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The Role of DNA Patents in Genetic Test Innovation and Access

By Andrew S. Robertson*

I. INTRODUCTION

¶1 Recent decades have seen great advances in the science and application of genetics. Within healthcare and the health sciences, enhanced knowledge of the human genome—coupled with rapidly evolving technologies—is providing new opportunities to assess common multifactor disorders, such as heart disease, diabetes, asthma, and mental illness.[1] Moreover, genetic testing has brought us closer to "personalized" or "individualized" medicine, which allows for targeted treatment selection, identification, and quantification of treatment risks; monitoring of treatment effectiveness and prognosis; and personalized disease management.[2] The use, understanding, and application of genetic information both in healthcare and in other aspects of society will continue to increase over time.

¶2 The effects of gene patents on genetics research and application have been debated in a variety of forums.[3] The economic and policy issues surrounding patents on genes, nucleotide sequences, expressed sequence tags (ESTs),[4] single nucleotide polymorphisms (SNPs),[5] and other genetics-based advances have the potential to significantly impact

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[1] Francis S. Collins, *A Brief Primer on Genetic Testing*, NAT'L HUMAN GENOME RESEARCH INST. (Jan. 24, 2003), http://www.genome.gov/10506784.

[2] *See* Alan E. Guttmacher & Francis S. Collins, *Welcome to the Genomic Era*, 349 NEW ENG. J. MED. 996 (2003); John Bell, *Predicting Disease Using Genomics*, 429 NATURE 453 (2004) (discussing the use of genetics in predicting disease, drug discovery, disease monitoring, and clinical practice).

[3] *See generally* NAT'L RESEARCH COUNCIL, NAT'L ACAD. OF SCIS., REAPING THE BENEFITS OF GENOMIC AND PROTEOMIC RESEARCH: INTELLECTUAL PROPERTY RIGHTS, INNOVATION, AND PUBLIC HEALTH (Stephen A. Merrill & Anne-Marie Mazza eds., 2006) [hereinafter NRC REPORT]; SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, DEP'T OF HEALTH & HUMAN SERVS., GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (2010) [hereinafter SACGHS REPORT], *available at* http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_patents_report_2010.pdf; World Health Organization Res. 62.16, Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property, 62nd World Health Assembly May 18–22, 2009, 8th Plenary Meeting, A62/VR/8 (May 22, 2009) [hereinafter WHA], *available at* http://apps.who.int/gb/ebwha/pdf_files/A62/A62_R16-en.pdf.

[4] *See* Mark D. Adams et al., *Complementary DNA Sequencing: Expressed Sequence Tags and Human Genome Project*, 252 SCI. 1651 (1991), *available at* http://www.sciencemag.org/cgi/pmidlookup?view=long&pmid=2047873 ("[Expressed sequence tags] have applications in the discovery of new human genes, mapping of the human genome, and identification of coding regions in genomic sequences.").

[5] *See* David G. Wang et. al, *Large-Scale Identification, Mapping, and Genotyping of Single-Nucleotide Polymorphisms in the Human Genome*, 280 SCI. 1077 (2007), *available at* http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.115.5841&rep=rep1&type=pdf ("Single-

public health, research, and biotechnology innovation. Despite these potential positive impacts, initial challenges to gene patents have focused on the moral concerns about making a commodity out of a part of ourselves.[6] Globally, the role of DNA sequence patents in addressing challenges—such as international development, global disease, and climate change—has often caused a divide between developed and developing countries.[7] These concerns have generated debate and led to the exploration of policy options to ensure that gene patents do not impede the practice of medicine and the progress of science.

¶3 The economic debate regarding patents, particularly in healthcare and drug development, is often framed as one of access versus innovation.[8] Indeed, this debate has persisted within the subject of DNA-sequence patents. While opponents of DNA-sequence patents cite the barriers that such patents pose to research and healthcare,[9] biotechnology and industry representatives claim that such patents are required for innovation in gene-based molecular diagnostics.[10] Often, the debate about gene patents is analogized to the role of patents in drug discovery and development,[11] an industry that is estimated to cost approximately $802 million per drug approved by the Food and Drug Administration (FDA) (in 2000 dollars).[12] However, several factors call into question the validity of this analogy and how it impacts the "innovation" argument in the context of DNA sequence patents.

¶4 This paper analyzes the role of patents in furthering innovation in gene-based molecular diagnostics. Part II provides a quick background of the science of genetic testing and an explanation of patent law as it pertains to DNA sequence patents. Part II also discusses in further detail the effect of gene-sequence patents in the field of DNA research and clinical healthcare. Part III discusses the barriers that patents represent in the field of genetic testing, both in terms of innovation and access. Part IV discusses whether there is a positive need for patents in genetic test development, with a focus on

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nucleotide polymorphisms (SNPs) are the most frequent type of variation in the human genome, and they provide powerful tools for a variety of medical genetic studies.").

[6] *See* Lori B. Andrews, *The Gene Patent Dilemma: Balancing Commercial Incentives with Health Needs*, 2 HOUS. J. HEALTH L. & POL'Y 65, 69–70 (2002).

[7] *See generally* WHA, *supra* note 3; SECRETARIAT OF THE CONVENTION ON BIOLOGICAL DIVERSITY, BONN GUIDELINES ON ACCESS TO GENETIC RESOURCES AND FAIR AND EQUITABLE SHARING OF THE BENEFITS ARISING OUT OF THEIR UTILIZATION (2002), *available at* www.cbd.int/doc/publications/cbd-*bonn*-gdls-en.pdf; WORLD INTELL. PROP. ORG. [WIPO], *Examination of Issues Regarding the Interrelation of Access to Genetic Resources and Disclosure Requirements in Intellectual Property Rights Applications*, WIPO Doc. WO/GA/32/8 (2005), *available at* http://www.wipo.int/export/sites/www/tk/en/laws/pdf/examination_of_issues.pdf.

[8] *See, e.g.*, Henry Grabowski, *Patents, Innovation and Access to New Pharmaceuticals*, 5 J. INT'L ECON. L. 849 (2002).

[9] For example, one such barrier posed by such patents is a patient's inability to test their susceptibility to a heritable disease, such as breast cancer.

[10] *See, e.g.*, Richard Van Noorden, *DNA Patent Ruling Hinders Monsanto*, NATURE NEWS (July 9, 2010), http://www.nature.com/news/2010/100709/full/news.2010.345.html; *Gene Patent Ruling Stalls Biotech Rally-Myriad (MYGN) Down 4.9%*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS BLOG (Mar. 30, 2010), http://www.genengnews.com/blog-biotech/gene-patent-ruling-stalls-biotech-rally-myriad-mygn-down-4-9/614/.

[11] *See, e.g.*, Brief for BayBio et al. as Amici Curiae Supporting Defendants, Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (No. 09 Civ. 4515).

[12] Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151, 180 (2003).

both the costs of gene test research and development (R&D) and the market rewards associated with bringing a genetic test to market. Part IV further discusses these associated costs and rewards in comparison to those of pharmaceutical development, where appropriate. Part V summarizes this discussion, concluding that even though patents provide inhibitive roles in genetic test innovation and access, it is also questionable whether DNA-sequence patents are necessary to incentivize genetic test development.

II. BACKGROUND

A. Science of Genetic Testing

¶5 Most aspects of human biology stem from either genetic (hereditary) or environmental (nonhereditary) factors. After the human genome was first sequenced, researchers increasingly studied how genetic variation contributes to heritable traits and disease.[13] While some genetic traits, such as height and eye color, are only slightly influenced by environmental factors, other traits, such as obesity and some forms of cancer, only manifest in combination with—or as a result of the absence of—certain environmental conditions.[14] Regardless, identifying genetic variations and understanding their physiological manifestation (termed phenotype) can offer valuable insights into human biology, predisposition to disease, and response to particular therapeutics. Applying these insights in clinical healthcare is the cornerstone of personalized medicine, specifically the ability to tailor medical care to an individual based on his or her particular genetic makeup.[15]

¶6 Utilizing these insights in clinical practice begins with knowledge about gene sequence and DNA sequence variation. There are many different kinds of variation, ranging from complete, extra, or missing chromosomes down to single nucleotide changes. Each variation utilizes a different laboratory technique for detection and analysis.[16] Most studies of human genetic variation begin with the full gene sequence and focus on SNPs, which are substitutions in individual bases along a chromosome.[17] Experts estimate that SNPs occur, on average, somewhere between one in every hundred and one in every thousand base pairs in the human genome.[18] By conducting familial studies or larger "genome-wide association studies" (GWAs), researchers look for statistically significant links between genetic variation and phenotypes.[19] This linkage

[13] *See* Bell, *supra* note 2; Elizabeth Pennisi, *Human Genetic Variation*, 318 SCI. 1842 (2007).

[14] *See generally* Muin J. Khoury et al., *Do We Need Genomic Research for the Prevention of Common Diseases with Environmental Causes?*, 161 AM. J. EPIDEMIOLOGY 799, 802 (2005) (discussing approaches to identifying gene-environment interaction).

[15] *See* Guttmacher & Collins, *supra* note 2, at 996–98; Bell, *supra* note 2, at 453–55 (discussing the use of genetics in predicting disease, drug discovery, disease monitoring, and clinical practice with respect to individualization).

[16] *See* Nicholas Wade, *Genetic Catalog May Aid Search for Roots of Disease*, N.Y. TIMES, Oct. 27, 2005, at A20, *available at* http://www.nytimes.com/2005/10/27/science/27genome.html.

[17] *See Id.*

[18] *See* Int'l HapMap Consortium, *A Haplotype Map of the Human Genome*, 437 NATURE 1299, 1301 (2005).

[19] Thomas A. Pearson & Teri A. Manolio, *How to Interpret a Genome-Wide Association Study*, 299 JAMA 1335 (2008).

serves as the scientific basis for genetic tests; by testing for specific genetic variations, physicians can determine risk for disease, understand behavioral characteristics, and identify genetic causes of existing conditions.[20] These studies have led to genetic tests for approximately 1,400 genetic variations, with more than 1,000 additional tests currently in development.[21]

B. Legal Issues Regarding Gene Patents

¶7 The number of DNA sequence patents grew dramatically during the Human Genome Project and similar international efforts to better understand the human genome.[22] Patents are designed to encourage innovation by granting to inventors, for a limited period of time, the right to exclude others from making, using, or selling the patented invention. This system was established in the U.S. Constitution two centuries ago in order to create incentives for technological innovation.[23] Accordingly, U.S. patent laws are designed to ensure that the public benefits from a new invention in exchange for the right to exclude others from making, using or selling his or her invention for twenty years from the date of the application.[24] In short, patents have a utilitarian function in U.S. law and exist to promote a positive good—specifically, "progress in the sciences and useful arts."[25] The legal requirements of obtaining a patent are multifold. First, patents are not allowed on products of nature or on scientific formulas, because the public would not be gaining anything new by virtue of the inventor.[26] As the U.S. Supreme Court has pointed out:

> The laws of nature, physical phenomena, and abstract ideas have been held not patentable. . . . Thus, a new mineral discovered in the earth or a new plant found in the wild is not patentable subject matter. Likewise, Einstein could not patent his celebrated law that $E=mc^2$; nor could Newton have patented the law of gravity. Such discoveries are "manifestations of . . . nature, free to all men and reserved exclusively to none."[27]

¶8 Further, for a gene to be patented, the patent applicant must show that his or her invention is (1) useful, (2) novel, and (3) nonobvious.[28] The usefulness of the inventions

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[20] *Id.*; *see also* Khoury, *supra* note 14, at 802.

[21] *See* Charles Schmidt, *Regulators Weigh Risks of Consumer Genetic Tests*, 26 NATURE BIOTECHNOLOGY 145, 145 (2008) (quoting Steve Gutman, FDA's director for *in vitro* diagnostics).

[22] Between 1990 and 2003, countries, such as the United States, the United Kingdom, Japan, France, Germany, and China, invested over an estimated $3 billion to sequence the 3.3 billion base pairs within the human genome. *See*, *The Human Genome Project Completion: Frequently Asked Questions*, NAT;L HUMAN GENOME RESEARCH INST. http://www.genome.gov/11006943 (last visited Mar. 22, 2011); Leslie Roberts, *Controversial from the Start*, 291 SCI. 1182 (2001).

[23] U.S. CONST. art. I, § 8, cl. 8. Article I of the U.S. Constitution gives Congress the power "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

[24] 35 U.S.C. §§ 154, 271 (2006).

[25] U.S. CONST. art. I, § 8, cl. 8.

[26] Andrews, *supra* note 6, at 67–68.

[27] Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980) (citations omitted).

[28] 35 U.S.C. §§ 101–103.

must be specific, substantive, and credible.[29] The patent application must also be adequately "enabling."[30] That is, it must describe the invention fully, in a way that would allow another person who is skilled in that field to reproduce the invention. Thus, the key tradeoff considered in patent law is the public disclosure of information in exchange for the right to exclude anybody from using that invention.

¶9 At present, the U.S. Supreme Court has made it clear that genetically engineered organisms can qualify as patentable subject matter,[31] and the U.S. Patent and Trademark Office (USPTO)[32] and the European Patent Office[33] have treated isolated and purified nucleotide sequences as if they were the same as patentable man-made chemicals.

¶10 DNA patents in particular raise several unique issues. DNA has an inherent duality, both as tangible material and intangible information, posing both practical and legal problems for gene patenting and patent enforcement.[34] Further, the finite number of genes within the human genome—approximately 23,000—makes it difficult (if not impossible) to "invent around" a genetic patent in order to create an equivalent, but non-infringing invention.[35] In addition, inventions such as genetic diagnostics could involve multiple patents or licensing agreements, giving rise to concerns of a "patent thicket" or "anti-commons effect," requiring multiple licensing agreements that potentially increase the costs of genetic tests.[36]

¶11 Philosophically, the question of "owning" human genes has been scrutinized significantly.[37] Allowing a company to exclude others from testing, using, or experimenting with genes present in every cell of our own bodies draws criticism from human rights experts. Gene patents directly prevent doctors from testing for various diseases, leaving patients no longer in control of their own bodies.[38] A patient who cannot get a doctor to test for a genetic condition inherent to his own genetic make-up can be said to have lost control over that genetic make-up, and thus, over himself. Moreover, opponents of gene patents argue that these practices violate the First Amendment by limiting an individual's freedom of expression.[39] Lori Andrews,

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[29] MANUAL OF PATENT EXAMINING PROCEDURE § 2107 (8th ed. revised Jul. 8, 2010), *available at* http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2107.htm.

[30] 35 U.S.C. § 112.

[31] *Diamond*, 447 U.S. at 303.

[32] Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001) ("[W]here the application discloses a specific, substantial, and credible utility for the claimed isolated and purified gene, the isolated and purified gene composition may be patentable.").

[33] European Patent Convention arts. 52, 53(a), 53(b), Oct. 5, 1973, *available at* http://www.epo.org/patents/law/legal-texts/html/epc/1973/e/apii.html. *See also Biotechnology in European Patents-Threat or Promise?*, EUROPEAN PATENT OFFICE (last updated Feb. 18, 2011), http://www.epo.org/topics/issues/biotechnology.html.

[34] Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences*, 49 EMORY L.J. 783, 786–89 (2000).

[35] NRC REPORT, *supra* note 3, at 22; *see also* Eisenberg, *supra* note 34, at 786–789.

[36] *See* NRC REPORT, *supra* note 3, at 125–28.

[37] *See, e.g.*, Cynthia M. Ho, *Splicing Morality and Patent Law: Issues Arising from Mixing Mice and Men*, 2 WASH. U. J.L. & POL'Y 247 (2000).

[38] Andrews, *supra* note 6, at 91–94.

[39] David Kravets, *Judge OKs Challenge to Human-Gene Patents*, WIRED (Nov. 2, 2009, 8:11 PM), http://www.wired.com/threatlevel/2009/11/genes/. Complaint at 19, 22–25, Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (No. 09 Civ. 4515).

Professor at Chicago-Kent College of Law, describes this loss of control as if "the first surgeon who took a kidney out of your body then patented the kidney."[40]

¶12 Currently, 20% of the approximately 23,000 genes in the human genome are covered by at least one active patent.[41] While supporters of gene patenting maintain that the patent system is a critical component of innovation and progress in the field of personalized medicine, opponents claim that the patents cause significant barriers to research into human genetics and proper healthcare through the use of gene-based molecular diagnostics.

C. AMP v. USPTO *("Myriad")*

¶13 In March 2010, a federal district court judge issued the first ruling directly addressing the patentability of DNA sequences.[42] The lawsuit was brought by the Association for Molecular Pathology (AMP), who was represented by the American Civil Liberties Union (ACLU), against Myriad Genetics and the USPTO. It challenged the idea that isolated nucleic acid molecules (the sequence of A, T, G, and C that comprise the human genome) can be patented. In his fifty-two page opinion, Judge Sweet found that the patented DNA sequences were not "markedly different" from DNA sequences found in nature within the human body, and as such were not patentable subject matter.[43] The federal court specifically cited the inherent qualities of DNA, stating, "DNA, and in particular the ordering of its nucleotides . . . serves as the physical embodiment of laws of nature—those that define the construction of the human body."[44] Although plaintiffs asserted that gene patents infringe on First Amendment liberties, the court did not fully address this legal question.[45] *Myriad* is currently being appealed to the Federal Circuit, and experts on both sides believe it will go all the way to the Supreme Court.

¶14 The *Myriad* case focused on Myriad's patented genetic tests for mutations in two breast-cancer genes, *BRCA1* and *BRCA2*.[46] As part of its patent, Myriad claimed the complementary DNA sequences of various tumorgenic *BRCA1* mutations and gene fragments.[47] Because testing for the *BRCA* mutated gene sequences typically involves

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[40] *60 Minutes: Patented Genes* (CBS television broadcast Apr. 4, 2010), *available at* http://www.cbsnews.com/video/watch/?id=6362525n.

[41] Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCI. 239 (2005).

[42] Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010).

[43] *Id.* at 229–30.

[44] *Id.* at 228.

[45] *Id.* at 238.

[46] *BRCA1* and *BRCA2* mutations (or "breast cancer 1" and "breast cancer 2") dramatically increase a woman's lifetime risk of developing breast or ovarian cancer. Women with *BRCA1* or *BRCA2* mutations have an 87% chance of developing breast cancer by age 70 (compared with 10% for the general population) and a 59% chance of developing the disease by age 50. Women with the *BRCA1* mutation have a 44% chance of developing ovarian cancer by age 70. About 5 to 10% of all female breast cancer is due to the inheritance of mutated copies of *BRCA1* or *BRCA2* genes. There are over 235 known genetic variations of *BRCA1* mutations, sprinkled through 100,000 bp in the gene, which encodes a protein made of 1,863 amino acids. There are about 100 mutations of the *BRCA2* gene, which encodes a protein made of 3,418 amino acids. Donna Shattuck-Eidens et al., BRCA1 *Sequence Analysis in Women at High Risk for Susceptibility Mutations*, 278 JAMA 1242 (1997); David Resnik, *Are DNA Patents Bad for Medicine?*, 65 HEALTH & POL'Y 181 (2003).

[47] "[Complementary DNA] is DNA that has been made from the messenger RNA (mRNA) transcript of

using reagents consisting of fragments of the *BRCA* genes, Myriad's exclusive rights over the mutated allele fragments enabled it to exclude others from performing *BRCA* testing (even preventing individuals performing tests on themselves). In essence, the patents granted to Myriad gave the company the exclusive right to perform diagnostic tests on the *BRCA1* and *BRCA2* genes and to prevent any researcher or individual from isolating and studying the genes without first getting permission from Myriad. Myriad charges between $350 and $3,150 for the *BRCA* test, and has succeeded in stopping many laboratories from performing the test if they lack the proper license.[48]

III. PRACTICAL CONSEQUENCES OF GENE PATENTING

¶15 *Myriad* illustrates the core issues surrounding gene patents—namely, their effect on research and development (innovation) and on clinical healthcare (access). Not addressed within *Myriad*, but equally relevant, is the effect of DNA sequence patents in human diagnostic contexts, including infectious disease diagnostics, genetically modified organisms, gene-based therapeutics, and synthetic biology technologies. These issues are discussed below in turn.

A. Effect of Gene Patents on Innovation and R&D

¶16 Despite numerous studies, the full impact that gene patents have had on academic research is still unclear.[49] With the advent of high-throughput DNA sequencing,[50] researchers and firms began patenting genes without fully understanding their physiological function. Patent applications filed by the National Institutes of Health on the first ESTs identified by Craig Venter set off alarm bells throughout the scientific community.[51] These patent applications were significantly upstream within the R&D pipeline, and the actual functions of these genes and their protein derivatives were unknown. Issuance of a patent on such an invention grants the patent-holder the right to prevent any additional researcher from investigating its properties further.[52] Following a

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a gene. A cDNA sequence, like a mature mRNA sequence, differs from a gene sequence in that it lacks the non-coding regions of the gene." SACGHS REPORT, *supra* note 3, at 13.

[48] Shannon Kieran et al., *The Role of Financial Factors in Acceptance of Clinical* BRCA *Genetic Testing*, 11 GENETIC TESTING 101, 101 (2007); Complaint at 19, 22–25, Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (No. 09 Civ. 4515).

[49] *See, e.g.*, NRC REPORT, *supra* note 3, at 127; Robert Cook-Deegan et al., *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers*, 12 GENETICS MED. S15, S28 (2010).

[50] High-throughput DNA sequencing automates the sequencing process, producing thousands or millions of sequences at once, resulting in a significant reduction in both time and cost. *See generally* Stephan C. Schuster, *Next-Generation Sequencing Transforms Today's Biology*, 5 NATURE METHODS 16 (2008); *Automated Sequencing and Genotyping*, EUROGENTEC, http://www.eurogentec.com/applications/automated-sequencing-and-genotyping.html?country=usa (last visited Mar. 28, 2011).

[51] NRC REPORT, *supra* note 3, at 72–73. *See also* David Dickson, *UK Clinical Geneticists Ask for Ban on the Patenting of Human Genes*, 366 NATURE 391, 391 (1993). Craig Ventor led a parallel private sector effort in competition with the publicly funded international Human Genome Project. The two projects were announced as a tie by then-President Clinton in 2003. Jamie Shreeve, *The Blueprint of Life*, U.S. NEWS & WORLD REP., Oct. 31, 2005, *available at* http://www.usnews.com/usnews/news/articles/051031/31genome.htm.

[52] Andrews, *supra* note 6, at 79, 81.

wave of genetic sequencing that occurred in the late 1990s, approximately 20% of the 23,000 human genes became protected by at least one patent.[53] From 1971 until 2006, approximately 33,000 nucleic acid patents were issued.[54]

¶17 Generally speaking, when encountering a patent-protected gene, research scientists are faced with three options: (1) stop or avoid researching the particular gene; (2) license the rights to research the gene from the patent holder; or (3) continue research regardless of legal liability. Studies suggest that each of these pathways is exercised; however, these studies conflict as to which of these three options is the overall dominant choice.[55] Indeed, the choice made is often dependent on the DNA sequence in question and the line of research pursued. Regardless, the exercise of any of these three options could potentially work to reduce fundamental R&D in human genetics.

¶18 The first two of these options faced by researchers interested in a patent-protected gene—stopping research and licensing the rights to research—can be illustrated by research conducted on the gene associated with hemochromatosis, a hereditary liver disease caused by progressive iron overload.[56] Approximately 80 to 85 % of hemochromatosis cases are caused by two specific mutations in the gene HFE, making it a prime candidate for genetic screening tests.[57]

¶19 SmithKline Beecham Clinical Laboratories (SBCL), owner of the patents of the gene and its two mutations, began enforcing the patents in 1998.[58] While many U.S. laboratories began genetic testing for hemochromatosis before the patents were awarded, as many as 30% of the 119 laboratories surveyed ceased research as soon as the patent rights were enforced.[59] For those researchers looking to continue developing a genetic test, SBCL asked for an upfront fee of $25,000 from academic laboratories and as much as $250,000 from commercial laboratories, plus a fee of $20 per test.[60] The patent interfered with clinical adoption of the test and potentially compromised the quality of testing by limiting the development of higher quality or lower cost alternative testing methods.

¶20 The hemochromatosis case study can demonstrate how a gene patent, when enforced, can serve to stifle or hinder human genetics research. Despite this example, however, several surveys and case studies indicate that many researchers would pursue the third option—choose to ignore, not inquire, or remain unaware of the intellectual property status of many of the genes being studied.[61] This can be attributed to a number of factors: for example, the decision not to enforce gene patents by patent holders or the assumption that fundamental research is exempt under U.S. patent law.[62] In a 2005

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[53] Jensen & Murray, *supra* note 41, at 239.

[54] NRC REPORT, *supra* note 3, at 101.

[55] *See, e.g.*, John P. Walsh et al., *View from the Bench: Patents and Material Transfers*, 309 SCI. 2002, 2002 (2005) (indicating that most researchers don't even consider whether patents are relevant to their research).

[56] *See* Jon F. Merz et al., *Diagnostic Testing Fails the Test: The Pitfalls of Patents are Illustrated by the Case of Haemochromatosis*, 415 NATURE 577, 577 (2002).

[57] *Id.*

[58] *Id.* at 578.

[59] *Id.* at 578–79.

[60] *Id.* at 578.

[61] *See, e.g.*, Walsh, *supra* note 55; SACGHS REPORT, *supra* note 3, at 52.

[62] *See, e.g.*, NRC REPORT, *supra* note 3, at 13 (indicating that academic researchers believe their research is exempt); *see also* Cook-Deegan et al., *supra* note 49, at S28 (describing Myriad's "*de facto*

survey of U.S. genetics researchers conducted by the National Academy of Sciences and John Walsh, a large majority of scientists failed to even consider whether the genes they were researching were covered by a patent.[63] Commonly, researchers assumed that any potentially infringing activity in which they were engaged was allowed under the "experimental use exemption," which grants infringers the right to use a patented invention for research and non-commercial purposes.[64]

¶21 However, in the landmark case *Madey v. Duke University*, the Federal Circuit made clear that the experimental use exemption was not applicable to certain academic research.[65] The case centered on a former Duke University professor who sued the university for patent infringement when, after he left, it continued to use equipment that he had patented.[66] The lower court held that the university could not be liable for patent infringement, because its uses were "solely for research, academic, or experimental purposes."[67] However, the federal court found that research that is part of the "legitimate business" of the university is not exempt from patent liability "regardless of commercial implications" or lack thereof.[68] In short, any researcher studying a patented gene, whether or not aware that he or she is infringing, is in violation of the patent-holder's rights.

¶22 Further, while many patent holders have not actively enforced their patent rights, many firms have failed to expressly state their intent to allow potentially infringing research to continue. For example, Myriad maintains it has never enforced its patents against researchers and does not enforce its patents against laboratories providing *BRCA* testing services in a form it does not do itself.[69] However,

> Myriad never publicly stated its *de facto* research use exemption policy. Myriad either passed on an opportunity to demonstrate its intentions publicly in written form or avoided comment to keep legal options open. And keeping options open equates to a chilling effect in zones of uncertainty. . . . Ambiguity may itself stifle basic or clinical research as researchers either avoid the work altogether or are wary of publicly reporting results.[70]

B. Effect of Gene Patents on Patient Access

¶23 Although the effect on R&D is uncertain, the negative effect that DNA sequence patents have in clinical healthcare has led to more conclusive findings. The barriers to access of gene-based molecular diagnostics by patients and healthcare can be characterized into two separate, nonexclusive categories—barriers due to test availability and barriers due to test price.

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research use exemption policy").

[63] NRC REPORT, *supra* note 3, at 121–22, 125–26.

[64] *See id.* at 13–14.

[65] Madey v. Duke Univ., 307 F.3d 1351, 1361–63 (Fed. Cir. 2002).

[66] *Id.* at 1352–53.

[67] *Id.* at 1361 (internal quotation marks omitted).

[68] *Id.* at 1362.

[69] Cook-Deegan et al., *supra* note 49, at S16.

[70] *Id.* at S28.

1. Reduced Availability of State-of-the-Art Genetic Tests Caused by DNA Patent Licensing Practices

¶24 The barrier to access due to test availability refers to the effect that patents and licensing practices have in restricting patient choice of genetic tests in terms of quality and accuracy. These harms are most clearly seen when an exclusive license is issued by a patent holder resulting in only a single laboratory that is allowed to perform a given test. For example, by preventing second opinion testing and obstructing access to top-quality testing, patient access to testing can suffer under these circumstances.

¶25 The case brought by the ACLU against Myriad offers a compelling and emotional example. Faced with a positive test result indicating a significant predisposition to breast cancer, Genae Girard had to make the difficult decision whether or not to undergo a preemptive dual mastectomy and hysterectomy.[71] These operations are life-altering and affect fundamental decisions regarding family, health, and lifestyle. Naturally, because human error is possible in any test of this sort, and Myriad utilizes only one of many diagnostic strategies for the *BRCA* genes, Ms. Girard sought a second opinion using a testing technique not utilized by Myriad.[72] However, within the United States, Myriad is the sole provider of the genetic tests for *BRCA1* and *BRCA2* by virtue of its patents.[73] By exercising its patent rights, Myriad eliminated the availability of second opinion *BRCA* testing.[74]

¶26 Without broad licensing, the availability of alternative testing techniques, medical second opinions, and testing verification is severely limited. This critique of patenting is related to the reduced incentives that monopoly holders have to introduce newer, cheaper, or alternative tests.[75] For example, consider MLPA:

> [T]here is an alternative diagnostic technique to *BRCA* called MLPA, a molecular way to detect genetic variations, including *BRCA1* and *BRCA2* mutations, under development at University of Washington. Using MLPA, a 2006 study published in the *JAMA* found that Myriad's testing strategy missed up to 12% of large genomic deletions or duplications. . . . [T]he missed mutations were not because of a technical error in Myriad's testing but a flaw in the testing strategy. . . . The article noted "many mutations are inherently not detectable by short-range [polymerase chain reaction used by Myriad] followed by genomic sequencing."[76]

Because it is already the patent holder and sole provider of the *BRCA* tests, Myriad has little incentive to adopt advanced testing techniques or allow patients to seek alternative or confirmatory testing.

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[71] *60 Minutes: Patented Genes*, *supra* note 40.
[72] *Id.*
[73] *Id.*
[74] *Id.*
[75] Cook-Deegan et al., *supra* note 49, at S29.
[76] *Id.* (footnotes omitted).

2. Question of Whether DNA Patents Create Access Barriers Due to Price Distortions

¶27 Price is a second key factor in preventing clinical access to genetic tests. Again, the ACLU provided a sympathetic story in their case against Myriad. Ms. Lisbeth Ceriani was diagnosed with breast cancer at age forty-two,[77] a younger age than is typically associated with these types of cancers. Breast cancer at a young age is often hereditary,[78] and it calls for more aggressive treatment, including preemptive removal of both breasts and ovaries. Although Ms. Ceriani had insurance that would pay for a portion of the test, which was a $3,200 cost, Myriad would not accept her insurance plan.[79] Without the insurance payment, she was unable to afford the test.[80]

¶28 While price can be prohibitive, it is unclear the extent to which this effect is a result of DNA patents. Studies conducted in the past few years have shown that between 19% and 74% of at-risk individuals who could benefit from *BRCA* testing are not being tested.[81] In these studies, the out-of-pocket costs to individual patients were reduced considerably for those who have health plans.[82] However, of the women who were eligible for testing and whose costs were covered—either through their insurance companies or through programs offered by Myriad—only 70% of them have had the *BRCA* test.[83] If price was the only consideration, presumably a higher percentage of women would have undergone testing. Regardless, price certainly had some effect, because only 22% of out-of-pocket payers chose to get the test performed.[84]

¶29 Whether this price effect was a result of patents, however, is less clear. The complaint states that costs of *BRCA* testing in the U.S. are expensive and could be lowered if researchers could move forward freely.[85] In fact, testing in the U.S. is five times as expensive as that of testing in places, such as France, where the patents on the *BRCA* genes were ruled invalid.[86] However, studies comparing the cost of the Myriad *BRCA* test, of which Myriad is the sole provider, with the costs of Myriad gene tests for the colon cancer genes *FAP* and *HNPCC*, in which fields Myriad has four and six competitors respectively, show little monopolistic effect on pricing.[87] Breaking the test down to price per amplicon (the price for each genetic test per DNA segment amplified per PCR), Myriad charges $38.05 per amplicon for their *BRCA* test, $40.80 per amplicon for their *FAP* test (nonprofit competitors charge between $28.57 and $39.88 per amplicon), and $49.17 per amplicon for their *HNPCC* test (nonprofit competitors charge between $30.00 and $77.44 per amplicon).[88] These studies indicate that competition does little to affect price overall.

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[77] *60 Minutes: Patented Genes*, *supra* note 40.
[78] *Id.*
[79] *Id.*
[80] *Id. See also* Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181, 188–89 (S.D.N.Y. 2010).
[81] Kieran et al., *supra* note 48, at 101.
[82] *Id.* at 102.
[83] *Id.*
[84] *Id.*
[85] Complaint at 27, Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (No. 09 Civ. 4515).
[86] *See* Cook-Deegan et al., *supra* note 49, at S28.
[87] *Id.* at S23–24.
[88] *Id.* at S17.

¶30 Disconnects between patents and price can be attributed to a number of factors. First, the downstream costs of a positive test, which can include counseling and possibly surgery, can be far greater than the test itself.[89] As such, when considering the combined costs of both diagnosis and treatment, the price of the genetic tests is relatively minor.[90] Further, at least in the case of *BRCA* testing, patentee monopolists benefit by directing the entirety of the market into their laboratories. Patent premiums depend on both the price elasticity of demand for a gene test and how the patent holder has chosen to set its price point for different purchasers.[91] Myriad has worked to set *BRCA* test prices to decrease access barriers and reduce what economists' term deadweight loss.[92] Further, by creating a number of patient access programs for those unable to cover the out-of-pocket expenses, Myriad adopted a de facto tiered pricing model to accommodate a majority of the demand.

¶31 While licensing practices appear to pose a more significant barrier to access than price, it is worth noting an example of how these two elements can overlap—consolidation of testing facilities.[93] Again, turning to the Myriad/*BRCA* example, Myriad has a strong incentive to develop the infrastructure to handle billing and payment for *BRCA* testing, because it captures all the revenues from market expansion. However, from a payer, health care provider, or patient point of view, this structure requires a redundancy of efforts if a patient is seeking genetic testing for multiple markers—for example, colon cancer, Alzheimer's, and Huntington's. Assuming that providers could achieve sufficient volume to justify setup costs, consolidation of these administrative tasks at a few broad-service genetic testing laboratories—as opposed to the establishment of several gene-specific testing facilities—could help spread and bring down the overall administrative costs of gene testing. However, licensing practices by many DNA patent holders have foregone this approach.

3. Ability of DNA Patents to Increase Access Through Improved Marketing

¶32 Finally, it is worth mentioning a potential benefit that DNA patents bring in the context of access to genetic testing: increased awareness through advertising. Securing a limited period of market exclusivity for gene patents creates an incentive for communication and marketing aimed at educating patients and health professionals who are interested in purchasing the product. As seen in the pharmaceutical sector, the incentive for direct-to-consumer (DTC) advertising to broaden the market is stronger for a monopoly provider than it is in a shared market, because a monopolist will gain the full benefit of market expansion.[94] In theory, this advertising creates a social benefit in terms of greater public knowledge of genetic testing and test availability.

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[89] *Id.* at S30.

[90] *Id.*

[91] *Id.* at S31.

[92] Deadweight loss in economic terms refers to the costs to society that occur through inefficiencies in the market. These inefficiencies are often due to the difference between market price and actual price, which can occur through factors such as monopolistic pricing or taxes. Here, by decreasing the price of BRCA tests closer to market prices, Myriad can reduce this inefficiency.

[93] *See* Cook-Deegan et al., *supra* note 49, at S33.

[94] *See generally* Julie M. Donohue et al., *A Decade of Direct-to-Consumer Advertising of Prescription Drugs*, 357 NEW ENG. J. MED. 673, 680 (2007) (indicating that generic drugs are typically not promoted).

¶33 Myriad launched several targeted DTC advertising campaigns to great effect.[95] In a study conducted by the Centers for Disease Control and Prevention, Myriad's advertising for *BRCA* testing increased the number of at-risk women who pursued genetic testing by close to 140%, yet there was no increase in the actual testing of low-risk women.[96] Further, the study found that anxiety associated with over-testing—an oft-cited downside of DTC advertising of genetic testing[97]—showed little difference in the targeted marketing areas.[98] This suggests that, at least in some contexts, patents may improve access through raising awareness among at-risk individuals.

IV. PATENTS AND INCENTIVES FOR INNOVATION IN GENETIC TESTING

¶34 Proponents of DNA patents maintain that, despite the negative effects cited in Part III.A and Part III.B, patents are required to incentivize innovation in personalized medicine.[99] These arguments are often made through analogies to drug development—patent incentives help secure commercial markets following development of a genetic test, discourage competition, attract investment, and draw creative minds to unmet social needs.[100]

¶35 However, the promise of market exclusivity is certainly not required in order to bring a product to market. One need only look to high-tech industries, such as generic drug manufacturing and software development, to observe that innovation can take place without a patent-created monopoly as an incentive. The past also provides many examples where innovation in biotechnology is not predicated on the promise of exclusivity—Jonas Salk, who in 1955 developed a vaccine for polio, endeared himself to the public by refusing to patent the vaccine.[101] In the context of personalized medicine, genetic testing for cystic fibrosis serves as a further example. When Francis Collins and colleagues "first cloned the [cystic fibrosis-linked] *CFTR* gene, they worked to ensure broad licensing."[102] Twenty years later, dozens of laboratories—both private and public—compete in *CFTR* testing on the basis of service, innovation, and quality.[103] While the steps of the drug development pathway mirror those of genetic test development, the costs, risks, and rewards of the two product development pathways differ significantly.

¶36 Principally, the question could perhaps be best phrased as: "Without DNA patents, would there be adequate incentive to innovate in the field of personalized medicine?" An immediate challenge arises in measuring innovation itself: at present, commonly agreed-upon metrics for innovation are not available, and proxies—such as patents, products

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[95] J. Jacobellis et al., *Genetic Testing for Breast and Ovarian Cancer Susceptibility: Evaluating Direct-to-Consumer Marketing—Atlanta, Denver, Raleigh-Durham, and Seattle, 2003*, 53 CENTERS FOR DISEASE CONTROL & PREVENTION: MORBIDITY & MORTALITY WKLY. REP. 603, 603 (2004).

[96] Cook-Deegan et al. et al., *supra* note 49, at S32.

[97] *See* Timothy A. Caulfield & E. Richard Gold, *Genetic Testing, Ethical Concerns, and the Role of Patent Law*, 57 CLINICAL GENETICS 370, 371 (2000).

[98] Cook-Deegan et al., *supra* note 49, at S32.

[99] *See, e.g.*, Brief for BayBio et al. as Amici Curiae Supporting Defendants, Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010) (No. 09 Civ. 4515).

[100] *See Id.*

[101] *60 Minutes: Patented Genes*, *supra* note 40.

[102] James P. Evans, *Putting Patients Before Patents*, 12 GENETICS MED. S3, S3 (2010).

[103] *60 Minutes: Patented Genes*, *supra* note 40.

brought to market, and R&D funding—are not each in themselves suitable.[104] For example, R&D costs are inherently difficult to quantify, since the process for discovery and development is often nonlinear. Establishing a fundamental understanding of scientific processes, biological pathways, or developing strategies for drug development is rarely a *de novo* process. Instead, it is the culmination of years of research from academic, government, and private sectors.

¶37 Without the availability of defined innovation metrics, the next best course of action is to consider innovation incentives as a function of two distinct variables: the cost of bringing a genetic test to market (costs) and the size of the market itself (rewards). The greater the ratio there is between "rewards" and "costs," the greater the incentive to innovate and bring a product to market. While this analysis may overlook additional incentives, including professional advancement and publication, it nonetheless is appropriate when considering the role of genetic testing in personalized medicine. This testing requires both knowledge and application—improving our scientific understanding of human genetics and applying this understanding in a healthcare setting.

A. The Costs of Bringing a Genetic Test to Market are Significantly Less than Those of Drug Discovery and Development

¶38 "Proponents of gene patents have tried to justify such patents by claiming that the arguments in favor of patenting drugs apply to patenting genes as well."[105] Patenting drugs may be justified considering the heavy investment needed to shepherd a drug candidate through development to market.[106] Drug development requires early capital to finance animal research and human clinical trials, as well as to obtain approval from the FDA. Likewise, the failure rate of drug candidates during the development phase is high and carries with it a significant cost of capital. These costs arguably require stronger guarantees for market exclusivity in order to recoup costs in the future. Patents, in turn, offer a tangible way of protecting the consumer market for their respective drugs, and they help to recoup the costs and risks undertaken by the drug developers.

¶39 The first component of determining how the drug development analogy applies to DNA patenting—the cost of bringing a genetic test to market—can be further separated into two distinct costs: R&D and marketing approval. Comparisons with drug development demonstrate that, in both R&D and marketing approval, the costs associated with bringing a genetic test to market are significantly lower than with a similar process in drug development.

1. Research and Development Costs of Genetic Tests Are Significantly Lower than Those in Drug Discovery

¶40 In the pharmaceutical industry, costs for early stage drug discovery are significant.[107] Candidate drug discovery involves different stages, including basic exploratory biology on target identification and validation, assay development, lead

[104] *See* Keith Smith, *Measuring Innovation*, *in* THE OXFORD HANDBOOK OF INNOVATION 148, 148 (Jan Fagerberg et al. eds., 2005).
[105] Andrews, *supra* note 6, at 77.
[106] *See* DiMasi, *supra* note 12, at 151–52.
[107] *Id.* at 152.

identification (which usually requires access to high-throughput screening), medicinal chemistry and pharmaceutical lead optimization, and drug candidate selection.[108] Drug candidates fail to achieve FDA approval for a variety of reasons. Approximately 39% of failures are caused by biopharmaceutical issues, such as oral bioavailability and formulation problems, whereas toxicity constitutes about 21% of failures.[109] Another crucial factor is lack of efficacy, which is responsible for about 29% of failures.[110]

¶41 Early-stage drug discovery involves several phases that can vary depending on the disease, state of the science, and approach used.[111] In general, however, this early discovery utilizes early stage research, which consists of target identification, hit generation, hit confirmation, and lead generation.[112] Hit generation typically involves high-throughput screening of various chemical libraries for known targets of bioactivity against an identified target or biomarker.[113] Following this, the hit confirmation phase is used to reevaluate the various leads and to perform additional research, such as dose response curves, functional assays, feasibility of synthesizing the compound, and binding assays, among others. These tests are performed over several weeks and are followed by the lead generation phase, the goal of which is to synthesize the lead compounds and structural homologues that show promise as drug candidates. The final price tag for this step in the drug development pipeline is estimated to be around $335 million in capitalized costs per marketed drug, with less than 5% of compounds screened making it through to the preclinical/animal model phase.[114]

¶42 In contrast to early stage drug discovery, identification of disease-linked genes is remarkably cheaper. High-density genotyping arrays used by GWAs are probably most analogous to the early stages of drug discovery, because they permit genome-wide genotyping of hundreds of thousands of SNPs.[115] These typically consist of developing a research cohort of individuals sharing a common illness or disease and studying their genome for statistically common SNPs that exist in higher frequency when compared to the control group. In the alternative, they involve monitoring a cohort whose genome profile is known for the development of a common disease. These GWAs are particularly suited to discovering previously unsuspected genes or pathways involved in a specific disease. The power of these hypothesis-free study designs in identifying the genetic factors of complex diseases is now well established.[116]

¶43 While the cost of conducting GWAs can still be partially prohibitive for many academic research laboratories, the price is substantially less than that of drug discovery.

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[108] *See* Robert G. Ridley, Plasmodium*: Drug Discovery and Development—An Industrial Perspective*, 87 EXPERIMENTAL PARASITOLOGY 293, 293–302 (1997). *See also* Simon A. Roberts, *Drug Metabolism and Pharmacokinetics in Drug Discovery*, 6 CURRENT OPINION IN DRUG DISCOVERY & DEV. 66, 66–68 (2003); Simon Frantz, *Screening the Right Candidate*, 2 NATURE REVS. DRUG DISCOVERY 331, 331 (2003).

[109] *See* Srini Venkatesh & Robert A. Lipper, *Role of the Development Scientist in Compound Lead Selection and Optimization*, 89 J. PHARMACEUTICAL SCI. 145, 147 (2000).

[110] *See Id.*

[111] *See generally* Konrad H. Bleicher et al., *Hit and Lead Generation: Beyond High-Throughput Screening*, 2 NATURE REVS. DRUG DISCOVERY 369 (2003).

[112] *Id.* at 369–375.

[113] *Id.* at 372–377.

[114] DiMasi et al., *supra* note 12, at 161–166.

[115] *See* Pearson & Manolio, *supra* note 19, at 1335.

[116] Yohan Bossé et al., *Identification of Susceptibility Genes for Complex Diseases Using Pooling-Based Genome-Wide Association Scans*, 125 HUM. GENETICS 305, 305–306 (2009).

Technological developments, such as next-generation DNA sequencing and high-density genotyping arrays, have led to the discovery of genetic risk-factors for many significant human diseases.[117] In 2000, a 2,000-person GWA covering ten million SNPs would carry a price tag of $20 billion, or $1.00 per SNP.[118] Compare this to 2007 estimates, when the price was $0.001 per SNP.[119] As technology and techniques continue to advance, the price of early stage discovery in genetic testing will continue to plummet.

¶44 Further, genetic research studies very often result in information that can be used directly for diagnostic testing in patients and their family members. Once a gene-trait association has been established, genetic tests are more "designed" than "discovered" and are developed through established scientific principles.[120] A sequencing-based test costs roughly $1,000 per exon to develop.[121] Given that the average gene has eight to ten exons (or coding regions),[122] the cost of developing a laboratory-developed genetic test that utilizes even the more expensive full gene sequencing diagnostic approach (as opposed to the cheaper probe hybridization approach used to detect a single mutation)[123] is on average between $8,000 and $10,000.

2. Costs Associated with Gaining Marketing Approval for Genetic Tests Are Lower than Drug Development Due to More Relaxed Government Regulation

¶45 As discussed in the above section, the costs for gene-based molecular diagnostics are likely to be less than those of drug development. However, proponents of DNA sequence patents might maintain that downstream costs for gaining FDA marketing approval for genetic tests could still pose significant barriers to test innovation and development. Within the field of drug development, FDA regulation is a critical concern underscoring the need for patents. The marketing of a new drug is prohibited unless that drug meets certain safety and efficacy standards.[124] The process of demonstrating safety

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[117] *See, e.g.*, Alan Herbert et al., *A Common Genetic Variant Is Associated with Adult and Childhood Obesity*, 312 SCI. 279 (2006) (describing a screening method to detect obesity-related genetic variants); Robert J. Klein et al., *Complement Factor H Polymorphism in Age-Related Macular Degeneration*, 308 SCI. 385 (2005) (describing a screening method to detect genetic variants associated with macular degeneration); John D. Rioux et al., *Genome-Wide Association Study Identifies New Susceptibility Loci for Crohn Disease and Implicates Autophagy in Disease Pathogenesis*, 39 NATURE GENETICS 596 (2007) (describing a screening method to detect genetic variants associated with Crohn's disease); Robert Sladek et al., *A Genome-Wide Association Study Identifies Novel Risk Loci for Type 2 Diabetes*, 445 NATURE 881 (2007) (describing a screening method to identify risk factors for Type 2 Diabetes); The Wellcome Trust Case Control Consortium, *Genome-Wide Association Study of 14,000 Cases of Seven Common Diseases and 3,000 Shared Controls*, 447 NATURE 661 (2007).

[118] Emma Hitt, *Microarray Technologies: Bench to Bedside*, 24 SCI. 1101, 1105 (2007); TERI A. MANOLIO, UPDATE ON GENOME-WIDE ASSOCIATION STUDIES: WE LIVE IN INTERESTING TIMES, NAT'L. HUM. GENOME RES. INST. (2007), *available at* http://www.genome.gov/Pages/About/OD/ReportsPublications/GWASUpdateSlides-9-19-07.pdf.

[119] Hitt, *supra* note 118, at 1105.

[120] Kathryn A. Phillips et al., *Diagnostics and Biomarker Development: Priming the Pipeline*, 5 NATURE REVS. DRUG DISCOVERY 463, 464 (2006). *See also* NRC REPORT, *supra* note 3.

[121] Soma Das et al., *Molecular Genetic Testing for Ultra Rare Diseases: Models for Translation from the Research Laboratory to the CLIA-Certified Diagnostic Laboratory*, 10 GENETICS MED. 332, 336 (2008).

[122] Meena Kishore Sakharkar et al., *Distribution of Exons and Introns in the Human Genome*, 4 IN SILICO BIOLOGY 387, 390 (2004).

[123] *See generally* NRC REPORT, *supra* note 3.

[124] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 201–704 (2006).

and efficacy ordinarily requires manufacturers to conduct clinical investigations of drugs that have not been previously tested, and it can carry significant costs and consume several years.

¶46 The process of gaining marketing approval from the FDA is extensive and costly. Following lead development, the compound undergoes preclinical animal safety studies under good laboratory practice (GLP) conditions.[125] At this stage, the pharmaceutical company would often file for an Investigational New Drug application, which is required to start clinical testing. If approved, the compound can undergo its first entry into humans through Phase I clinical trials designed to identify any immediate safety problems and a safe clinical dosage range.[126] Those compounds that survive the Phase I trials proceed to Phase II, which involves well-controlled clinical investigations designed to determine the therapeutic effectiveness of the drug, typically consisting of several hundred participants who have the pertinent condition or disease.[127] If the drug is considered sufficiently safe and effective following Phase II trials, it enters the pivotal Phase III trial. Phase III studies confirm the therapeutic effectiveness of the drug, provide more information on the drug's side effects, reveal whether it interacts with foods or other medications, and determine whether certain patient populations should avoid its use altogether.[128]

¶47 The journey from initial concept to a marketed drug is long and statistically more likely to end in failure than success.[129] The average time for a drug to reach the market is around twelve to fifteen years,[130] and only one in 5,000 compounds screened in early-stage discovery successfully makes it through to market, although both figures vary dramatically with disease area. Most failures occur at the early or preclinical stage, and only 20% of compounds that enter human trials are ever successfully approved. The estimated costs of clinical trials average $467 million, bringing the total cost of drug development (R&D plus clinical approval) to approximately $802 million (in 2000 dollars).[131]

¶48 In contrast, governmental regulation of genetic tests is much less defined than governmental regulation of drug approval.[132] At present, genetic tests are used in one of two separate forms: *in vitro* diagnostic devices (IVDs) or laboratory developed tests (LDTs).[133] FDA regulation of genetic tests varies significantly depending on the manner in which these tests are produced and sold.

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[125] *See* Kendy L. Keatley, *A Comparison of the U.S. EPA FIFRA GLP Standards with the U.S. FDA GLP Standards for Nonclinical Laboratory Studies*, 7 QUALITY ASSURANCE 147, 147 (1999).

[126] Richard J. Findlay, *Originator Drug Development*, 54 FOOD & DRUG L.J. 227, 227–228 (1999).

[127] *See* 21 C.F.R. § 312.21(a)–(b) (2010).

[128] John Patrick Dillman, Note, *Prescription Drug Approval and Terminal Diseases: Desperate Times Require Desperate Measures*, 44 VAND. L. REV. 925, 929 (1991).

[129] *See generally* DiMasi, *supra* note 12.

[130] *Id.* at 167.

[131] *Id.* at 151.

[132] Andrew S. Robertson, *Taking Responsibility: Regulations and Protections in Direct-to-Consumer Genetic Testing*, 24 BERKELEY TECH. L.J. 213, 221–225 (2009).

[133] *Id.* at 223; GENETICS & PUB. POL'Y CTR., FDA REGULATION OF GENETIC TESTS 1 (2006) (discussing how IVDs are defined as "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.").

¶49 The FDA is responsible for regulating tests sold as IVDs, defined as "reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions . . . ."[134] This definition includes tests manufactured by one company and then sold as a single-unit kit to a laboratory for genetic testing. Such kits must undergo successful pre-market review before they may be commercially distributed. In order to receive FDA authorization to sell the kits, companies must submit information to the FDA demonstrating that the test is safe and effective.[135]

¶50 The FDA's review of IVD test kits, like other products the agency regulates, is limited to the manufacturer's "intended use," as evidenced by the claims that the manufacturer makes about the product in labeling.[136] A manufacturer may not promote a test kit for an "off-label" use, such as one not approved by the FDA. However, it is important that the FDA does not regulate claims made by laboratories using FDA-regulated test kits that go beyond the approved labeling. The FDA has, to date, reviewed fewer than twenty genetic test kits.[137] These include tests for mutations causing the blood clotting disorders Factor II and Factor V, some of the mutations that cause cystic fibrosis, two genes within the cytochrome *P450* family of enzymes, which are involved in drug metabolism, and variants in the *UGT1A1* gene, which are also involved in metabolism of certain drugs.

¶51 Most genetic tests available today are not marketed as complete FDA-approved IVD test kits, but they are instead derived or assembled within the clinical laboratories themselves.[138] These LDTs, or home brews, fall outside of FDA regulatory authority.[139] Clinical and research laboratories often develop and prepare their own tests that are intended to diagnose various medical conditions, using ingredients that they frequently purchase from biological or chemical suppliers. The "active ingredients" of a test refer to the marketed ingredients and materials composed of chemicals or antibodies, which are useful only in testing for one specific disease or condition. In laboratory terms, the chemical for which one conducts an analysis is called the analyte. Therefore, these active ingredients are referred to as analyte specific reagents (ASRs). Marketing of ASRs is permitted, however, and is outside the regulatory purview of the FDA.

¶52 Myriad's *BRCA* genetic tests are considered LDTs, along with a wide variety of tests used in the diagnosis of infectious diseases, cancer, genetic conditions, and various other conditions. These tests are developed in-house and are not actively regulated by the FDA. Thus, the ingredients used in the tests are generally not produced under FDA-assured manufacturing quality control. Because of this regulatory exception, genetic testing services using home brewed tests can be marketed directly to both the medical

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[134] 21 C.F.R. § 809.3 (1980).

[135] *How Drugs are Developed and Approved*, U.S. FDA, http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/default.htm (last updated Apr. 23, 2010).

[136] 21 U.S.C. § 352(f) (2006).

[137] For a current list of clinically used genetic tests, *see* GENETESTS, NAT'L. CTR. FOR BIOTECHNOLOGY INFO., http://www.ncbi.nlm.nih.gov/sites/GeneTests (last visited Mar. 16, 2011).

[138] *See Diagnostics Kits/USA Regulations Review*, COMMONS BASED RESEARCH, http://cyber.law.harvard.edu/commonsbasedresearch/Diagnostic_Kits/USA_Regualtion_Review (last visited April 12, 2011).

[139] Robertson, *supra* note 132, at 221–22.

community and the public without FDA regulation or oversight.[140] As a result, costs of market entry for genetic tests are significantly lower than those associated with drug development.

B. Rewards for Genetic Test Development Are Partially Secured by Government Sponsorship

¶53 In addition to the significantly lower cost of genetic test development relative to drug development, it is important to recognize two additional incentives that contribute to innovation: governmental contribution to initial R&D and governmental interest in promoting personalized medicine in clinical healthcare.

¶54 Regarding basic research, a large portion of the information required for early discovery in gene-based molecular diagnostics is heavily sponsored by government and philanthropic funding. The publicly funded International HapMap Project, for example, produced a resource with 3.9 million SNPs entered for each of the samples, and the results are publicly available.[141] The information from the HapMap has already led to multiple genetic tests, including the identification of genes for age-related macular degeneration and autism.[142] Likewise, large GWAs conducted by organizations, such as the Coriell Institute and Kaiser Permanente, have received near-full funding from public sources, and they should produce a significant foundation of information regarding genotype/phenotype associations.[143] These studies will provide countless hits that will, in turn, be developed into gene-based molecular diagnostics.

¶55 Market entry into clinical healthcare, likewise, is starting to gather significant government support without the aid of patents. As discussed in Part III(B)(2), patient use of genetic testing is heavily reliant on adoption by third-party payers, as only one-fifth of out-of-pocket payers who would benefit from genetic testing are likely to pursue testing. The decision to reimburse for genetic testing rests heavily on the predicted utility in a clinical setting, including its ability to affect clinical outcomes and promote informed decision-making. However, clinical utility in itself is difficult to measure.

¶56 Here, again, the U.S. government is showing signs of significant support. The potential savings to healthcare following the widespread adoption of genetic testing has prompted U.S. policies that not only provide Medicare coverage of genetic tests where utility is already demonstrated, but also cover the costs of genetic tests where clinical utility is *only suspected*. For this, we turn to the example of genetic tests used to determine the dosage level of warfarin.

¶57 The anticoagulant medication warfarin is used to prevent and treat blood clots.[144] Approximately two million people start taking warfarin each year; physicians commonly

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[140] *Id.*

[141] *Id. See also* Int'l HapMap Consortium, *A Haplotype Map*, *supra* note 18; Int'l HapMap Consortium, *A Second Generation Human Haplotype Map of Over 3.1 Million SNPs*, 449 NATURE 851, 851 (2007).

[142] *Coriell Awarded $3.1 Million for Next Phase of the HapMap Project*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Dec. 12, 2006), http://www.genengnews.com/gen-news-highlights/coriell-awarded-3-1m-for-next-phase-of-the-hapmap-project/10146726.

[143] *See* Int'l HapMap Consortium, *A Haplotype Map*, *supra* note 18; Int'l HapMap Consortium, *A Second Generation Human Haplotype Map*, *supra* note 141.

[144] *See generally* Daniel S. Budnitz et al., *National Surveillance of Emergency Department Visits for Outpatient Adverse Drug Events*, 296 JAMA 1858 (2006). The cases that are seen in emergency departments represent a subset of total adverse drug events, but the precise fraction they represent is

prescribe it for patients with a history of atrial fibrillation, recurrent stroke, deep vein thrombosis, or pulmonary embolism, as well as for patients who have had heart valve replacements.[145] A major challenge in treating patients with warfarin is that the optimal dose varies greatly from person to person. If the dose taken is too high, users are subject to an increased risk of serious bleeding. On the other hand, if the dose is too low, users are subject to an increased risk of stroke. Indeed, warfarin is the second most common drug—after insulin—among those implicated in emergency room visits for adverse drug events, causing an average of more than 43,000 cases per year in 2004 and 2005.[146]

¶58 In 2008, the FDA approved a genetic test that can help physicians prevent adverse responses to warfarin.[147] The test, which costs up to $500, could potentially lead to other healthcare savings by leveraging personalized medicine to reduce the number of problems that result from improper dosing. A report published by the American Enterprise Institute–Brookings Joint Center (AEI-Brookings) (with input from the FDA) reached some very impressive conclusions. Specifically, the report concluded:

> We estimate that formally integrating genetic testing into routine warfarin therapy could allow American warfarin users to avoid 85,000 serious bleeding events and 17,000 strokes annually. We estimate the reduced health care spending from integrating genetic testing into warfarin therapy to be $1.1 billion annually, with a range of about $100 million to $2 billion.[148]

Interestingly, the Centers for Medicare and Medicaid Services (CMS) disagreed with the AEI–Brookings report, stating, "[A]vailable evidence does not demonstrate that pharmacogenomic testing to predict warfarin responsiveness improves health outcomes in Medicare beneficiaries."[149] Regardless, the significant potential healthcare savings associated with genetic tests for warfarin dosing prompted CMS to take an unprecedented track. While CMS would not directly reimburse for warfarin genetic tests, they did decide to pursue a strategy known as "coverage with evidence development," authorized

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uncertain. An estimate of total adverse drug events would include those occurring among hospital and nursing home inpatients, those treated in clinics, offices, and homes, and those not treated—in addition to those treated in emergency departments.

[145] Andrew McWilliam et al., *Health Care Savings from Personalizing Medicine Using Genetic Testing: The Case of Warfarin* 1, 2 (AEI-Brookings Joint Ctr. for Regulatory Studies, Working Paper No. 06-23, 2006).

[146] *Id.*

[147] Genetic tests for warfarin sensitivity are comprised of two separate genetic analyses coupled with a linkage algorithm. The test that can estimate a patient's sensitivity to warfarin is referred to as the *VKORC1* (vitamin K epoxide reductase) test. *VKORC1* is the gene that codes for the enzyme that is the site of action where warfarin exerts its effect. Genetic testing can indicate whether the patient may be more sensitive or less sensitive to warfarin than "average." The test that can estimate a patient's rate of warfarin metabolism is referred to as the *2C9* or *CYP2C9* test. *CYP2C9* refers to the particular liver enzyme that is primarily responsible for metabolizing (breaking down) the most active component of warfarin. *See* Henry I. Bussey et. al, *Genetic Testing for Warfarin (Coumadin) Dosing? – Not Yet Ready for Prime Time*, CLOTCARE ONLINE RESOURCE (July 2007), http://www.clotcare.com/clotcare/wararingenetictesting.aspx.

[148] McWilliam, *supra* note 145, at Executive Summary.

[149] *Proposed Decision Memo for Pharmacogenomic Testing for Warfarin Response (CAG-00400N)*, CENTERS FOR MEDICARE & MEDICAID SERVICES (May 4, 2009) [hereinafter *Proposed Decision Memo*], *available at* http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=224&ver=15.

under the Social Security Act.[150] This strategy allows CMS to cover the cost of genetic tests for warfarin responsiveness if they are a part of a "prospective, randomized, controlled clinical study."[151] In short, instead of requiring that clinical utility of genetic tests be provided prior to coverage, CMS will cover the costs of clinical genetic testing as a means to demonstrate its clinical utility.

¶59 While this situation is the first of its kind in genetic testing, it illustrates two important points. First, the potential value that personalized medicine holds in improving cost-effectiveness of medical care is significant. In the case of warfarin dosing, genetic tests can reduce the number of adverse events that lead to serious bleeding incidents, heart stroke, and increased hospital visits.

¶60 Second, relevant to reward incentives in genetic test innovation, this example demonstrates that the government recognizes the potential clinical utility of genetic testing and is willing to sponsor clinical studies to that effect. Applying the coverage with evidence development strategy to FDA-approved and home-brewed genetic testing represents a significant investment by the U.S. government to fully explore the cost-saving potential of genetic testing. Similar provisions are present in subsequent legislation, including the Genomics and Personalized Medicine Act of 2007,[152] introduced by then-Senator Barack Obama, and the recent healthcare legislation.[153]

¶61 Government confidence in personalized medicine represents—at least for the short-term—a decreased market risk for genetic testing. Potential market size and security represent a key reward incentive in commercial innovation. Patents serve as a mechanism to artificially decrease market risk by reducing competition. However, government sponsorship of the genetic testing market can also serve to reduce this risk and can help investors better predict market size, reliability, and duration with greater accuracy. As such, in terms of incentive mechanisms, government investment in genetic tests can function analogous to patents.

V. SUMMARY AND DISCUSSION

¶62 The debate over DNA patents has intensified following the federal court ruling in *AMP v. USPTO*.[154] DNA patents have the potential to pose significant barriers to gene test innovation as well as access to gene tests in the clinical setting.[155] In terms of R&D, DNA patents force researchers to choose amongst ceasing research activities on a patented DNA sequence, licensing the rights to research the gene from the patent holder, or ignoring the gene's patent status and risk legal liability. While the predominant choice among academic researchers is unclear, each of these choices would only hamper their research efforts.

¶63 In terms of clinical access to genetic tests, patents have the potential to create barriers due to limited availability of genetic tests and price distortions caused by market

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[150] *Id.*; 42 U.S.C. §§ 1320b-12, 1862 (2006).

[151] *Proposed Decision Memo*, *supra* note 149.

[152] S. 976, 110th Cong. (2007).

[153] *See* Ewen Callaway, *US Healthcare Bill Gets Personal*, NEW SCIENTIST (Mar. 24, 2010 at 12:45 PM), http://www.newscientist.com/article/dn18698-us-healthcare-bill-gets-personal.html. *See also* Patient Protection and Affordable Care Act of 2009, Pub. L. No. 111-148, 124 Stat. 119 (2010).

[154] *See supra* Part II(C).

[155] *See supra* Part III(A), III(B).

exclusivity.[156] Case studies demonstrate that the limited availability of genetic tests, caused primarily by exclusive licensing practices, can prevent patients and healthcare providers from obtaining top quality genetic tests and second-opinion testing. Price barriers due to patents, however, are not as evident in genetic tests; indeed, tests in both competitive and non-competitive markets are priced similarly.[157] Nonetheless, it is clear that patients have greater access to genetic tests within competitive markets.

¶64 With respect to the requirement of patents for innovation, many proponents of DNA patenting cite drug development as a proper analogy.[158] Patenting of drugs is arguably justified because of the heavy investment needed to shepherd a drug candidate through development to market. For drug development, early capital is required to finance animal research and human clinical trials and also to obtain FDA approval. Likewise, the failure rate of drug candidates in the development pipeline is high, and carries with it a significant capital cost. Recouping these costs requires stronger guarantees for market exclusivity. Patents, in turn, offer a tangible way of protecting the consumer market for their respective drugs, while helping recoup the costs and risks undertaken by the drug developers.

¶65 But research and marketing efforts for gene-based diagnostic tests do not require the same investment or carry the same risks as drug development.[159] First, in terms of costs, R&D is heavily funded by government and public sponsorship, including international collaborations like the Human Genome Project and the HapMap Project. Simultaneously, the costs of research in genetic testing are decreasing rapidly as technology advances. In addition, approval to market genetic tests can be obtained without the expensive clinical trials associated with drug approval. Safety and efficacy can be demonstrated through much smaller trials, and the scientific standard for statistically significant gene-disease correlations has yet to be established. These more relaxed approval standards should significantly decrease the price of clinical trials for genetic testing, estimated to constitute approximately half of the $802 million price tag, or $454 million in the drug development context.

¶66 Further, the costs of clinical testing can be avoided altogether as genetic tests can still be used in a clinical setting without FDA approval.[160] As discussed, there are multiple market points-of-entry for genetic tests, either through FDA-approved "test kits" or through the selling of ASR reagents to be used in home-brewed genetic tests. Unlike drug development, the fundamental technologies required for genetic testing are typically designed rather than discovered, and can undergo continuous modifications throughout the product life cycle, even after market entry. In some cases, such as the discovery of the hemochromatosis gene, discovery of a genetic marker for a particular disease has been applied to the clinical setting almost immediately following publication.[161] As such, the risk that a disease-linked gene will not make it to market is much lower than that of a drug candidate.

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[156] *See supra* Part III(A).
[157] *See supra* Part III(B).
[158] *See supra* Part IV.
[159] *See supra* Part IV(A)(1)–(2).
[160] *See supra* Part IV(A).
[161] *See* Andrews, *supra* note 6, at 77. *See also* Merz, *supra* note 56, at 577–79.

¶67 Finally, the U.S. government has shown significant interest in developing the personalized medicine market, thereby decreasing the risks associated with market rewards for genetic test development.[162] The use of coverage with evidence development in warfarin gene testing demonstrates how CMS is willing to pay for genetic tests even before clinical utility has been proven. While these actions may not become commonplace, they do underscore the U.S. government's commitment to fostering the growth of the genetic testing market.

¶68 In summary, the costs involved in the development of genetic testing, in terms of both R&D and obtaining marketing approval, are much lower than that of drug development. Likewise, the market for genetic tests is growing rapidly, with significant support from the federal government. While downstream patents may help competition in the genetic testing market, upstream patents on DNA sequences can actually hinder innovation and can limit patient access to quality testing due to exclusive licensing practices. These considerations suggest that not only are DNA sequence patents not required for innovation in the development of gene-based molecular diagnostics, but also they actually hinder the advancement and clinical adoption of personalized medicine.

[162] *See supra* Part IV(B).