circuit invalidated claims purporting to encompass the cDNA encoding human insulin for failure to comply with the written description requirement.[260] 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.[261]

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heterodimeric human FSH comprising culturing mammalian cells capable of glycosylating proteins, said cells comprising an expression vector encoding the alpha and beta subunits of said FSH.).

[253] *Ares-Serono, Inc.*, 862 F. Supp. at 615.

[254] LIFE SCIENCE ANALYTICS, INC., SERONO MARKET RESEARCH REPORT 12-13 (Jan. 27, 2006), *available at* http://www.market-research-report.com/datamonitor/lsa_deals.pdf.

[255] Transkaryotic Therapies, Inc., Annual Report (Form 10-K), at 7 (Mar. 15, 2004), *available at* http://www.shire.com/shire/uploads/reports/12003AR.pdf.

[256] Amended Complaint by Novo Nordisk of N. Am., Novo Nordisk of N. Am., Inc. v. Genentech, Inc., No. 97-4848 (D.N.J. Jan. 12, 1999) (involving U.S. Patent No. 5,618,697 (filed Jan. 13, 1995)).

[257] Order Dismissing as Settled, Novo Nordisk of N. Am., Inc., No. 97-4848.

[258] Genentech, Inc., Nutropin Product Information, http://www.gene.com/gene/products/information/opportunistic/nutropin/index.html. (last visited Jan. 30, 2008).

[259] Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212-14 (Fed. Cir. 1991).

[260] Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1568-69 (Fed. Cir. 1997).

[261] *Id.*

In a number of cases, an alleged infringer has been able to escape liability by successfully arguing that its processes do not infringe the asserted patent; in other words, the alleged infringer has successfully designed around the patent. For example, in *Genzyme Corp. v. Transkaryotic Therapies, Inc.*, the alleged infringer, TKT, was able to successfully avoid Genzyme's patent relating to the recombinant expression of human α-galactosidase A by employing gene activation (an alternate, later-developed technology) to express the same gene.[262] 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.[263] Gene activation appears to have been developed around the time Genzyme filed its patent application, but it was not public knowledge at that time.[264] 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 gene activation expressed a gene that was "endogenous" to the cultured cell.[265] 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.[266]

Similarly, in *Biogen v. Berlex*, the alleged infringer, Biogen, was able to avoid literal infringement of Berlex's patent covering the recombinant expression of human interferon in CHO cells.[267] The patent describes genetic constructs and

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[262] Genzyme v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1105-06 (Fed. Cir. 2003).

[263] *See supra* text accompanying notes 206-22 (discussion of *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006)).

[264] Genzyme filed its patent application on October 24, 1990. U.S. Patent No. 5,356,804. The gene activation technology employed by TKT is claimed in TKT patents having 1991 priority dates. *See* U.S. Patent No. 5,641,670 (filed May 13, 1994); U.S. Patent No. 5,968,502 (filed May 26, 1995); U.S. Patent No. 5,733,761 (filed May 26, 1995). The technology was claimed in more general terms in a patent with a priority date of December 22, 1989. U.S. Patent No. 5,272,071 (filed May 28, 1992). None of these patent applications would have published prior to 1991.

[265] *See supra* text accompanying note 194.

[266] *Genzyme*, 346 F.3d at 1105-06. Although TKT markets its α-galactosidase product (Replagal) in Europe and other parts of the world, it failed to get approval from the Food and Drug Administration and does not sell the drug in the U.S. Transkaryotic Therapies, Inc., *TKT to End Efforts to Seek U.S. Approval of Replagal*, PR Newswire, Jan. 12, 2003, *available at* http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/01-12-2004/0002087878&EDATE (last visited Jan. 30, 2008) The Orphan Drug Act apparently contributed to keeping Replagal off the U.S. market, perhaps because TKT could not show either superior safety or efficacy, or was unwilling to pay for the necessary clinical trials. *Id.* This appears to be an example of where FDA regulatory requirements, rather than a patent, are keeping a follow-on biologic off the U.S. market.

[267] Biogen, Inc. v. Berlex Labs., Inc., 318 F.3d 1132, 1141 (Fed. Cir. 2003). Chinese Hamster Ovary cells (CHO cells), a cell line derived from Chinese Hamster ovary cells, are used in

expression methodologies employing what the court referred to as "linked co-transformation."[268] In contrast, the Biogen process involved "unlinked co-transformation."[269] The court construed the claims as limited to linked co-transformation and, hence, not literally infringed by Biogen's process.[270] The court left open the possibility of finding infringement under the doctrine of equivalents, but the parties settled prior to any determination regarding equivalence.[271]

In a number of cases, patent claims directed to methods or systems for expressing a human gene directly have been avoided by expressing the protein as a fusion protein.[272] For example, in *Regents of the University of California v. Eli Lilly*, the court held that the university'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 cleavable fusion protein.[273] Not only did the use of protein fusion technology circumvent the patent, but it also probably provided a better vehicle for expressing and purifying the desired protein.[274] This case represents an example of an adaptation of technology that not only circumvents a patent but also provides substantial technical advantages, and might be employed even if patent avoidance were not a consideration. Note that the university was unable to successfully patent fusion proteins because it was required during prosecution of the patent to amend its 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.[275] 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

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biological and medical research, and to express recombinant proteins. Wikipedia, Chinese hamster ovary cell, http://en.wikipedia.org/wiki/Chinese_hamster_ovary_cell (last visited Jan. 15, 2008).

[268] *Biogen, Inc.*, 318 F.3d at 1134.

[269] *Id*.

[270] *Id*. at 1140.

[271] *See supra* text accompanying notes 248-51.

[272] Essentially, a fusion protein is a genetically modified, non-naturally occurring protein that is formed by fusing together two protein or peptide 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. *See* Wikipedia, Fusion protein, http://en.wikipedia.org/wiki/Fusion_protein (last visited Jan. 30, 2008). 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. *Id.* 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. *Id.* Examples of fusion protein drugs include Etanercept, Infliximab, and Adalimumab. *Id.*

[273] Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d. 1559, 1571-74 (Fed. Cir. 1997).

[274] *See* Wikipedia, Protein Purification, http://en.wikipedia.org/wiki/Protein_purification (last visited Jan. 30, 2008).

[275] *Regents of the Univ. of Cal.*, 119 F.3d at 1572-73.

patent issued and generally applicable to protein expression.[276] This is an example of a situation in which a patent that might appear on its 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 that involved the production of a cleavable fusion product.[277]

The trend in biotechnology is a move toward the development of second-generation protein therapeutic variants comprising structural changes relative to the naturally occurring protein, for example, non-naturally occurring synthetic proteins.[278] This development is often accomplished by modifying the sequence of a native gene.[279] These modifications have not only resulted in superior therapeutic efficacy,[280] but have also, in many cases, successfully designed around human gene patents.

An early example of this can be seen in *Genentech v. Wellcome*, in which the Federal Circuit determined that a patent broadly claiming the "human tissue plasiminogen activator gene" was limited to the native gene and naturally occurring variants thereof.[281] 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.[282] These modifications were reflected in the genetic sequence used to encode the protein.[283] 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 ten-fold increase in half-life, the court held that the non-naturally occurring gene sequence used by Wellcome did not infringe Genentech's gene patent either directly or under the doctrine of equivalents.[284]

More recently, in *Schering v. Amgen*, the defendant, Amgen, avoided a Schering patent purporting to cover any genetic sequence encoding human interferon alpha (IFN-α), a therapeutically relevant cytokine.[285] Instead of employing a gene sequence encoding a native IFN-α, Amgen developed a

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[276] The patent, U.S. Patent No. 4,431,740 (filed June 8, 1982), actually describes the fusion technology which the court found had been disclaimed by amendment.
[277] Novo Nordisk of N. Am., Inc. v. Genentech, Inc., 77 F.3d 1364, 1371 (Fed. Cir. 1996).
[278] Windover Information, Inc., *Second-Generation Proteins*, 7 START-UP 11 (Feb. 2002); *see also* Ian M. Tomlinson, *Next-Generation Protein Drugs*, 22 NATURE BIOTECHNOLOGY 521, 521-22 (2004).
[279] Tomlinson, *supra* note 278, at 521-22.
[280] *Id.*
[281] Genentech v. Wellcome Found. Ltd., 29 F.3d 1555, 1560 (Fed. Cir. 1994).
[282] *Id.* at 1559 n.4.
[283] *Id.*
[284] *Id.* at 1569.
[285] Schering Corp. v. Amgen Inc., 222 F.3d 1347, 1356 (Fed. Cir. 2000).

consensus IFN-α sequence based on genetic variations that were known to exist in naturally occurring subtypes of IFN-α.[286] Some of these subtypes were not even known at the time the patent was filed.[287] 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.[288] Patent considerations aside, the consensus product is purported to have distinct, improved therapeutic utility relative to naturally occurring subtypes.[289]

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, such as genital herpes and possibly some cancers.[290] Schering dropped its suit after Interferon Sciences agreed to avoid the patent by substituting IFN-αa for IFN-αb.[291] At the time, Interferon Sciences stated that the substitution was not expected to alter the product's effectiveness, but that it would necessitate more tests to obtain FDA approval.[292] *Schering v. Interferon Sciences* was terminated at an early stage, prior to any substantive ruling by the court.[293]

B. Research Tools

The term "research tool" comes up often in patent policy debates, and generally refers to instruments, reagents, methods, and information "the main commercial value of which is in furthering research."[294] Research tool status is often associated with so-called "upstream" technologies, which are useful in early-stage research, which ultimately may lead to "downstream" commercial products.[295] It has been argued that excessive patenting of upstream technologies might unduly impede the development of the downstream products desired by society.[296]

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 have occurred in this context. In most cases, the gene is used as a

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[286] *Id.* at 1351. 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.
[287] *Id.* at 1352-53.
[288] *Id.* at 1353-54.
[289] U.S. Patent No. 5,372,808 (filed Apr. 15, 1992) (Amgen patent claiming method of treatment using consensus interferon and asserting that the consensus product reduces side effects normally associated with interferon therapy).
[290] Schering Corp. v. Interferon Sciences Inc., No. 89-131 (D. Del. Mar. 20, 1989).
[291] *Schering-Plough Drops Suit*, N.Y. TIMES, Mar. 21, 1991, at D10.
[292] *Id.*
[293] Case Closed, *Schering Corp.*, No. 89-131.
[294] REAPING THE BENEFITS, *supra* note 3, at 51.
[295] *Id.* at 22.
[296] Heller & Eisenberg, *supra* note 13, at 700; Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 LAW & CONTEMP. PROBS. 1, 10 (2002).

tool for expressing and 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 hopes of identifying a lead compound that will form the basis for identifying an actual drug.[297] Drugs typically function by specifically binding to and interacting with a targeted protein, 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.[298] In some cases, the human gene is expressed to produce purified protein for use in in vitro screening assays.[299] Also, sometimes cell-based assays are used to assess the effect of test compounds on cells recombinantly expressing a cloned human gene.[300] 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.[301] 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 alleged the use of the patented human gene either as a component of a research tool, or in the production of a research tool. Three of the cases allege the sale of a research tool product, in which the user of the research tool was actually a customer of the alleged infringer.[302] 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 third-party clients in their own discovery efforts, such as by contract research organizations (CROs).[303] Finally, in one case, the allegation of patent infringement occurred in the context of a litigation primarily alleging misappropriation of trade secrets.[304] The patent infringement claim was never seriously pursued; in fact, the patent owner filed a declaration early in the course of the litigation agreeing not to sue for patent infringement after the

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[297] Wikipedia, Drug Discovery, http://en.wikipedia.org/wiki/Drug_discovery (last visited Jan. 30, 2008).
[298] *Id.*
[299] *Id.*
[300] *Id.*
[301] Elan Pharms., Inc. v. Mayo Found. for Med. Educ. and Research, 346 F.3d 1051, 1053 (Fed. Cir. 2003); U.S. Patent No. 5,612,486 (filed Nov. 1, 1993); U.S. Patent No. 5,850,003 (filed Jan. 22, 1997).
[302] *Elan Pharms. Inc.*, 346 F.3d at 1052-54; New England Med. Ctr. Hosp., Inc., v. PeproTechPeproTech, No. 91-5584, 1994 WL 613021 (D.N.J. Oct. 17, 1994); Incyte Genomics, Inc. v. Invitrogen Corp., No. 01-2141 (S.D. Cal. Nov. 21, 2001).
[303] Synaptic Pharm. Corp. v. MDS Panlabs, Inc., No. 00-2728 (D.N.J. June 6, 2000); Ligand Pharms., Inc., v. La Jolla Cancer Research Found., No. 93-01895 (S.D. Cal. Dec. 10, 1993); Alzheimer's Inst. of Am., Inc. v. Mayo Clinic, No. 03-02645, (D. Kan. Dec. 18, 2003). Pharmaceutical companies often out-source various research and development projects to independent CROs. For a definition of CROs, see Wikipedia, Contract Research Organization, http://en.wikipedia.org/wiki/Contract_Research_Organization (last visited Jan. 30, 2008).
[304] Cistron Biotechnology, Inc. v. Immunex Corp., No. 93-4322 (D.N.J. Sept. 28, 1993).

alleged infringer filed counterclaims asking that the patent be found invalid, unenforceable, and not infringed.[305]

In *New England Medical Center Hospitals, Inc. v. PeproTech*, one of the litigations regarding the sale of a research tool, the alleged infringement involved a research tool company's production of recombinant interleukin 1β (IL-1B).[306] The protein product was sold to drug companies, who would presumably use it in drug discovery efforts directed toward this important human cytokine.[307] The asserted claim did not cover the gene *per se*, but was limited to methods of recombinantly expressing the gene in a microbe.[308] This case is notable as the only case brought in the research tool context where a human gene patent has been found valid and infringed by a court.[309] The parties settled in March 1997 while the case was on appeal to the Federal Circuit, with PeproTech reportedly paying $718,000 for "licensing fees and other expenses."[310]

The real interested party in *New England Medical Center* was the medical center's exclusive licensee, Cistron Biotechnologies, a small company whose primary focus at the time of the lawsuit centered on the development of therapeutic and diagnostic products targeting IL-1B.[311] PeproTech was using the patented process to produce IL-1B for commercial sale,[312] and presumably some was purchased by other laboratories for use in their own research efforts targeting IL-1B, which would directly compete with Cistron.[313] Cistron's IL-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 therapeutics that

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[305] Immunex Corp., Annual Report (Form 10-K), at 17 (Dec. 31, 1995), *available at* http://www.secinfo.com/dRqWm.94Ga.htm.

[306] New England Med. Ctr. Hosp., Inc. v. PeproTech, Inc., 1994 WL 613021 at *2-3 (D.N.J. Oct. 17, 1994).

[307] Press Release, Federal Trade Commission, *Resolving Anticompetitive Concerns, FTC Clears $16 Billion Acquisition of Immunex Corp. by Amgen Inc*, (July 12, 2002), *available at* http://www.ftc.gov/opa/2002/07/amgen.shtm (reporting consent agreement requiring Amgen and Immunex to license intellectual property rights relating to IL-1 inhibitors in view of the potential therapeutic relevance of these drugs).

[308] *New England Med. Ctr. Hosp., Inc.*, 1994 WL 613021, at *1 (asserting Claim 12 of U.S. Patent No. 4,766,069 (filed Jan. 8, 1987): A process for preparing human IL-1B which comprises culturing a microbe hosting a cloning vehicle comprising DNA encoding human IL-1B and recovering human IL-1B.).

[309] *See New England Med. Ctr. Hosp., Inc.*, 1994 WL 613021, at *4. The court awarded Cistron $2.7 million for damages, interest, and attorney's fees. Cistron Biotechnology Inc., Annual Report (Form 10-K, EX-99), at 2 (Mar. 1, 1996), *available at* http://www.secinfo.com/dX73y.93.6.htm.

[310] Cistron Biotechnology, Inc., Annual Report (Form 10-K), Notes to Financial Statements, at n.9 (Sept. 28, 1999), *available at* http://sec.edgar-online.com/1999/09/28/15/0000793725-99-000013/Section30.asp [hereinafter Cistron Notes to Financial Statements]; *see also* New England Med. Ctr. Hosp., Inc. v. PeproTech, Inc., 111 F.3d 141 (Fed. Cir. 1997).

[311] Cistron Notes to Financial Statements, *supra* note 310, at n.9.

[312] *Id.*

[313] This inference flows from the fact that IL-1B was known to be an important drug target, *see supra* note 309 and *infra* note 314.

targeted to IL-1.[314] 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 (and likely incentivized by) the asserted patent.[315]

The second case involving the sale of a research tool, *Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research*, was brought by a biotechnology company heavily engaged in drug discovery research targeting Alzheimer's disease.[316] Elan 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."[317] 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 eventually developing an effective drug.[318] 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.[319] The district court initially found the claims at issue invalid on a motion for summary judgment, but the Federal Circuit reversed,[320] and the parties settled while the case was pending in the district court on remand.[321] Pursuant to the settlement, Mayo was granted a license to use the patented technology.[322] Note that Elan's claim is limited to transgenic rodents incorporating a mutant human gene. This is clearly important technology, but the patent in no way restricts the use or study of the gene outside of the claimed embodiment.

The third litigation, involving the sale of a research tool, *Incyte Genomics, Inc. v. Invitrogen Corp.*, is the only case identified in this study that involved the

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[314] *See* Cistron Biotechnology, Inc., Business-Combination Transaction Communication (Form 425) (Mar. 22, 2000), *available at* http://www.secinfo.com/dX73y.57.htm. 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. *Id.*

[315] Cistron was exclusive licensee of the '069 patent since at least 1991. New England Med. Ctr. Hosp., Inc. v. PeproTech, Inc., 1993 WL 402936. Presumably some of the companies intellectual property relating to IL-1B was generated after it obtained this exclusive license.

[316] Elan Pharms., Inc. v. Mayo Found. for Med. Educ. and Research, 346 F.3d 1051, 1052-54 (Fed. Cir. 2003); *see also* Elan Corp., Annual Report (Form 10-K), at 11-13, 55 (1998) *available at* http://www.elan.com/Images/ElanAR98_tcm3-4226.pdf (discussing Elan's involvement with Alzheimer's disease).

[317] *Elan Pharms., Inc.*, 346 F.3d at 1052-54.

[318] *See* U.S. Patent No. 5,850,003 (filed Jan. 22, 1997) (describing methods for using the claimed transgenic animals in pharmaceutical screening and as commercial research animals for modeling neurodegenerative diseases such as Alzheimer's disease).

[319] Rex Dalton, *Patent Suit on Alzheimer's Mouse Rejected*, 405 NATURE 989 (2000). The high price demonstrates the perceived high commercial value of these mice. Lawrence Osborne, *Fuzzy Little Test Tubes*, N.Y. TIMES, July 30, 2000, § 6 (Magazine), at 40.

[320] *Elan Pharms., Inc.*, 346 F.3d at 1057.

[321] Press Release, Elan Corp., *Elan and Mayo Announce Settlement of Patent Suit Involving Alzheimer's Disease Research*, (Nov. 12, 2004), http://www.elan.com/News/2004/20041112.asp .

[322] *Id.*

actual sale of a cloned human gene *per se*,[323] as opposed to the sale of a product incorporating the gene (for example, 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. Notably, however, this lawsuit clearly appears to have been filed merely in retaliation for a patent infringement lawsuit filed by Invitrogen against Incyte one month earlier.[324] In any event, *Incyte v. Invitrogen* settled quickly, prior to any substantive action, and resulted in Incyte granting a nonexclusive license to Invitrogen.[325]

In one of the research tool litigations, *Synaptic Pharmaceutical Corp. v. MDS Panlabs, Inc.*, the company accused of infringement, MDS Panlabs, was a CRO allegedly using the patented gene in a cell-based drug screening assay.[326] MDS Panlabs' customers were presumably using the results in their own drug discovery efforts.[327] A total of twelve patents were ultimately asserted by Synaptic.[328] Some of the asserted patents claim assays for identifying chemical compounds which specifically bind to various human receptor proteins, with the assays employing cells that have been transfected with DNA encoding a human receptor protein and which express the receptor on their cell surface.[329] Other

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[323] Complaint for Patent Infringement and Demand for Jury Trial, ¶ 28, Incyte Genomics, Inc. v. Invitrogen Corp., No. 01-2141 (S.D. Cal. Nov. 21, 2001). Invitrogen purportedly sold the actual cDNA clones under the trade name, "GeneStorm cDNA clones." Incyte Corp., Quarterly Report (Form 10-Q), at n.1 (Aug. 14, 2002), *available at* http://sec.edgar-online.com/2002/08/14/0001021408-02-010918/Section9.asp.

[324] *See* Invitrogen Corp. v. Incyte Genomics, Inc, No. 01-692, 2002 WL 883963 (D. Del. May 1, 2002). Incyte's answer was filed on November 21, 2001, the same day as it filed its human gene patent infringement action against Incyte. *See* Incyte Corp., Quarterly Report, *supra* note 323, at n.1.

[325] Stipulation and Order of Dismissal, *Incyte Genomics Inc*., No. 01-2141 (S.D. Cal. Feb. 10, 2004). *See also* Incyte Corp., Annual Report (Form 10-K), at 13 (Dec. 31, 2003), *available at* http://www.secinfo.com/d14D5a.1193e.htm.

[326] Synaptic Pharm. Corp. v. MDS Panlabs, Inc., 265 F. Supp. 2d 452, 455 (D.N.J. 2002).

[327] *Id.*

[328] *Id.* The twelve patents allegedly infringed were the following: U.S. Patent No. 6,156,518 (filed Dec. 29, 1999); U.S. Patent No. 5,885,785 (filed Mar. 8, 1996); U.S. Patent No. 5,861,309 (filed Aug. 21, 1995); U.S. Patent No. 5,985,585 (filed June 15, 1995); U.S. Patent No. 5,661,024 (filed Nov. 30, 1994); U.S. Patent No. 6,083,749 (filed July 27, 1994); U.S. Patent No. 5,786,157 (filed May 2, 1994); U.S. Patent No. 5,882,855 (filed Oct. 5, 1993); U.S. Patent No. 5,595,880 (filed Oct. 22, 1992); U.S. Patent No. 5,155,218 (filed May 8, 1990); U.S. Patent No. 5,053,337 (filed Oct. 30, 1989).

[329] *See, e.g.*, U.S. Patent No. 6,156,518 (filed Dec. 29, 1999). Claim 1:

> A process for identifying a chemical compound which specifically binds to a human α_1 adrenergic receptor, wherein the human α_1 adrenergic receptor is selected from the group consisting of a human α_1A adrenergic receptor and a human α_1B adrenergic receptor, which comprises contacting cells transfected with DNA encoding and expressing on their cell surface, the α_1 adrenergic receptor or a membrane fraction from such cells, with the compound under conditions suitable for binding, and detecting specific binding of the chemical compound to the α_1 adrenergic receptor, wherein such cells or membrane fraction do not normally express the α_1 adrenergic

asserted patents claim isolated nucleic acids encoding various human adrenergic receptor subtypes, as well as recombinant vectors comprising the nucleic acids, plasmids comprising the vectors, and mammalian cells comprising the plasmids.[330] The major obstacle facing Synaptic was that MDS had outsourced the performance of the assays to an affiliate in Taiwan, thus probably avoiding liability under conventional theories of patent liability.[331] A ruling at the district court level on various summary judgment motions was generally favorable to MDS, rejecting most of the theories of infringement put forth by Synaptic.[332] The parties settled on terms reportedly favorable to MDS Panlabs, which allowed it to continue engaging in the activities that led to the original allegation of infringement.[333]

Two research tool cases involved allegations of infringement based on the use of a patented research tool by a company in its own internal drug discovery program. The first of these was *Ligand Pharmaceuticals v. La Jolla Research*.[334] Ligand's patent claims "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.[335] Ligand alleged that that La Jolla Research, a start-up biotechnology company, was using the patented gene in the company's internal drug discovery efforts focused on the development of

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> receptor, and wherein the human α_1A adrenergic receptor has an amino acid sequence identical to the amino acid sequence shown in FIGS. 1A-1I (SEQ ID NO: 2) or that encoded by plasmid pcEXV- α_1a (ATCC Accession No. 75319); and the human α_1B adrenergic receptor has an amino acid sequence identical to the amino acid sequence shown in FIGS. 2A-2H (SEQ ID NO: 4) or that encoded by plasmid pcEXV- α_1b (ATCC Accession No. 75318).

Id.

[330] *See, e.g.,* U.S. Patent No. 5,882,855 (filed Oct. 5, 1993) (Claim 1: An isolated nucleic acid encoding a human dopamine D.sub.1.beta. receptor, wherein the human D.sub.1.beta. receptor has the amino acid sequence shown in Seq. I.D. No. 2.; Claim 4: A recombinant vector comprising the nucleic acid of claim 1 or 2.; Claim 8: A plasmid comprising the vector of claim 4.; and Claim 12: A mammalian cell comprising the plasmid of claim 9.).

[331] *Synaptic Pharm. Corp.*, 265 F. Supp. 2d at 455.

[332] *Id.* at 468.

[333] *See* Foley Hoag LLP Website, *Intellectual Property Litigation/Representative Engagements*, *available at*, http://web.archive.org/web/20050101-20050301re_/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.") (last visited Jan. 30, 2008).

[334] Ligand Pharms., Inc. v. La Jolla Cancer Research Found., No. 93-01895 (S.D. Cal. Dec. 10, 1993).

[335] U.S. Patent No. 5,171,671 (filed Aug. 6, 1990). Ligand Pharms., Inc., Quarterly Report, Settlement Agreement, License and Mutual General Release, (Form 10-G), at B-2 (Mar. 31, 1997), *available at* http://www.secinfo.com/dR1Cs.8c.d.htm. Also asserted were U.S. Patent Nos. 4,981,784 (filed Nov. 30, 1988); 5,091,518 (filed Nov. 16, 1989); and 5,071,773 (filed Oct. 20, 1987) but I would not classify these as human gene patents.

therapeutic compounds highly specific for individual retinoid receptors.[336] Ligand Pharmaceuticals, the patent owner, was engaged in a substantial drug development program targeting the same proteins.[337] The case settled at an early stage, prior to any substantive rulings,[338] with the defendant 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.[339]

A more recent case, *Alzheimer's Institute of America v. Mayo Clinic*, involves an allegation that the Mayo Clinic, which self-identifies as a non-profit research institute, is conducting infringing commercial drug discovery research in collaboration with Myriad Genetics, a private company.[340] The patent at issue in this case broadly claims any isolated nucleic acid encoding the "Swedish mutation" of human APP (the same mutation at issue in *Elan v. Mayo*), as well as vectors and immortalized mammalian cell lines comprising the mutant gene.[341] A district court characterized the litigation as primarily a contract dispute and ordered the parties to arbitrate the matter; in the meantime, the court has stayed the case.[342]

C. Genetic Testing

The seven remaining human gene patent litigations identified in the study all fall within the category of "genetic testing."[343] In four of the seven litigations, 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, such as the BRCA1 gene, and the genes associated with TPMT-

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[336] *See* Ligand Pharms., Inc., Quarterly Report, Settlement Agreement, *supra* note 335, at B-2. The receptors are promising targets for anticancer drugs. *See, e.g.*, David R. Shalinsky et al., *A Novel Retinoic Acid Receptor-Selective Retinoid, ALRT1550, Has Potent Antitumor Activity Against Human Oral Squamous Carcinoma Xenografts in Nude Mice*, 57 CANCER RESEARCH 162 (1997).

[337] *See* Ligand Pharms., Inc., Prospectus Filed Pursuant to Rule 424 (Form 424B1), at 3 (Oct. 25, 1996), *available at* http://investors.ligand.com/sec.cfm?DocType=&Year=1996.

[338] *See* Ligand Pharms., Inc., Quarterly Report, Settlement Agreement, *supra* note 335.

[339] *See id.* at 2.

[340] Defendants' Memorandum in Response to Plaintiffs' Motion to Compel Arbitration and Stay the Pending Action at 3, Mayo Clinic v. Alzheimer's Inst. of Am., Inc., No. 05-00639, 2005 WL 3636214 (M.D. Fl. Sept. 2, 2005).

[341] *Id.* at 1; *see also* U.S. Patent No. 5,455,169 (filed Oct. 3, 1995). Claim 1:

> An isolated nucleic acid encoding human amyloid precursor protein 770 (APP No) including the nucleotides encoding codon 670 and 671 of human amyloid precursor protein 770, wherein the nucleic acid encodes asparagine at codon 670 and/or leucine at codon 671 or an isolated fragment of said nucleic acid having at least ten nucleotides and encoding at least positions 4 and 5 of SEQ ID NO:1.

Id.

[342] Order at 3, *Alzheimer's Inst. of Am., Inc.*, No. 05-00639.

[343] For the purposes of this article I have defined "genetic testing" broadly. *See supra* Section IV.

deficiency and Long QT syndrome.[344] In a fifth litigation, the allegedly infringing test was not directed toward a particular human gene, but rather to a set of probes useful in detecting a chromosomal aberration known to be associated with leukemia, in which the aberration involves the fusing of two genes that normally reside on different chromosomes (thereby fusing the chromosomes with resultant deleterious effect).[345] The final two litigations involved a single patent which claims a stretch of non-protein encoding genomic DNA useful in genetic identification for forensic and paternity testing applications.[346]

Two of the single gene 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.[347] 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 gene.[348] In one case, Myriad and OncorMed (competing genetics diagnostic companies) sued one another for allegedly infringing each other's BRCA1 patents.[349] 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.[350] The cases settled prior to any substantive legal rulings regarding patent validity or infringement.[351]

The second BRCA1 lawsuit was filed by Myriad against the University of Pennsylvania for allegedly providing commercial BRCA1 genetic testing

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[344] Myriad Genetics, Inc. v. OncorMed, Inc., No. 97-922 (D. Utah filed Dec. 2, 1997); Myriad Genetics, Inc. v. OncorMed, Inc., No. 98-35 (D. Utah filed Jan. 20, 1998); OncorMed, Inc. v. Myriad, Inc., No. 97-2722 (D.D.C. filed Nov. 17, 1997) (all lawsuits between Myriad and OncorMed are tallied as a single litigation); Myriad Genetics, Inc. v. Univ. of Pa., No. 98-829 (D.C. Utah 1998), *dismissed* (Apr. 20, 1999); Prometheus Labs, Inc. v. Quest Diagnostics, Inc., No. 06-00415 (S.D. Cal. 2006), *dismissed* (May 21, 2007); and DNA Sciences, Inc. v. GeneDx, Inc., No. 02-5578 (N.D. Cal. 2002), *dismissed* (Feb. 14, 2003).

[345] Complaint, Ventana Med. Sys., Inc. v. Vysis, Inc., No. 03-04870, 2003 WL 23800108 (N.D. Ill. July 15, 2003).

[346] Promega Corp. v. Lifecodes Corp., No. 93-0184, 1999 U.S. Dist. LEXIS 21094,*3-5 (D. Utah Oct. 27, 1999); Genmark, Inc. v. Lifecodes Corp., No. 91-0707 (D. Utah filed July 11, 1991).

[347] *See* REAPING THE BENEFITS, *supra* note 3, at 62-63.

[348] *Id.* at 63-68.

[349] *See Myriad Genetics, Inc.*, No. 97-922; *Myriad Genetics, Inc.*, No. 98-35; *OncorMed, Inc.*, No. 97-2722. *See also* REAPING THE BENEFITS, *supra* note 3, at 62-63 (describing the patent dispute between Myriad and OncorMed in more detail).

[350] REAPING THE BENEFITS, *supra* note 3, at 63.

[351] See the electronic dockets, available through PACER, for *Myriad Genetics, Inc.*, No. 97-922; *Myriad Genetics, Inc.*, No. 98-35; and *OncorMed, Inc.*, No. 97-2722.

services, reportedly for a price of $1900.[352] The case was quickly dismissed for Myriad's failure to serve process on the defendant.[353] However, Myriad's decision to dismiss was apparently premised on the university's agreement to withdraw from the commercial testing market.[354] The university subsequently reported that its decision to stop offering the test was a result of Myriad's decision to enforce its patents.[355]

The finding that Myriad has apparently only sought to enforce its BRCA patents in court on two occasions, and that both cases were dismissed relatively early on, might come as a surprise to some. A great deal of commentary has decried the chilling effect of gene patents on accessibility to health care, particularly in the U.S., 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.[356] Clearly, this chilling effect is based on an unwillingness to challenge the patents. 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 if someone were to challenge them. Note that Myriad appears to have never asserted its patents based on genetic testing research, but only against substantial direct commercial competitors.

In *DNA Sciences v. GeneDx*, the allegedly infringing activity involved commercial genetic testing for Long QT syndrome,[357] a genetic disorder that can cause sudden death in young people.[358] DNA Sciences asserted three patents claiming, inter alia, DNA sequences corresponding to certain genetic mutations associated with the syndrome,[359] nucleic acid probes that would hybridize to a

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[352] Myriad Genetics, Inc. v. Univ. of Pa., No. 98-829 (D.C. Utah Nov. 19, 1998). *See also* Bryn Williams-Jones, *History of a Gene Patent: Tracing the Development and Application of Commercial BRCA Testing*, 10 HEALTH 123, 134 (2002).

[353] *See* Order of Dismissal, *Univ. of Pa.*, No. 98-829.

[354] Tom Reynolds, *NCI-Myriad Agreement Offers BRCA Testing at Reduced Cost*, 92 J. NAT'L CANCER INST. 596, 596 (Apr. 2000).

[355] *Id.*

[356] *See* Caulfield et al., *supra* note 15.

[357] DNA Sciences, Inc. v. GeneDx, Inc., No. 02-5578 (N.D. Cal. Nov. 22, 2002).

[358] *See,* Sudden Arrhythmia Death Syndromes Foundation, *About SADS*, http://www.sads.org/about.html (last visited Jan. 30, 2008).

[359] *DNA Sciences, Inc.*, No. 02-5578; U.S. Patent No. 6,207,383 (filed Mar. 27, 2001). Claim 1:

> An isolated DNA fragment or polynucleotide comprising nucleic acid of SEQ ID NO:1 comprising an alteration wherein said alteration is selected from the group consisting of A at position 87, C at position 98, A at position 132, T at position 140, C at position 157, A at position 167, G at position 196, G at position 209, A at position 215, deletion of positions 221-251, C at position 232, a duplication of positions 234-250, T at position 241, G at position 257, insertion of a C between positions 422 and 423, insertion of a C between positions 453 and 454, insertion of a C between positions 724 and 725, deletion of G at position 885, T at position 934, T at position 1039, A at position 1128, G at position 1129-2, A at position 1592, C at position 1655, T at position 1714, A at position 1750, T at position 1755, G at position 1762, C at position 1778, A at position 1810, A at position 1825, T at position 1838, T at position 1841, G at position 1843, A at position 1876, G at position 1881, C at

DNA having any one of several specific mutations associated with the syndrome,[360] and methods for diagnosing the syndrome by testing for the specified mutations.[361] As with the Myriad's BRCA1 patents, DNA Sciences' patent protection appears to effectively encompass most, if not all, practical methods of testing for these mutations.[362] The parties settled the lawsuit less than three months after the complaint was filed, prior to the filing of an answer, and the case was dismissed without prejudice.[363]

In the most recently filed genetic testing litigation, *Prometheus Labs v. Quest Diagnostics*, Prometheus asserted patents covering mutant forms of the thiopurine S-methyltransferase (TPMT) gene, as well as reagents and methods for identifying the mutations.[364] The mutations are associated with TPMT-deficiency, a potentially serious genetic condition which results in an inability to

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position 1889, T at position 1894, G at position 1912, deletion of positions 1913-1915, T at position 1933, T at position 2044, insertion of a T between positions 2218 and 2219, T at position 2254, deletion of position 2395, C at position 2398+1, C at position 2414, G at position 2414, T at position 2467, T at position 2582, A at position 2592+1, deletion of G at position 2660, T at position 2750, deletion of G at position 2762, T at position 2764, insertion of a G between positions 2775 and 2776, deletion of G at position 2906, deletion of positions 2959-2960, A at position 3003, T at position 3040, deletion of C at position 3094, and insertion of a C between positions 3303 and 3304.

Id.

[360] *DNA Sciences, Inc.*, No. 02-5578; U.S. Patent No. 5,599,673 (filed Feb. 4, 1997). Claim 1: A nucleic acid probe which will hybridize to a DNA coding for SCN5A polypeptide containing a mutation which causes long QT syndrome, said mutation being either an alteration of or deletion of any one or more of amino acid residues 1505, 1506 or 1507 of the SCN5A polypeptide but will not hybridize to DNA encoding wild type SCN5A under hybridization conditions which only permit hybridization products to form which are fully complementary in the region of the mutation.

Id.

[361] DNA Sciences, Inc., No. 02-5578; U.S. Patent No. 6,432,644 (filed Aug. 13, 2006). Claim 1: A method for diagnosing the presence of a polymorphism in human KCNE1 (the coding region of which is bases 193-579 of SEQ ID NO:3) which causes long QT syndrome wherein said method is performed by means which identify the presence of said polymorphism, wherein said polymorphism is one which results in the presence of a KCNE1 polypeptide of SEQ ID NO:4 with an altered amino acid, said altered amino acid being selected from the group consisting of: a) a Leu at residue 74.

Id.

[362] In particular, Claim 1 of '644 Patent would appear to encompass diagnosis for the recited mutation by any methodology.

[363] *See* Plaintiff's Notice of Dismissal Without Prejudice, *DNA Sciences, Inc.*, No. 02-5578 (N.D. Cal. filed Feb. 14, 2003).

[364] Complaint at 1, Prometheus Labs, Inc. v. Quest Diagnostics, Inc., No. 06-00415, 2006 WL 535305 (S.D. Cal.); *see also* U.S. Patent No. 5,856,095 (filed Jan. 5, 1999) (Claim 1: An isolated polynucleotide molecule comprising a mutant allele of thiopurine S-methyltransferase (TPMT) or a fragment thereof, which is at least ten consecutive bases long and contains a point mutation at cDNA position 238.).

tolerate thiopurine drugs.[365] Although the complaint does not specifically identify the nature of the alleged infringement, it can be inferred that Prometheus sued Quest for providing commercial genetic testing for TPMT deficiency.[366] Prometheus licensed the technology from DNA Sciences, the plaintiff in the Long QT Syndrome litigation, who had licensed the technology from the St. Jude Children's Research Hospital.[367] On May 14, 2007, the court dismissed the case without prejudice after it found that Prometheus had failed to meet its burden of proving it is an exclusive licensee of the asserted patent, and therefore had failed to establish standing.[368] According to the Prometheus and Quest Diagnostics' websites, both companies continue to offer genetic testing for TPMT deficiency.[369]

The fifth genetics testing case, *Ventana v. Vysis*, was filed by Ventana, the exclusive licensee of patents claiming DNA probes specifically useful for detecting a specific human chromosomal aberration.[370] The aberration involves

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[365] *See* Wikipedia, Pharmacogenetics, http://en.wikipedia.org/wiki/Pharmacogenetics (last visited Jan. 30, 2008). Important examples of these drugs include 6-mercaptopurine and azathioprine, two drugs used in a range of indications, from childhood leukemia to autoimmune diseases. *Id.* The FDA has recommended that individuals be tested for this genetic condition before being put on a regimen that includes these drugs. *Id.* An unrecognized TPMT-deficiency can result in potentially fatal drug toxicity in patients treated with thiopurines. *Id.*

[366] *See* Quest Diagnostics, Website, *available at* http://www.questdiagnostics.com/hcp/intguide/jsp/showintguidepage.jsp?fn=TS_TPMT_Genotype.htm (last visited Jan. 30, 2007) (Quest advertises the availability of these tests on its website and acknowledges that its test targets the specific mutations claimed in the patent asserted by Prometheus.).

[367] Press Release, Prometheus, *Prometheus Laboratories Obtains License to Patent for Pharmacogenetic Test: Prometheus and DNA Sciences Form Research and Development Collaboration*, (Oct. 15, 2002), *available at* http://phx.corporate-ir.net/phoenix.zhtml?c=130685&p=irol-newsArticle&ID=465184&highlight=; Press Release, Prometheus, *Genaissance Pharmaceuticals Expands Licensing Agreement with Prometheus Laboratories for TPMT Diagnostic Test: Collaboration Focused on Developing Additional Pharmacogenomics-Based Tests*, (May 16, 2003), *available at* http://phx.corporate-ir.net/phoenix.zhtml?c=130685&p=irol-newsArticle&ID=464952&highlight=.

[368] Order Granting Quest Diagnostics, Inc.'s Motion to Dismiss Without Prejudice and Denying Quest Diagnostics, Inc.'s Motion for Summary Judgment Based on Lack of Subject Matter Jurisdiction, *Prometheus Labs, Inc.*, No. 06-00415 (S.D. Cal. May 14, 2007.).

[369] *See* Quest Diagnostics, Website, *supra* note 366. Prometheus, http://www.prometheuslabs.com/Authenticate_Healthcare.asp?f_URL=/products_diagnostics_ptm.asp (last visited Jan. 30, 2008).

[370] *See* Complaint at 1-2, Ventana Med. Sys., Inc. v. Vysis, Inc,, No. 03-4870, 2003 WL 23820077 (N.D. Ill. July 15, 2003); *see also* U.S. Patent No. 6,025,126 (filed Feb. 15, 2000). Claim 1:

> A composition comprising at least two probes, each labeled with a distinguishable label, for detecting a chromosomal aberration involving the BCR and ABL genes, said chromosomal aberration having an ABL gene side and a BCR gene side, wherein one of said probes hybridizes to the ABL gene side of said chromosomal aberration and the other of said probes hybridizes to the BCR gene side of said chromosomal aberration, wherein said probes hybridize to an aberrant chromosome wherein said probes are of sufficient length to be specifically detected in cytogenetic analysis.

the fusion of portions of the BCR gene from chromosome 22 and the ABL gene from chromosome 9, which often results in leukemia.[371] 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.[372] 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 patent interference dispute involving the two asserted patents.[373] While the stay was pending, the parties settled and the case was dismissed with prejudice;[374] shortly thereafter, final judgment was entered against Ventana in the interference with respect to at least some of the asserted claims.[375]

The sixth genetics testing case, *Promega v. Lifecodes*, 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.[376] Nevertheless, although some might characterize the patented sequences as "junk DNA," they are actually quite useful in genetic identity testing because they include variable number of tandem repeat (VNTR) sequences.[377] Essentially, these regions

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Id.; U.S. Patent No. 6,414,133 (filed July 2, 2002). Claim 1:

> A DNA probe set, said probe set comprising a first probe set and a second probe set, said first probe set being sufficient in length and substantially complementary to an entire breakpoint region of a first DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said first probe set will hybridize to both sides of the breakpoint region regardless of whether the first DNA has been broken in the breakpoint region and either end fused to another DNA, and said second probe set being sufficient in length and substantially complementary to an entire breakpoint region of a second DNA and nucleotides on both sides of the breakpoint region but less than an entire chromosome such that said second probe set will hybridize to both sides of the breakpoint region regardless of whether the second DNA has been broken in the breakpoint region and either end fused to another DNA.

Id.

[371] U.S. Patent No. 6,414,133 (filed July 2, 2002).

[372] *Id.* 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.

[373] Agreed Motion to Stay Litigation Pending Resolution of Interferences in the United States Patent Office at 1-3, Ventana Med. Sys., Inc. v. Vysis, Inc., No. 03-4870 (N.D. Ill. April 15, 2004).

[374] Notice of Agreed Motion and Motion to Dismiss With Prejudice, Ventana Med. Sys., Inc. v. Vysis, Inc., No. 03-4870 (N.D. Ill. Jan. 4, 2005).

[375] United States Patent and Trademark Offices, Official Gazette Notices, Adverse Decisions in Interference (Feb. 22, 2005), *available at* http://www.uspto.gov/web/offices/com/sol/og/2005/week08/patadve.htm (noting judgments adverse to the patentees regarding claims 1-3, 5-12, and 14-19 of the '133 Patent).

[376] Promega Corp. v. Lifecodes Corp., No. 93-0184, 1999 U.S. Dist. LEXIS 21094, *3-5 (D. Utah Oct. 27, 1999); U.S. Patent No. 4,963,663 (filed Oct. 16, 1990) (Claim 1: A nucleic acid fragment selected from the group consisting of pYNH24, the VNTR-containing fragment of pYNH24, a nucleic acid fragment having substantial sequence homology to said VNTR-containing fragment and a nucleic acid fragment which is capable of hybridizing to the single locus specified by pYNH24.).

[377] '663 Patent.

contain a genetic sequence that is repeated multiple times, with the number of repeats varying between individuals.[378] 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.[379] The importance of these sequences is underscored by the fact that this is the only genetic testing patent litigation that was litigated to a final judgment – 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.[380]

The seventh genetics testing case involved the same patent at issue in *Promega v. Lifecodes*, and was brought by the original patent owners, Genmark and the University of Utah, against Lifecodes.[381] Shortly after the complaint was filed and prior to the filing of an answer, the parties entered a settlement agreement, pursuant to which Genmark assigned exclusive license under the patent for $600,000.[382] In an unusual twist, Lifecodes was subsequently sued years later by Promega, its exclusive licensee, for infringing the same patent.[383]

VII. CONCLUSION: ASSESSING THE IMPACT OF HUMAN GENE PATENT LITIGATION

Criticism of human gene patents is largely based 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 response embodied in proposed legislative solutions such as the GRAA. However, these fears have, for the most part, not materialized in the form of actual patent enforcement, and a patentability bar specifically targeting genes or DNA seems unwarranted at the current time.

Not surprisingly, none of the fears regarding patent holders asserting ownership in other people's bodies have materialized, nor have people been sued for patent infringement based on the presence of patented genes in their bodies. While there are many who would maintain that the mere existence of patents relating to human genes is immoral and offensive,[384] gene patents have not been asserted in a manner that would directly impact human dignity or personal autonomy.[385] Of course, some might argue that a patent that delays or adds to

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[378] *Id.*
[379] *Id.*
[380] *Promega Corp.*, 1999 U.S. Dist. LEXIS 21094, at *58-59.
[381] Genmark, Inc. v. Lifecodes Corp., No. 91-0707 (D. Utah July 9, 1991).
[382] *Promega Corp.*, 1999 U.S. Dist. LEXIS 21094, at *10.
[383] *Id.* at *14.
[384] *See supra* notes 7-12 and accompanying text.
[385] Some would argue that cases like the dispute between the patent owner and patient families over control of Canavan gene patents are offensive to human dignity and autonomy, but this dispute did not involve any assertion of the patent alleging infringement and did not seek to restrict the use of

the cost of genetic testing or lifesaving drugs is an affront to human dignity.[386] But, such concerns are by no means specific to gene patents, but would apply to patents in general, particularly those claiming drugs or general molecular biology methods and reagents used in drug development and genetic testing.

To objectively assess the impact of these patents, it would be informative to calculate the rate at which human gene patents are litigated compared to the rate at which patents are litigated in general. Unfortunately, the total number of issued human gene patents would be extremely difficult to ascertain, at least as I have defined the term in this article.[387] However, Jensen and Murray specifically identified a total of 4,270 patents as satisfying their definition of a human gene patent, which provides a denominator for calculating the litigation rate.[388] Furthermore, their dataset forms the basis for the frequent assertion that twenty percent of human genes are patented,[389] so it is interesting to consider to what extent these patents have been the subject of actual judicial enforcement.

In view of the angst inspired by the Jensen and Murray article, it might surprise some to learn that my study identified only six litigations alleging infringement of a patent that appears in Jensen and Murray's dataset,[390]

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the patented subject matter, but rather to restrict use of the patent. REAPING THE BENEFITS, *supra* note 3.

[386] *See supra* notes 7-12 and accompanying text.

[387] My search strategy for patent litigations was designed to be over-inclusive, and I would have had to actually read each patent claim to determine if it involved a human gene patent, as opposed to a patent claiming a non-human gene or a patent claiming a general genetic invention, but actually reading that many issued patents is impractical. The inherent limitations of entirely mechanized search strategies is illustrated by the fact that the Jensen & Murray approach did not identify most of the litigated human gene patents I found by using a broader search query and manually sifting through the results for true human gene patent litigations. *See supra* text accompanying notes 126-34.

[388] Jensen & Murray, *supra* note 13, at 239.

[389] *See supra* Section IV.

[390] For the sake of completeness, note that U.S. Patent No. 5,843,725 (filed June 7, 1995) appears in the Jensen & Murray dataset and was asserted by Zymogenetics against Immunex and Bristol-Myers Squibb. However, that patent actually does not appear to satisfy even the Jensen & Murray definition of human gene patent, since the patent is not directed to a specific genetic sequence, but rather claims general methods for making dimerized polypeptide fusions *See, e.g.,* Claim 1:

> A method for producing a secreted active dimerized polypeptide fusion, comprising: introducing into a eukaryotic host cell a DNA construct comprising a transcriptional promoter operatively linked to a secretory signal sequence followed downstream by and in proper reading frame with a DNA sequence encoding a non-immunoglobulin polypeptide requiring dimerization for biological activity joined to a dimerizing protein heterologous to said non-immunoglobulin polypeptide; growing said host cell in an appropriate growth medium under physiological conditions to allow the secretion of a dimerized polypeptide fusion encoded by said DNA sequence; and isolating said dimerized polypeptide fusion from said host cell.)

Id. The inclusion of the patent in the dataset is an artifact of the nature of the search query. Also, in *Synaptic v. MDS Panlabs*, discussed *supra* in Section VI, a Jensen & Murray patent was asserted in the originally filed complaint, but was removed from the first amended complaint and never actually part of the patent litigation. 265 F.Supp.2d at 456, n. 1.

involving a total of eighteen patents with claims reciting thirteen distinct human genes.[391] Only one of the litigations, *Genzyme v. Transkaryotic Therapies, Inc.*, resulted in a substantive court decision, and in that case the court found the patent had not been infringed.[392] Of the five remaining litigations, four settled at an early stage, prior to any substantive decision by the court,[393] and one was recently dismissed based on the court's determination that the patent owner lacked standing to bring suit.[394] As far as I can ascertain, not one of the 4,270 patents in the dataset has ever been found to have been infringed or been the basis of a preliminary injunction.

In addition, half of the litigated Jensen and Murray patents (nine of eighteen), representing almost three quarters of the claimed human genes (nine of thirteen), were asserted in a single litigation, *Incyte v. Invitrogen*.[395] 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.[396] This case would appear to have had little negative 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.[397]

Four of the six Jensen and Murray litigations involved genetic testing, targeting a total of three single gene mutations associated with either a genetic

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[391] *See* DNA Sciences, Inc. v. GeneDx, Inc., No. 02-5578 (N.D. Cal. Nov. 22, 2002) (involving U.S. Patent No. 6,207,383 (filed Jan. 6, 1999) and U.S. Patent No. 6,432,644 (filed Nov. 22, 1999)); Myriad Genetics, Inc. v. Univ. of Pa., No. 98-829 (D.C. Utah 1998), *dismissed* (Apr. 20, 1999) and Myriad Genetics, Inc. v. OncorMed, Inc., No. 97-922 (D. Utah filed Dec. 2, 1997) (both cases involving U.S. Patent No. 5,753,441 (filed Jan. 5, 1996); U.S. Patent No. 5,747,282 (filed June 7, 1995); U.S. Patent No. 5,709,999 (filed June 7, 1995); U.S. Patent No. 5,693,473 (filed June 7, 1995); and U.S. Patent No. 5,654,155 (filed Feb. 12, 1996)), Prometheus Labs, Inc. v. Quest Diagnostics, Inc., No. 06-00415 (S.D. Cal. 2006), *dismissed* (May 21, 2007) (involving U.S. Patent No. 5,856,095 (filed Aug. 14, 1995)); Incyte Genomics, Inc. v. Invitrogen Corp., No. 01-2141 (S.D. Cal. Nov. 21, 2001) (involving U.S. Patent No. 6,001,598 (filed Jan. 20, 1998); U.S. Patent No. 5,962,263 (filed Jan. 8, 1998); U.S. Patent No. 5,925,542 (filed May 5, 1997); U.S. Patent No. 5,853,997 (filed June 11, 1997); U.S. Patent No. 5,840,535 (filed June 2, 1997); U.S. Patent No. 5,817,497 (filed Nov. 26, 1996); U.S. Patent No. 5,776,753 (filed June 11, 1997); U.S. Patent No. 5,637,462 (filed Apr. 19, 1995); and U.S. Patent No. 5,633,149 (filed Dec. 7, 1994)), and Genzyme v. Transkaryotic Therapies, Inc., 346 F.3d 1094, 1105-06 (Fed. Cir. 2003) (involving U.S. Patent No. 5,356,804 (filed Oct. 24, 1990)).

[392] *See supra* note 262 and accompanying text.

[393] *See DNA Sciences, Inc.*, No. 02-5578; *Myriad Genetics, Inc. v. Univ. of Pa.*, No. 98-829; *Myriad Genetics, Inc. v. OncorMed*, No. 97-922; and *Incyte Genomics, Inc.*, No. 01-2141.

[394] *See Prometheus Labs, Inc.*, No. 06-00415.

[395] *See supra* Section VI.

[396] *See supra* notes 324-29 and accompanying text.

[397] Mark A. Lemley, *Are Universities Patent Trolls?* 4 (Stanford Public Law, Working Paper No. 980776, 2007), *available at* http://papers.ssrn.com/sol3/papers.cfm?abstract_id=980776 (positing that in patent-intensive industries such as biotechnology, it is assumed "that if a competitor sues you for infringement you can sue them back," and that this symmetry deters patent litigation).

disease or a genetic predisposition to disease or drug-sensitivity (for example, BRCA1, TPMT and Long QT Syndrome).[398] These litigations have presumably had some impact on the availability of these tests, or at least their cost. In particular, the defendants in the BRCA1 and Long QT Syndrome cases (the University of Pennsylvania, Oncormed and GeneDx) reportedly exited the market in response to the lawsuits.[399] 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 benefits that accrued from market competition, particularly with respect to the cost of testing, it did not prevent patients from being tested for mutations in the BRCA1 gene.[400] On the other hand, the patent owner in the case involving Long QT Syndrome, 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.[401] Research laboratory-based tests were probably still available.[402] However, shortly thereafter, DNA Sciences was acquired by Genaissance Pharmaceuticals,[403] which began offering the test on a commercial basis in 2004.[404] The TPMT-deficiency case was recently dismissed, and, while this article was being written, both the patent owner and the alleged infringer (Prometheus and Quest Diagnostics) were advertising the availability of TPMT deficiency testing on their websites.[405]

In total, I found that only about 0.4% of the Jensen and Murray patents have ever been the subject of infringement litigation.[406] If we exclude the patents asserted in the retaliatory lawsuit filed by Incyte, only about 0.2% of the patents have been asserted, with those patents having claims relating to only four human genes.[407] In contrast, it has been reported elsewhere that about 1-2% of issued

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[398] *See supra* note 344 and accompanying text.

[399] *See supra* notes 347-51 and accompanying text.

[400] Myriad Genetics, Inc. v. Univ. of Pa., No. 98-829 (D.C. Utah 1998), *dismissed* (Apr. 20, 1999); Myriad Genetics, Inc. v. OncorMed, Inc., No. 97-922 (D. Utah filed Dec. 2, 1997). However, it has been alleged that competitors could have provided more effective BRCA1 mutation screening. Williams-Jones, *supra* note 352, at 139.

[401] *Stifling or Stimulating – The Role of Gene Patents in Research and Genetic Testing Before the Subcomm. on Courts, the Internet and Intellectual Property*, 110th Cong. (2007) (statement of Dr. Marc Grodman, CEO, Bio-Reference Laboratories, Inc.); GeneDx is currently not advertising testing for Long QT Syndrome; however, GeneDx continues to offer genetic testing for a host of other genetic diseases. *See* GeneDx, *Diseases for Which GeneDx Offers Tests*, http://www.genedx.com/tests.php.

[402] Personal Conversation with Alice Lara, President and CEO, Sudden Arrhythmia Death Syndromes (SADS) Foundation (June 9, 2007).

[403] Gennaisance Pharms., Annual Report (Form 10-K), at 66 (March 15, 2005), *available at* http://sec.edgar-online.com/2005/03/15/0001047469-05-006537/Section19.asp.

[404] SADS Foundation, Genetic Testing for the Congenital Long QT Syndrome, http://www.sads.org/Genetics/Clinical%20Testing.htm (last visited Jan. 30, 2008).

[405] *See supra* note 369 and accompanying text.

[406] Eighteen of the 4270 patents, see *supra* this section.

[407] Nine of the 4270 patent, see *supra* this section.

patents are litigated,[408] and that "biotechnology patents" (a broader category than human gene patents) are litigated at a substantially higher rate than patents in general.[409] Of course, most of the patents in the Jensen and Murray dataset are still in force, so it is possible that some of the patents will be the subject of future lawsuits. But, as described above, I have found that 1.1% of a random sample of 1,000,000 patents issued in the same time frame as the patents in the Jensen and Murray database have already been the subject of lawsuits, very close to the previously estimated 1-2% for patents in general.[410]

Most of the human gene patent litigations identified in this study, particularly those occurring in the context of research tools and protein therapeutics, involved patents that did not appear in the Jensen and Murray dataset.[411] A majority of these lawsuits were brought in the context of therapeutic proteins, usually in a dispute between innovator biotechnology company patent owners and firms attempting to market a competing product.[412] 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 cost and availability of protein therapeutics, but, overall, the impact is likely a positive one. Convincing arguments have been made that patents play a critical (some would argue necessary) role in the development of drugs, largely due to the need for innovator companies to recoup the huge expenses associated with drug development (particularly as required to gain FDA approval).[413] 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.[414]

It seems apparent that the use of human gene patents to provide 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 likely support an argument in favor of allowing gene patents. However, as the chemical structure of therapeutic proteins continue to diverge farther from naturally-occurring human proteins, human gene patents will probably play a diminishingly important role in

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[408] *See supra* note 157 and accompanying text.

[409] Lemley & Shapiro, *supra* note 56 at 79. This finding seems consistent with my own experience after reviewing a large number of biotechnology patent litigations, although I have made no attempt to quantify the rate at which biotechnology patents in general are litigated.

[410] *See supra* note 157 and accompanying text.

[411] *See supra* Section VI.

[412] *See supra* Section VI.A.

[413] Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1581-82 (2003); *see also* ORTON HUANG ET AL., BIOTECHNOLOGY PATENTS AND STARTUPS 1 (2003) (stating that "patents are absolutely essential to the success of traditional biotech startups"); TED BUCKLEY, THE MYTH OF THE ANTICOMMONS, Biotechnology Indus. Org.,4 (May 31, 2007), *available at* http://www.bio.org/ip/domestic/TheMythoftheAnticommons.pdf.

[414] Burk & Lemley, *supra* note 413, at 1625.

providing market exclusivity for these important products. It is already the case that effective market exclusivity for protein therapeutic products relies less on patents and more on the time and expense necessary to achieve FDA approval for a competing follow-on biologic product.[415] Pending legislation would recognize this fact by providing a statutory abbreviated approval process for biologics, analogous to the ANDA process for drugs as specified by the Hatch-Waxman Act.[416] Interestingly, the current version of the bill would provide innovator biotechnology companies with twelve years of market exclusivity independent of any patent rights,[417] perhaps in recognition of the more limited role of patents in this context, relative to the preeminent role they play in providing exclusivity for conventional small molecule drugs.

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, Inc. v. Peprotech, Inc.*[418] and *Promega Corp. v. Lifecodes Corp.*,[419] has a court found a human gene patent to be infringed but not invalid.[420] Both cases probably had a relatively minimal impact on public health.

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.[421] However, given that the protein and gene sequences were public knowledge, a research laboratory with competency in molecular biology should have, without undue effort, been able to clone the gene and produce the protein itself,[422] or even bought the gene off the shelf.[423] 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 resembled that natural human protein. While purchasing the protein from Peprotech was apparently more cost effective for its customers than producing the protein internally, removal of the Peprotech 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

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[415] Biotechnology Industry Organization (BIO), *BIO Principles on Follow-on Biologics*, (Mar. 26, 2007), http://www.bio.org/healthcare/followonbkg/Principles.asp; Joyce Cutler, *Generic Biologics Debate Needs Facts*, 74 PAT., TRADEMARK & COPYRIGHT J. 248 (2007) (reporting remarks of Pamela Jones, FTC Commissioner).

[416] S. 1695, 110th Cong. (2007)

[417] *Id.* § 2.

[418] 1994 WL 613021 (D.N.J. Oct. 17, 1994).

[419] 1999 U.S. Dist. LEXIS 21094 (D. Utah Oct. 27, 1999).

[420] *See supra* notes 310 & 380 and accompanying text.

[421] *See supra* notes 306-15 and accompanying text.

[422] *See, e.g.*, JOSEPH SAMBROOK & DAVID W. RUSSELL, MOLECULAR CLONING: A LABORATORY MANUAL (Cold Spring Harbor Press, 3d. ed. 2001).

[423] *See, e.g.*, DNA 2.0 Homepage, http://www.dna20.com/ (last visited Jan. 30, 2008). DNA 2.0 is a company that provides customized full-length synthetic genes on demand. *Id.*

of Amgen's IL-1 inhibitor, Kineret, and the fact that Immunex and Regeneron had competing IL-1 inhibitors in clinical trials by 2002.[424]

Likewise, the outcome of *Promega* probably had little impact on biomedical research or public health. For one thing, the infringing activity involved genetic identification technology, not health care.[425] 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.[426] 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.[427] Anyone willing to invest in identifying alternate sequences for genetic identification could have done so, though 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.

New England and *Promega* are the exception; for the most part, genetic testing and research tool patent cases settle, and do so at an early stage in the litigation. In this article, I have assumed that the filing of a lawsuit is an indication of patent impact, but the inference of impact is attenuated in cases 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. Settlement terms will vary on a case-by-case basis, but in many instances, a settlement agreement will allow the alleged infringer to continue using the contested technology, although 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 suggesting that use of the technology was not viewed as especially valuable.[428]

Of course, a patent can have an impact even in cases where the patent is never asserted. If researchers agree to license the patent and pay 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

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[424] Complaint at 4, In re Amgen Inc. and Immunex Corp., No. C-4053 (July 12, 2002), *available at* http://www.ftc.gov/os/2002/07/amgencomplaint.pdf.

[425] *See supra* note 376 and accompanying text.

[426] Promega Corp. v. Lifecodes Corp., 1999 U.S. Dist. LEXIS 21094,*41 (D. Utah Oct. 27, 1999).

[427] *See* U.S. Patent No. 4,963,663 (filed Feb. 8, 1989).

[428] Allison et al., *supra* note 51, at 442 (positing that when the stakes are high, even a slim chance of success will motivate a company to expend the money on a patent litigation). This likely accounts for my observation that a relatively large proportion of the protein therapeutic disputes are fully litigated, consistent with the high commercial value of protein therapeutics compared to research tools and genetic testing services.

using the technology to escape 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 and licensing agreements are often not publicly available.[429]

Lemley has posited that patents are only licensed at about three times the rate they are litigated,[430] and if that statistic holds true for human gene patents, one can speculate that the rate at which human gene patents are the subject of licensing fees is likewise relatively infrequent. A low rate of licensing, and more generally a low rate of commercial relevance, might explain why Incyte, the assignee of the largest number of human gene patents in the Jensen and Murray dataset, is letting many of its patents lapse for failure to pay maintenance fees.[431] It might also account for a recently noted drop-off in the rate at which patent applications claiming genetic sequences are being filed.[432]

I would argue that litigation frequency provides an indirect measure of non-litigation impact. As noted above, Allison has posited that it is relatively rare for patents to be licensed at a substantial level without some lawsuit being filed.[433] 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, my finding that the impact of human gene patent litigation has been relatively modest suggests that non-litigation impact is not as extensive as commonly perceived.

While avoidance of patented technologies by researchers based on fear of patent infringement liability is clearly a real effect; that fear might not always be entirely rational. To the extent action is taken that is based on a misperception of risk, the impact is not caused so much by patents, but by the misperception. For example, if academic researchers face little or no real threat of a 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. Perhaps the solution is to correct the misperception instead of altering the law.

The relatively modest impact of human gene patents in the context of genetic testing and research tools, at least as measured by the rate of enforcement and litigation outcome, simply does not warrant 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

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[429] Scott A. Moss, *Illuminating Secrecy: A New Economic Analysis of Confidential Settlements*, 105 MICH. L. REV. 867, 869 (2007).

[430] Lemley, *supra* note 157, at 1507 n.55.

[431] *See, e.g.*, U.S. Patent No. 5,853,997 (filed June 11, 1997); U.S. Patent No. 5,817,497 (filed Nov. 26, 1996); U.S. Patent No. 5,776,753 (filed June 11, 1997). These patents were all asserted in *Incyte v. Invitrogen*, *supra* Section VI.

[432] *See* Michael M. Hopkins et al., *DNA Patenting: The End of an Era?*, 25 NATURE BIOTECHNOLOGY 185, 185-86 (2007).

[433] Allison et al., *supra* note 51, at 442.

"nucleotide sequences" that have nothing to do with genes, or even biology.[434] 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, that 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.[435]

In my view, the GRAA is overly broad, for example, in failing to distinguish between naturally and non-naturally occurring nucleotides sequences, and between genetic and non-genetic uses of DNA. At the same time, its narrow focus on polynucleotides falls short of addressing the more general and pressing problem of U.S. patent law's over-expansive definition of patentable subject matter.[436] Although genes are important, gene patents have had a relatively minor impact compared to other patents claiming fundamental biological principles that generally do not claim DNA or genes. Examples include Ariad's NF-kB patent,[437] WARF's embryonic stem cell patents,[438] Metabolite's patent that claims virtually any practical use of the discovery of a correlation between homocysteine and B vitamins,[439] Classen's patent that claims the use of the discovery of a correlation between vaccination schedule and risk of developing an immune disorder in vaccination protocols,[440] and JN MacRi's patent that claims 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 a fetus with Down syndrome.[441]

The focus on gene and gene patents appears to be a manifestation of a general phenomonen often referred to as "genetic exceptionalism," a tendency of legislators and the public to pursue gene-specific policy solution based on an unwarranted perception that genes and genetics raise concerns that are fundamentally different and more compelling than other biological subject

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[434] Others have pointed out the potential for unintended negative consequences that might occur if the patenting of genetic sequences is banned. *See, e.g.*, Graham Dutfield, *DNA Patenting: Implications for Public Health Research*, 84 BULLETIN OF THE WORLD HEALTH ORG. 388, 391 (2006).

[435] Genomic Research and Diagnostic Accessibility Act of 2002, H.R. 3967, 107th Cong. (2002).

[436] Holman, *Patent Border Wars*, *supra* note 5, at 541.

[437] *See* Ariad Pharms., Inc. v. Eli Lilly & Co., 2007 WL 2011279 (D. Mass. July 6, 2007); U.S. Patent No. 6,410,516 (filed June 5, 1995).

[438] *See* Andrew Pollack, *Agency Agrees to Review Human Stem Cell Patents*, N.Y. TIMES, Oct. 4, 2006, at C5.

[439] *See* Lab. Corp. of Am. Holdings v. Metabolite Labs., Inc., 126 S. Ct. 2921 (2006) (per curiam) (Breyer, J., dissenting); U.S. Patent No. 4,940,658 (filed Nov. 20, 1986).

[440] *See* Classen Immunotherapies, Inc. v. Biogen Idec, 381 F. Supp. 2d 452, 453-54 (D. Md. 2005); U.S. Patent No. 6,420,139 (filed July 6, 2000).

[441] J.N. Macri Techs., LLC, No. 04-953 (E.D.N.Y. Mar. 5, 2004); U.S. Patent No. 5,324,668 (filed Feb. 3, 1993).

matter.[442] Instead of focusing solely on genes and DNA, legislators and policy advocates would do better to address the wider 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 primarily 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 account for the positive benefits of human gene patents. Any analysis of the patent system that focuses solely on the negative attributes of patents will surely lead to a conclusion that patents are a detriment to society; however, the analysis is flawed because it fails to account for the substantial benefits to innovation.[443] 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 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.

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[442] Another example is a genetics discrimination bill also being considered by Congress at this time. *See* Genetic Information Nondiscrimination Act of 2007, H.R. 493, 110th Cong. (2007) (The purpose of this act is "[t]o prohibit discrimination on the basis of genetic information with respect to health insurance and employment."). *Cf.* Timothy Caulfield & Barbara von Tigerstrom, *Gene Patents, Health Care Policy and Licensing Schemes*, 24 TRENDS IN BIOTECHNOLOGY 251, 251 (2006) (arguing that compulsory licensing of genetic technologies is unwarranted owing to the minor role these technologies play in most health care systems). For general discussions of "genetic exceptionalism," see Mark A. Rothstein, *Genetic Exceptionalism & Legislative Pragmatism*, 35 HASTINGS CENTER REPORT 27 (2005) and Stephen Fink, *EEOC v. BNSF: The Risks and Rewards of Genetic Exceptionalism*, 42 WASHBURN L.J. 525 (2003).

[443] F. Scott Kieff, *Property Rights and Property Rules for Commercializing Inventions*, 85 MINN. L. REV. 697, 707-13 (2001).