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# European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent Law and Public Policy: A Case Study of the Myriad Genetics' BRCA Patent Controversy

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# European Opposition to Exclusive Control Over Predictive Breast Cancer Testing and the Inherent Implications for U.S. Patent Law and Public Policy: A Case Study of the Myriad Genetics' BRCA Patent Controversy

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## I. OVERVIEW

The human genome contains an estimated 30,000 to 35,000 genes[1] from which more than 100,000 proteins[2] can be derived.[3] Between 1980 and 2001, the U.S. Patent and Trademark Office (USPTO) awarded over 8,000 patents on genes and genetic material,[4] including at least 1,500 claiming sequences of human genetic material.[5] This trend continues following the simultaneous publications of the preliminary sequence of the human genome in 2001,[6] with thousands of human gene patent applications awaiting examination in the United States alone,[7] and a mere three prominent U.S. biotechnology companies having filed applications on a total of over 20,000 full-length human gene sequences.[8] With such a vast number of scientists, research institutions, hospitals, and corporations seeking exclusive control over products naturally contained within the

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[1] A gene refers to the "basic physical and functional unit of heredity that is transmitted from one generation to the next and can be transcribed into a polypeptide or protein." DAVID SUZUKI & PETER KNUDTSON, GENETHICS 343 (Harvard Univ. Press 1990).

[2] A protein is a molecule composed of interacting polypeptides (chains of three or more amino acids joined together) that are folded or twisted into characteristic shapes. Proteins serve essential functions in the human body (e.g., they regulate metabolism (enzymes); make up skin, bones, and ligaments (keratin and collagen); produce movements (muscle proteins); transport oxygen (haemoglobin); and regulate movement into and out of cells (membrane proteins)). HUTCHINSON DICTIONARY OF SCIENCE 15, 265 (Brockhampton Press Ltd. 1997).

[3] Anne E. Guttmacher & Francis S. Collins, eds., *Genomic Medicine—A Primer,* 347 NEW ENG. J. MED. 1512, 1514 (2002).

[4] The monumental Supreme Court case *Diamond v. Chakrabarty*, 447 U.S. 303 (1980) determined that genetic material was subject to patent protection.

[5] *Genomic Research and Diagnostic Accessibility Act of 2002 and Genomic Science and Technology Innovation Act of 2002: Remarks on H.R. 3967 and H.R. 3966 Before the House of Representatives*, 107th Cong. E353 (2002) (statement of Rep. Lynn Rivers).

[6] Human International Genome Sequencing Consortium, *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860-921 (2001); J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCI. 1304-51 (2001).

[7] Rivers Remarks, *supra* note 5.

[8] David Malakoff, *Will a Smaller Genome Complicate the Patent Chase?*, 291 SCI. 1194, 1194 (2001). It is important to note that with the current estimates of 30,000 to 35,000 genes in the human genome, this accounts for 57% to 66% of the genome. Essentially, these three companies (Incyte Genomics, Human Genome Sciences, and Hyseq) could have claims on up to 66% of the human genome if all of the applications are issued patent protection.

human body, concerns over the patenting of this genetic material are gaining momentum and are now the source of extensive international debate.[9]

Gene patents are controversial because of a variety of issues, including their relatively recent arrival into the patent realm, their grant of exclusivity over specific sequences of human genes, and their affect on research and diagnosis. Ultimately, these issues reflect both legal factors, dealing directly with the application of patent laws, and policy factors, implicating problems of access, cost, and quality in both the patient realm and the research setting. Because many gene patents either directly claim or include genes and/or the corresponding proteins that are essential to genetic diagnosis, a grant of exclusivity may hinder both healthcare and the advancement of scientific technology.[10]

Currently, there is an unparalleled legal challenge underway in the European Union (EU) regarding a number of human gene patents held by a U.S. corporation for sequences of two genes, BRCA1 and BRCA2, mutations in which indicate a predisposition to breast cancer. This type of legal challenge is commonly known as an "opposition" to a granted patent under European patent law and allows third parties to challenge the validity within nine months from the grant of the patent.[11] Because the BRCA gene is under exclusive patent protection, no European nation can undertake breast cancer testing but instead must send patient samples to the patent holder in the United States. Specifically, the most recent opposition challenges the patent as not fulfilling relevant provisions in the European patent law, as well as impeding healthcare and scientific discovery.[12] With scientific innovation and patient care no longer confined to single countries or continents in this age of technology and rapid-development, the European opposition's surrounding controversy inevitably will have a profound impact on U.S. policy and patent law largely because similar legal and policy concerns presently are being voiced in the United States by physicians,[13] scientists,[14] and legal scholars.[15] In theory, comparable claims potentially could be brought regarding any number of the thousands of U.S. human gene patents. This article addresses the European controversy over the BRCA1 gene patent and offers potential mechanisms to resolve similar legal and policy concerns in the United States.

## II. EUROPEAN OPPOSITION

### A. *BRCA Genes and Their Role in Breast Cancer Detection*

The European challenge involves a gene linked to breast cancer, a disease that has a cumulative lifetime risk of one in eight and is the most common cancer among women in

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[9] *See infra* Part II.B.

[10] For a discussion on the negative impact of gene patents on biotechnology and research, see Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation?: The Anticommons in Biomedical Research*, 280 SCI. 698-701 (1998).

[11] *See* European Patent Convention, Art. 99 (1998), *available at* http://www.european-patent-office.org/legal/epc/ (last visited Feb. 19, 2004) [hereinafter EPC].

[12] Press Release, Institut Curie, Assistance Publique-Hopitaux de Paris, Institut Gustave-Roussy, Against Myriad Genetics' Monopoly on Tests for Predisposition to Breast and Ovarian Cancer Associated With the BRCA1 Gene 4, 6 (Sept. 26, 2002) *available at* http://www.curie.fr/home/presse/actu_list.cfm/actu/presse/affaire/3/lang/_fr.htm (last visited Feb.19, 2004) [hereinafter Joint Press Release].

[13] *See infra* Part II.B.

[14] *See, e.g.*, Jon F. Merz, *Disease Gene Patents: Overcoming Unethical Constraints on Clinical Laboratory Medicine*, 45 CLIN. CHEM. 324-30 (1999).

[15] *See* Heller & Eisenberg, *supra* note 10.

the Western World.[16] Each year in the United States alone, 203,500 women are diagnosed with breast cancer and an estimated 39,600 women will die from its effects.[17] Hereditary breast cancer accounts for approximately five to ten percent of all breast cancers,[18] with mutations in BRCA1 and BRCA2 thought to be responsible for the overwhelming majority of inherited cases.[19] Women with a strong family history of breast cancer and who carry a germ-line mutation of BRCA1 have been found to have an approximate 85% lifetime risk of developing breast cancer,[20] as opposed to a general population risk of about 12%.[21] The statistics for BRCA2 are strikingly similar, with approximately 5% of hereditary breast cancer being tied to mutations in BRCA2 and comparable lifetime risks as are attributed to BRCA1.[22]

Both BRCA1 and BRCA2 are expressed largely in breast tissue, as well as ovary, thymus, and various other hormonal tissues.[23] Researchers described the complete sequences of these genes within a few years of each other, and both are fairly large genes encoding for separate proteins.[24] The BRCA1 gene is a large nucleoprotein that lies on chromosome 17.[25] Over 700 mutations of BRCA1 have been discovered to predispose to the development of both breast and ovarian cancer.[26] Of particular significance is the 185delAG mutation, which is prevalent in the Ashkenazi Jewish population, affecting about one percent of Ashkenazi Jews (as compared to just over .1 percent of the general population).[27] The 185delAG mutation is a frame shift mutation involving a deletion of adenine and guanine on position 185 of chromosome 17.[28] BRCA2 is a much larger gene lying on chromosome 13,[29] with over 800 reported mutations,[30] many often associated with early onset breast cancer.[31]

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[16] Francis S. Collins, *BRCA1—Lots of Mutations, Lots of Dilemmas*, 334 NEW ENG. J. MED. 186, 186 (1996). *See also* Jon Emory, *Is Informed Consent in Genetic Testing a Different Breed of Informed Decision-Making?*, 4 HEALTH EXPECTATIONS 81, 81 (2001); Alan Peterson, *Counselling the Genetically 'At Risk': The Poetics and Politics of 'Non-Directiveness'*, 1 HEALTH, RISK & SOCIETY 253, 254 (1999).

[17] Myriad Genetics, Inc., SEC Annual Report (Form 10-K) for fiscal year ending June 30, 2002, at 10 [hereinafter Myriad SEC Report].

[18] Lori d'Agincourt-Canning, *Experiences of Genetic Risk: Disclosure and the Gendering of Responsibility*, 15 BIOETHICS 231, 234 (2001). *See also* Ian C. Bennett et al., *The Genetic Basis of Breast Cancer and its Clinical Implications*, 69 AUST. N.Z. SURG. 95, 95 (1999); A.E. Murphy, *Dealing with the Uncertainty of Developing a Cancer*, 8 EUR. J. CANC. CARE 233, 233 (1999); Nina Hallowell, *Doing the Right Thing: Genetic Risk and Responsibility*, 21 SOC. HEALTH & ILLNESS 597, 600 (2000).

[19] Michael Balter, *Transatlantic War Over BRCA1 Patent*, 292 SCI. 1818 (2001). Approximately 90% of familial breast cancers are attributed to BRCA1 or BRCA2. Bennett et al., *supra* note 18, at 96.

[20] Bernadine Healy, *BRCA Genes-Bookmaking, Fortunetelling, and Medical Care*, 336 NEW ENG. J. MED. 1448, 1448 (1997); Collins, *supra* note 16, at 186; M. Cappelli et al., *Psychological and Social Predictors of Decisions About Genetic Testing for Breast Cancer in High-Risk Women*, 6 PSYCH. HEALTH & MED. 321, 322 (2001).

[21] Myriad SEC Report, *supra* note 17.

[22] Bennett et al., *supra* note 18, at 97.

[23] *Id.*

[24] *See* S. Tavatigan et al., *The Complete BRCA2 Gene and Mutations in Chromosome 13q Linked Kindreds*, 12 NATURE GENET. 333-37 (1996); R. Wooster et al., *Identification of the Breast Cancer Gene BRCA2*, 378 NATURE 789-91 (1995); Y. Miki et al., *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1*, 266 SCI. 66-71 (1994); R. Wooster et al., *Localization of a Breast Cancer Susceptibility Gene, BRCA2, to Chromosome 13q12-13*, 265 SCI. 2088-90 (1994).

[25] Bennett et al., *supra* note 18, at 96.

[26] *See* Breast Cancer Information Core, National Human Genome Research Institute, *available at* http://research.nhgri.nih.gov/bic/ (last visited Feb. 19, 2004) [hereinafter BIC].

[27] Collins, *supra* note 16, at 186. The high frequency of this mutation in Ashkenazi Jews establishes the 185delAg mutation as potentially the most common serious single-gene disease yet identified in a population. *Id.*

[28] K. Offit et al., *Germline BRCA1 185delAG Mutations in Jewish Women with Breast Cancer*, LANCET, June 15, 1996, at 1643.

[29] Bennett et al., *supra* note 18, at 97.

[30] *See* BIC, *supra* note 26.

[31] Bennett et al., *supra* note 18, at 97.

Presently, genetic diagnostic testing is available for detection of the BRCA1 and BRCA2 mutations, although the testing method is covered under a variety of exclusive gene patents held by Myriad Genetics, an American biopharmaceutical corporation.[32] The corporation currently holds approximately twenty patents worldwide on the use of the BRCA1 and BRCA2 genes and has developed automated tests to detect the presence of mutations in the two genes.[33] To date, Myriad holds eight U.S. patents relating to BRCA1 and/or BRCA2,[34] four European patents,[35] four Canadian patents,[36] two Australian patents,[37] and one New Zealand patent.[38]

## B. *Myriad's European Patents*

The European Patent Office (EPO) has granted four patents to Myriad Genetics covering the BRCA1 gene (EP0699754,[39] EP0705903,[40] and EP0705902[41]) and BRCA2 gene (EP0785216[42]). Essentially, these four patents grant an exclusive monopoly to Myriad over diagnostic breast and ovarian cancer testing in all European countries because they serve to cover all methods of diagnosis (EP0699754), specific mutations (EP0705903), and diagnostic kits (EP0705902).[43] While oppositions have also been filed regarding the first two patents, EP0705902 is the broadest patent and is causing widespread outcry due to its stalling effects on access, cost, and quality in healthcare and research. The broad application of EP0705902 most clearly illustrates the heart of both the legal and policy challenges, so this article will closely analyze that opposition.

The patent challengers claim that EP0705902 apparently protects the isolated gene as a chemical molecule, as well as the corresponding protein, and also includes the possible future therapeutic uses of the BRCA1 gene that are not yet developed (such as gene therapy and transgenic animals).[44] It grants Myriad exclusive rights over BRCA1 itself because it is the first patent to indicate a use of the gene.[45] They argue that the

[32] Myriad Genetics, Inc. began operations in 1991 and is located in Salt Lake City, Utah. It is a major force in the development of diagnostic and therapeutic products for a vast array of human genetic disorders. As one of its key goals, Myriad strives to discover and sequence genes related to major diseases. *See* Myriad's corporate information, *available at* http://www.myriad.com/corporate/index.htm and http://www.myriad.com/research/index.htm (last visited Feb. 19, 2004).

[33] Balter, *supra* note 19. Myriad introduced BRCAnalysis® for commercial use in October 1996 as its first predictive medicine product. Myriad SEC Report, *supra* note 17, at 16.

[34] These patents are U.S. Pat. No. 5,693,473, *Linked breast and ovarian cancer susceptibility gene;* U.S. Pat. No. 5,709,999, *Linked breast and ovarian cancer susceptibility gene*; U.S. Pat. No. 5,710,001, *17q-linked breast and ovarian cancer susceptibility gene*; U.S. Pat. No. 5,753,441, *170-linked breast and ovarian cancer susceptibility gene*; U.S. Pat. No. 6,030,832, *Carboxy-terminal BRCA1 interacting protein*; U.S. Pat. No. 6,162,897, *17q-linked breast and ovarian cancer susceptibility gene*; U.S. Pat. No. 6,033,857, *Chromosome 13-linked breast cancer susceptibility gene*; and U.S. Pat. No. 5,837,492, *Chromosome 13-linked breast cancer susceptibility gene.* The last of these eight patents was filed by Myriad on April 29, 1996 (issued Nov. 17, 1998), essentially extending patent protection over breast cancer screening until April 29, 2016.

[35] EP0699754, EP0705903, EP0705902, and EP0785216.

[36] Can. Pat. No. 2,196,790, Can. Pat. No. 2,196,795, Can. Pat. No. 2,196,797, and Can. Pat. No. 2,239,733.

[37] Aus. Pat. No. 686004 and Aus. Pat. No. 691958.

[38] N.Z. Pat. No. 326525.

[39] *Method for diagnosing a predisposition for breast and ovarian cancer* (issued Jan. 10, 2001).

[40] *In vivo mutations and polymorphisms in the 17q-linked breast and ovarian cancer susceptibility gene* (issued May 23, 2001).

[41] *17q-linked breast and ovarian cancer susceptibility gene* (issued Nov. 28, 2001).

[42] *Chromosome 13-linked breast cancer susceptibility gene BRCA2* (issued Jan. 8, 2003).

[43] Joint Press Release, *supra* note 12, at 4.

[44] *Id.* at 3.

[45] *Id.* at 4.

patent is being exploited by Myriad to block all research investigations of BRCA1 through stringent enforcement of its exclusive patent rights,[46] as well as preventing adequate patient care through restricted access to diagnostic tests,[47] high testing fees,[48] and limited quality of test results.[49]

A number of U.S. medical organizations agree with the grounds of the European opposition, in that gene patents pose a threat to access, cost, and quality in patient care, and have adopted policy statements to express this view.[50] The College of American Pathologists specifically offers that patents on gene sequences "inhibit access to the basic knowledge of the genes" and "limit the development, improvement and eventual use of tests from that knowledge."[51] Likewise, the American College of Medical Genetics states "genes and their mutations are naturally occurring substances that should not be patented" and "patents on genes with clinical implications must be very broadly licensed."[52]

In addition, the American Medical Association suggests an imposition of special standards for physicians in calling for "equitable access to licenses … of gene patents for diagnostic genetic tests … at a reasonable royalty … and development of special guidelines for … promoting research and other benefits."[53] Related recommendations are being made by members of Congress for an action similar to the recent statutory provision exempting licensed medical physicians from patent infringement for use of medical procedures under patent protection,[54] or, alternatively, a method of mandatory government-imposed compulsory licensing for all uses of gene patents.[55]

With respect to the other international BRCA patents held by Myriad Genetics, many countries similarly are fighting back. Numerous hospitals and research institutions in Canada have refused to recognize Myriad's Canadian patents over BRCA breast cancer testing.[56] On January 6, 2003, Ontario Health Minister Tony Clement announced his intent to ignore any patent infringement threats from Myriad Genetics.[57] Clement reports that with the assistance of a $1.2 million grant, seven cancer centers[58] across the province will perform the BRCA testing services for one third of the cost charged by Myriad laboratories, and will produce results that are 95% accurate.[59] (This is an improvement over the Myriad method, which fails to detect 10% to 20% of expected

[46] *See infra* Part IV.C.

[47] *See infra* Part IV.B.

[48] *Id.*

[49] *See infra* section IV.A.

[50] College of American Pathologists, Gene Patents Detrimental to Care, Training, Research, *available at* http://www.cap.org/apps/docs/advocacy/advocacy_issues/Issue_Genepat.html (last visited Feb. 19, 2004) [hereinafter CAP statement]; American College of Medical Genetics, Position Statement on Gene Patents and Accessibility of Gene Testing (Aug. 2, 1999), *available at* http://www.acmg.net/resources/policies/pol-015.asp (last visited Feb. 19, 2004) [hereinafter ACMG statement]; American Medical Association, Report 9 of the Council on Scientific Affairs (I-00); Patenting of Genes and Their Mutations (2000), *available at* http://www.ama-assn.org/ama/pub/article/2036-3603.html (last visited Feb. 19, 2004) [hereinafter AMA statement].

[51] CAP statement, *supra* note 50.

[52] ACMG statement, *supra* note 50.

[53] AMA statement, *supra* note 50.

[54] *See* discussion *infra* Part V.A.

[55] *See* discussion *infra* Part V.C.

[56] Deborah Smith, *Cancer Capitalists*, SYDNEY MORNING HERALD, Nov. 9, 2002, at 37.

[57] *Myriad Genetics: Biotech Firm in Dispute With Canada Over Genetic Test*, BIOTECH WEEK, Jan. 29, 2003, at 77. The government already has received notice from Myriad that such testing is considered a violation of the patent. Zulekha Nathoo, *London to Offer Cancer Test*, LONDON FREE PRESS, Jan. 7, 2003, at B4.

[58] These are McMaster Medical Centre, Credit Valley Hospital, Mount Sinai Hospital, North York General Hospital, Children's Hospital of Eastern Ontario, Kingston General Hospital, and London Health Sciences Centre. Nathoo, *supra* note 57.

[59] *Id.*

mutations.)[60] The Centre for Law and Genetics at the University of Tasmania in Australia continues to offer testing services despite Myriad's enforcement of its patents and responds with the stance, "take us to court."[61]

Following notification by Myriad of its patent rights and its intention of stringent enforcement of its patents at research centers in Canada offering screening to patients, British Columbia has ceased BRCA testing while their governmental lawyers examine the validity of the patent claims.[62] The B.C. Health Minister, Colin Hansen, refuses to pay the high cost of the test,[63] commenting, "(t)here is maybe merit in patenting the applications of how we use gene sequencing, but to actually patent the sequence is something I certainly have great difficulty with."[64] Ontario has chosen to ignore Myriad's patent rights and continues to screen for BRCA mutations, while Alberta continues to finance Myriad cancer screening through funds provided by the Alberta Cancer Genetics Program.[65] Other Canadian provinces such as Quebec currently are not offering the test because of Myriad's strenuous patent enforcement tactics.[66] Regarding the Australian patents, Myriad entered into an agreement with Genetic Technologies, an Australian biotechnology company, giving them exclusive rights in Australia and New Zealand to conduct testing services for BRCA1 and BRCA2 mutations in November 2002.[67]

## C. *Opposition History*

In response to Myriad's monopoly in Europe, numerous genetics societies and research institutes across Europe have banded together and filed notices of opposition to the BRCA1 patents with the EPO.[68] The opposition to patent EP0705902 was filed August 28, 2002 by organizations from eleven European countries[69] on the grounds that there is an absence of novelty and lack of priority, lack of inventive step, insufficient description, and lack of industrial application.[70] The opposition also calls attention to the negative policy implications in granting a monopoly over tests that are an important diagnostic indicator in detecting hereditary breast cancer, in addition to the chilling effects such a monopoly has on scientific research.[71] The previous two oppositions were filed with the EPO in October 2001 and February 2002, respectively, on similar grounds.[72] No opposition to the fourth European patent has yet been filed, but the patent will most likely meet with similar challenges.

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[60] D. Stoppa-Lyonnet et al., *Identification of a Large Rearrangement of the BRCA1 Gene Using Colour Bar Code on Combed DNA in an American Breast/Ovarian Cancer Family Previously Studied by Direct Sequencing*, 38 J. MED. GEN. 388-91 (2001). *See infra* Part IV.A.

[61] Smith, *supra* note 56.

[62] Heather Kent, *Patenting Move Ends BC's Gene-Testing Program*, 165 CMAJ 812, 812 (2001).

[63] B.C. is able to conduct the BRCA testing for CAN$1,200, but Myriad is charging CAN$3,500. *Id.*

[64] David Charbonneau, *Fight Against Gene-Testing Patent Is the Right Move for B.C. Women*, KAMLOOPS DAILY NEWS, Nov. 12, 2002, *available at* http://www.cariboo.bc.ca/carryon/dcharbon/kdn02/genepatent.htm (last visited Feb. 19, 2004).

[65] Laura Eggertson, *Ontario Defies US Firm's Genetic Patent, Continues Cancer Screening*, 166 CMAJ 494, 494 (2002).

[66] It appears that Quebec has agreed to Myriad's request as it is sending samples to Utah for testing. *Id*.

[67] Smith, *supra* note 56.

[68] Press Release, Institut Curie, European-Wide Opposition against the Breast Cancer Patents (Sept. 26, 2002), *available at* http://www.curie.fr/home/presse/actu_list.cfm/actu/presse/affaire/3/lang/_fr.htm (last visited Feb. 19, 2004) [hereinafter European-Wide Opposition].

[69] These countries are Austria, Belgium, Czech Republic, Denmark, Finland, Germany, Greece, Italy, the Netherlands, Switzerland, and the United Kingdom.

[70] Joint Press Release, *supra* note 12.

[71] *Id.*

[72] European-Wide Opposition, *supra* note 68.

The opposition to the first Myriad patent, EP0699754, was instigated on September 6, 2001 by the French Institut Curie and was supported publicly by both Roger-Gerard Schwartzenberg, the French Minister for Research, and Bernard Kouchner, the French Minister for Health.[73] Subsequently, on October 4, 2001, the European Parliament announced its support for the Institut Curie in a drafted resolution.[74] Five days later, the Assistance Publique-Hopitaux de Paris (the public Paris hospitals authority) and the Institut Gustave-Roussy joined the Institut Curie in its opposition and filed a formal statement of opposition with the EPO.[75] The Belgian Human Genetics Society, along with the Belgian and Dutch human genetics centers, and the German, Dutch, and British genetics societies also filed a separate formal statement of opposition with the EPO.[76]

On February 22, 2002, the Institut Curie, the Assistance Publique-Hopitaux de Paris, and the Institut Gustave-Roussy joined forces again in filing another joint opposition, this time to Myriad's second patent, EP0705903.[77] In addition, the Belgian Ministries of Health, Social Affairs, and Scientific Research, the Dutch Ministry of Health, the Belgian and Dutch human genetics centers, and the German league against cancer and Greenpeace Germany filed an independent statement of opposition shortly thereafter.[78]

The third, and most recently opposed, patent, EP0705902, has been cited as the broadest of the patents relating to both the gene and the protein and to diagnostic testing kits, as well as to therapeutic uses that do not yet exist.[79] Because of the expansive protection afforded by patent EP0705902, research centers and hospitals throughout the EU actively pursued filing legal challenges with the EPO. Statements of opposition were formally filed on August 28, 2002 jointly by the Institut Curie, the Assistance Publique-Hopitaux de Paris, and the Institut Gustave-Roussy, as well as by the Belgian Society of Human Genetics, together with Belgian and Dutch human genetic centers; German, Dutch, Czech, Austrian, Swiss, British, and Finnish genetics societies; the Greek National Center for Scientific Research; the Swiss Institute for Applied Cancer Research; and patient associations in the Netherlands (Borstkanker Vereniging Nederland) and Belgium (Vlaamse Liga tegen Kanker).[80] The Swiss Social Democrat Party, Greenpeace Germany, the Dutch and Austrian Health Ministers, and an individual German doctor also filed a notice of opposition to the third patent.[81]

## D. *Grounds for Opposition*

Two international agreements form the basis of the legal challenge to Myriad's patent in the European Union. European patent law is codified in the European Patent Convention (EPC), an international agreement among twenty-seven nations, including all of the EU Member States.[82] The EPC was devised as a centralized method to enable a patent

[73] Press Release, Institut Curie, The Key Dates (Sept. 26, 2002), *available at* http://www.curie.fr/home/presse/actu_list.cfm/actu/presse/affaire/3/lang/_fr.html (last visited Feb. 19, 2004) [hereinafter Key Dates].

[74] *Id.*

[75] *Id.*

[76] *Id.*

[77] *Id.*

[78] *Id.*

[79] *Id.*

[80] *Id. See also* European-Wide Opposition, *supra* note 68; Joint Press Release, *supra* note 12, at 3.

[81] Key Dates, *supra* note 73.

[82] The European Patent Convention was convened October 5, 1973, and was later amended by an act revising Article 63 in December 1991 and by a number of decisions of the Administration Council of the European Patent Organization in 1978 and throughout the 1990s. Presently, there are twenty-seven nations to the EPC, including Austria, Belgium, Switzerland, Cyprus, Germany, Denmark, Spain, Finland, France, the United Kingdom, Republic of Bulgaria, Czech Republic, Republic of Estonia, Hungary, Hellenic Republic, Ireland, Italy, Liechtenstein, Luxembourg, Monaco, Netherlands, Portugal, Sweden, Turkey, Republic of Romania, Slovenia, and Slovak Republic. *See* EPC, *supra* note 11.

applicant seeking patent rights in more than one nation to file a single application, which, if granted, becomes a national patent in each signatory nation named in the application.[83] Each nation retains the right, however, to interpret and modify a patent according their national patent system, leading to varying degrees of protection to the patentee.[84] As a means to create uniformity in intellectual property rights as applied to biotechnological inventions throughout the European Union, Directive 98/44/EC of the European Parliament and Council of the European Union was drafted in 1996. It requires the EU Member States to amend their national laws in compliance.[85] Both the EPC and the Directive contain provisions indicating that morality is an inherent aspect of patentability and can be cited as a basis to refuse patent protection.[86]

Similar to U.S. patent law, the EPC requires that the inventor prove that the invention is novel, involves an inventive step, and is susceptible of industrial application.[87] After a showing of the preceding three factors, as well as the disclosure of a sufficiently clear description of the invention[88] and establishment of all other statutory requirements, the applicant is awarded a twenty-year patent term as measured from the date of the filing of the application.[89] The goal of granting these exclusive rights is both to protect the time and money that the company or individual put into the development of the invention and to motivate innovation and promote disclosure.[90] The EPC, however, offers both that "discoveries, scientific theories and mathematical methods" are not regarded as patentable subject material[91] and, subsequently, that "methods for treatment of the human … body by … diagnostic methods practiced on the human … body shall not be regarded as inventions."[92] Furthermore, Article 53 tenders an overriding policy determination expressed in the provision that establishes "inventions contrary to 'ordre public' or morality" will not be granted patent protection.[93]

The Directive specifically addresses the legal protection of biotechnological inventions by reiterating the basic requirements for patent protection as introduced in the EPC, but clarifies how these requirements shall be applied to biological materials.[94] The Directive similarly reflects the EPC's concern for not allowing the patenting of inventions that are "ordre public" or contrary to public morality,[95] and also specifically provides that the simple discovery of one of the elements of the human body, "including the sequence or partial sequence of a gene," cannot constitute a patentable invention."[96] A sequence or partial sequence of a gene that is isolated from the human body

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[83] Donna M. Gitter, *Led Astray by the Moral Compass: Incorporating Morality into European Union Biotechnology Patent Law*, 19 BERKELEY J. INT'L L. 1, 19 (2001).

[84] *Id*. at 20.

[85] Directive 98/44/EC of the European Parliament and of the Council of the European Union on the Legal Protection of Biotechnological Inventions, July 6, 1998, Art. 15(1). *See also* Gitter, *supra* note 83, at 20.

[86] Gitter, *supra* note 83, at 21.

[87] *See* EPC Art. 52(1). U.S. patent law describes this industrial application as "utility" and provides for inventive step in its requirement of "non-obviousness." *See* 35 U.S.C. §§ 101 and 103 (2002).

[88] EPC Art. 83.

[89] *Id*. Art. 63(1).

[90] *See* Center for Bioethics, Univ. of Pennsylvania, Patent Primer, *available at* http://www.bioethics.upenn.edu/prog/benefit/c.shtml (last visited Feb. 19, 2004).

[91] EPC Art. 52(2).

[92] *Id*. Art. 52(4). The emphasis of this provision turns on the fact that such diagnostic methods for use on the human body are not susceptible of industrial application.

[93] *Id*. Art. 53(a).

[94] Directive 98/44/EC, Art. 3(1), (2).

[95] *Id*. Art. 6(1).

[96] *Id*. Art. 5(1).

or produced by means of a technical process may constitute a patentable invention, however, if the sequence is disclosed, even if the structure of the element is identical to a natural element.[97]

Significantly, the morality provisions expressed in both the EPC and the Directive are extremely porous in implementation and, to date, have not been utilized to reject patent protection for genetic sequences. Throughout the 1990s, challenges to gene patents were brought in front of the EPO on morality grounds.[98] The EPO Opposition Division in *Hormone Relaxin*[99] decided that there was no moral distinction between the patenting of genes and other human substances for medical applications.[100] Furthermore, they held that an invention may be rejected on morality grounds only in very limited cases where there is an overwhelming consensus that the exploitation of an invention would be immoral under EPC Article 53(a).[101] This determination is often viewed as precluding any claims of inherent immorality of a patent involving genetic sequences—and may be why opponents did not include such arguments in their legal challenge.

Rather than focusing on morality, the defining aspect of the patentability of a gene sequence or partial gene sequence turns on whether it was isolated from its natural environment by means of a technical industrial process evincing novelty and inventive step.[102] This industrial application essentially requires that the inventor specify which protein or part of a protein was produced or what function it performs because a "mere DNA sequence without an indication of a function does not contain any technical information and is therefore not a patentable invention."[103]

The patent EP0705902 issued to Myriad is by traditional form a process patent, where the claims include "methods and materials used to isolate and detect a human breast … cancer predisposing gene (BRCA1)."[104] Process patents are granted where the applicant discloses the processes used to identify, purify, or classify the subject matter outside of the human body.[105] Under provisions contained within the Directive, however, the EPO grants patents for genetic material a protection similar to that of a product patent, meaning that the protection extends not only to the process by which the gene is isolated, but also to the gene itself and all its possible uses.[106] The challengers offer that the patent claims also appear to cover all diagnostic uses of the gene and any proteins as a chemical product, even those not described and disclosed within the

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[97] *Id*. Art. 5(2).

[98] Gitter, *supra* note 83, at 21. As a result, two distinct tests of morality evolved at the opposition level—the "public abhorrence test," which denies a patent grant to an invention where the public consensus determines that such a patent would be abhorrent, and the "unacceptability test," where a patent is denied when the disadvantages to society would outweigh the advantages. *Id*.

[99] 1995 O.J. E.P.O. 388 (Opp. Div.)

[100] *Id*.

[101] Gitter, *supra* note 83, at 26.

[102] This idea is further illustrated in Directive 98/44/EC, Arts. 3(1) and 3(2), which respectively read "inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used" and "(b)iological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature." *See* Directive 98/44/EC, at conclusions 22-24.

[103] *Id*. at conclusion 23.

[104] *See* EP 7050902, Description.

[105] United Nations Educational, Scientific and Cultural Organization: International Symposium, Ethics, Intellectual Property and Genomics 16 (Jan. 30-Feb. 1, 2001), *available at* http://unesdoc.unesco.org/images/0013/001306/130646e.pdf (last visited Feb. 19, 2004).

[106] *Id*. *See also* Directive 98/44/EC, at Preamble § 21 (offering that an element isolated from the human body by means of technical process described in the application is patentable).

patent.[107] This is problematic because healthcare providers are not allowed even to examine the DNA of their patients in order to detect hereditary breast cancer; instead they must send tissue samples to another country for testing. Also, scientists interested in studying the genetic material in order to develop drugs or therapies for use in breast cancer are completely prohibited from using the patented sequence.

### 1. *Absence of Novelty and Lack of Priority*

As an initial argument, the opposition to Myriad's EP0705902 is based on an absence of novelty. EPC Article 54 expressly describes what the EPO considers a "new" invention subject to patent protection.[108] In particular, an invention is considered novel if it does not form part of the state of the art, which is defined as "everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application."[109] Myriad had filed a previous patent application in the United States in September 1994, which actually had contained the incorrect gene sequence for BRCA1.[110] The sequence was later amended by Myriad in March 1995 to reflect the corrected sequence.[111] In its European application in continuation of its acquired U.S. patents, Myriad utilized September 1994 as the relevant date for novelty of the subject material despite the fact that they had disclosed an incorrect sequence at that time. The challengers contend that in Europe novelty attaches from the date of the application containing the correct sequence.[112] Accordingly, the subject matter is not patentable because by March 1995, the BRCA1 sequence already had been isolated by other researchers and posted in the public domain on scientific databases and in numerous articles.[113]

Closely related to novelty of an invention are priority rights that arise when the patent applicant files a subsequent application for the same subject matter as contained in a previous first application, where the first application has been withdrawn, abandoned, or refused without having been open to public inspection.[114] The right of priority attaches for a period of twelve months from the date of the filing of the first application[115] and has the effect that the date of priority (the prior filing related to the same subject matter) counts as the date of filing of the subsequent patent application for purposes of novelty requirements presented in EPC Article 54.[116] For purposes of the European patent, the EPO attached the priority date as the date of the first application filing in the United States, despite the fact that the previous filing contained the erroneous sequence and thus did not comprise the same subject matter as the subsequent application.[117]

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[107] Dominique Stoppa-Lyonnet, *How Genes May Limit Genetic Tests*, Institute Curie PowerPoint presentation (acquired through email correspondence Mar. 24, 2003) [hereinafter *How Genes*].

[108] EPC Art. 52(1) reads "European patents shall be granted for any inventions which are susceptible of industrial application, which are new and which involve an inventive step."

[109] *Id*. Art. 54(1), (2).

[110] Joint Press Release, *supra* note 12, at 3.

[111] 35 U.S.C. § 255 allows a patent applicant to correct an application if the correction "does not involve such changes in the patent as would constitute new matter or would require re-examination" and it "shall have the same effect and operation in law … as if the same had been originally issued in such corrected form."

[112] Joint Press Release, *supra* note 12, at 3.

[113] *Id*.

[114] EPC Art. 87(4).

[115] *Id*. Art. 87(1).

[116] *Id*. Art. 89.

[117] Joint Press Release, *supra* note 12, at 3.

### 2. *Lack of Inventive Step*

The opposition contends that if the previous argument fails, the patent is still invalid on lack of inventiveness grounds because it was possible at the time of filing of the EPO patent application to isolate the gene with elements that already were known.[118] The EPC elects that the subject matter of an application involves an inventive step if, "having regard to the state of the art, it is not obvious to a person skilled in the art."[119] This sets up a subjective reasonable scientist standard when dealing with genetic material, where the level of inventiveness is measured against persons with similar interests and skills. Because the BRCA gene could have been, and essentially was being, sequenced by other institutions and individual researchers, challengers purport that the sequencing lacked inventive step and, accordingly, is not patentable subject material.[120]

Prior to Myriad's filing for patent protection, the groundwork for the sequence of BRCA1 already was largely in the public domain because of numerous scientific papers and public databases.[121] Myriad essentially utilized material in the public domain as the foundation for its research, thereby merely building on publicly-available knowledge. Specifically, the Breast Cancer Linkage Consortium (Consortium) was founded in 1989 by a number of European and American research laboratories whose members localized the BRCA1 gene in late 1990.[122] The Consortium was composed of fourteen independent research teams openly exchanging data and ideas on the BRCA1 gene sequence in a joint effort to discover the genetic basis of breast cancer.[123] Any researcher in the world was eligible to join if they were "willing to pool results from their studies."[124] In September 1992, the Consortium narrowed the region down considerably and one researcher reported that the BRCA1 gene was "very close" and that "(i)t will probably be luck, whoever finds it."[125]

Following the localization of the BRCA1 gene by a team from the Consortium in 1990,[126] a member of the Consortium, Mark Skolnick from the University of Utah, founded Myriad Genetics in 1991 as a means to exploit the research commercially once the complete gene was discovered.[127] He continued to be involved with the Consortium, despite criticisms that he sought to personally commercialize on the discovery of the gene.[128] Skolnick ultimately applied for and was granted a patent for the complete BRCA1 gene sequence that he reported in late 1994.[129] Immediately after the filing of this initial application with the USPTO, conflict erupted over the actions of Myriad in attempting to gain exclusive rights over genetic information acquired through open research collaboration.[130] The Consortium's underlying motive had been to prevent a

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[118] *Id*.

[119] EPC Art. 56.

[120] Joint Press Release, *supra* note 12, at 3.

[121] *See* Declan Butler & Sally Goodman, *French Researchers Take a Stand Against Cancer Gene Patent*, 413 NATURE 95, 95 (2001).

[122] Key Dates, *supra* note 73.

[123] Robert Cooke, *A United Effort Is Likely to Pinpoint Key Genetic Site Soon*, NEWSDAY, Sept. 29, 1992, at 59.

[124] *Id*.

[125] *Id*.

[126] *See Localization of a Breast Cancer Susceptibility Gene, BRCA2, to Chromosome 13q12-13*, 265 SCI. 2088 (1994).

[127] Steve Connor, *Concern Over Cancer Gene Patent*, THE INDEPENDENT, Sept. 15, 1994, at 3.

[128] Phyllida Brown & Kurt Kleiner, *Patent Row Splits Breast Cancer Researchers*, NEW SCIENTIST, Sept. 24, 1994, at 44.

[129] Connor, *supra* note 127.

[130] Brown & Kleiner, *supra* note 128.

for-profit company from holding exclusive patent control over a disease gene as a means to commercializing DNA.[131] Skolnick justified having patented the gene by stating "(i)f it's not patented, you won't get some group to spend money to develop it, and you won't get a high quality, inexpensive test."[132] Because the information was largely in the public domain, however, Myriad spent minimal funds discovering it and it is the present high cost of Myriad's test, as well as its inaccurate results, that the European challengers highlight as the key public policy concerns in their opposition.

### 3. *Insufficient Description*

Requirements for a European patent application include a description of the invention together with one or more claims,[133] any drawings referenced in either the description or the claims, and an abstract.[134] In addition, the applicant must disclose the invention in a manner "sufficiently clear and complete for it to be carried out by a person skilled in the art."[135] Challengers of the Myriad patent focus on the disclosures presented for the therapeutic uses included in the patent, which they maintain are not drafted in terms clear and complete enough to allow persons skilled in the art to carry them out.[136] Specifically, the challengers claim that the sequence claimed was a polypeptide and not the nucleotide itself, which is useless in terms of therapeutic uses in gene therapy for the molecular pathologist in terms of accessing the nucleotide.[137] At the present time, gene therapy has not been proven effective as a method of patient care, and has not even been developed by Myriad for use in the treatment of breast cancer.

### 4. *Lack of Industrial Application*

Because Myriad's claims disclose a clear function of the BRCA1 sequence as a method to detect the presence or absence of breast cancer mutations, it is deemed by the EPO as having an industrial application, or utility. Article 52(4) of the EPC, however, expressly states "methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body shall not be regarded as inventions which are susceptible of industrial application."[138] This explicit exemption to the patent law precludes protection for diagnostic methods, even if the method is disclosed in the application and is acquired through a technical process. Based on this language, the challengers assert that the BRCA1 sequence should never have been granted a patent based on lack of industrial application because it clearly discloses a diagnostic method for use on the human body.[139] Furthermore, the challengers contend that all of the mutations in the BCRA1 gene were claimed to be useful for genetic predisposition, but Myriad offered no function of the mutations at the time of the filing of the application.[140]

If the European challenge is successful, it may be the catalyst for change in European patent law and, ultimately, will have a powerful effect on U.S. patent law and policy. An

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[131] *Id*.

[132] *Id*.

[133] The claims must define the subject matter for which the patent is sought and shall be clear and concise and supported by the description. EPC Art. 84.

[134] *Id*. Art. 78(1)(a)-(e).

[135] *Id*. Art. 83.

[136] Joint Press Release, *supra* note 12, at 3.

[137] *How Genes*, *supra* note 107.

[138] EPC Art. 52(4).

[139] *How Genes*, *supra* note 107.

[140] *Id*.

opposition determining that Myriad holds an invalid patent on the basis of one or more of the factors above will strip the corporation of its exclusive European patent rights for the claimed material, effectively putting the information in the public domain to be used freely by researchers and physicians. As precedent, such a result may cause a re-examination of all existing European gene patents and may serve as a bar to the grant of any gene patents in the future that do not withstand the requirements laid out by the Opposition Division in their decision. In response to this result, the United States will need to reconsider its policy stance on the issuance of gene patents in similar situations.

## III. U.S. PATENT LAW

The U.S. patent system provides for a sort of trade-off between the USPTO and the applicant, as is likewise evident in the EPC. Whoever "invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvements" may obtain a patent subject to the conditions of the application requirements.[141] In return for publicly disclosing an invention through the specification,[142] the applicant is rewarded with exclusive rights to the invention from the issuance date until twenty years from the date that the application was filed with the USPTO.[143]

In the United States, novelty is fundamentally the same requirement as in the EPC, both in name and in application. It generally is described as what it does not include: an invention is not novel if it is "known or used by others in this country, or patented or described in a printed publication" prior the invention by the patent applicant,[144] if it is "in public use or on sale in this country" for over a year prior to the date of the application,[145] if it has been abandoned by the inventor,[146] if it was patented for more than a year prior to the U.S. application in a foreign country,[147] if it was described in another patent,[148] if the subject matter of the application was not invented by the applicant (as in the case of theft),[149] or if it was made by another (this addresses the situation where an applicant lacks priority over the subject matter of the claimed invention).[150] The EPC, on the other hand, has absolute novelty, in which an invention goes into the public domain the instant it is described in a publication or is used commercially in Europe.[151]

Nonobviousness is the parallel to the EPC requirement of inventive step and requires a comparison of the prior art with the claimed subject matter of the application.[152] If the patent examiner determines that the differences between the subject matter in the application and the prior art renders the subject matter as a whole obvious at the time the invention was made to a person having ordinary skill in the art, it will be deemed obvious and unable to acquire patent protection.[153]

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[141] 35 U.S.C. § 101.

[142] *Id*. § 112.

[143] *Id*. § 154(a)(2). The patent holder holds the right to exclude others from "making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States …." *Id*. § 154(a)(1). Note that if a patent was applied for prior to June 8, 1996, the term of the exclusive rights extends seventeen years from the application filing date.

[144] *Id*. § 102(a).

[145] *Id*. § 102(b).

[146] *Id*. § 102(c).

[147] *Id*. § 102(d).

[148] *Id*. § 102(e)(2).

[149] *Id*. § 102(f).

[150] *Id*. § 102(g)(2).

[151] Daniel N. Christus et al., *Intellectual Property in The Americas*, 13 AM. U. INT'L L. REV. 1095 (1998).

[152] 35 U.S.C. § 103(a).

[153] *Id*.

In addition to showing novelty, nonobviousness, and utility, the applicant must also include a specification, which contains a written description of the claims of the invention.[154] This description must include the manner and process of making and using it in such concise, exact terms as to "enable any person skilled in the art" to make and use the invention.[155] Pursuant to this section, the applicant also must set forth the best mode of carrying out the invention.[156] The specification requirement serves the function of offering to the public the general knowledge and information included in the patent in return for the exclusive patent rights to the invention.[157]

The key difference between the U.S. and European patent law is in relation to the utility of the claimed invention. The utility requirement is equivalent to the industrial application provision of the EPC and provides that an invention must be "useful" to obtain patent protection.[158] There is fundamental difference in the application of this utility in the United States, however, as opposed to in Europe. As a policy matter, the USPTO has explicitly provided in a set of revised guidelines that all purified gene sequences necessarily evince utility.[159] In contrast, as discussed earlier, the EU arguably has an express provision contained within the EPC that is relevant to gene patents, stating that methods used for diagnosis on the human body are not patentable because they *per se* have no industrial application.[160]

The USPTO, foreseeing a rush to patent genes given the tremendous burst of technological innovation in isolating, identifying, and sequencing proteins and genes over the closing years of the twentieth century, introduced revised utility guidelines for patent applications at the end of 1999.[161] A number of corrections and improvements to these revised utility guidelines were initiated throughout 2000[162] and, in January 2001, the final revised guidelines were published in the *Federal Register*.[163] Within these revised guidelines, the USPTO expressly provides that the sequence of a DNA molecule is simply a property of that molecule and may not be patented.[164] The purified DNA molecule, when isolated from its natural environment, is a chemical compound, however, and patentable if all of the statutory requirements are met.[165] The USPTO explicitly offers that a "purified DNA molecule may meet the statutory utility requirement if (e.g., it can be used to produce a useful protein or if it hybridizes[166] near and serves as a marker for a disease gene)."[167] Ultimately, the utility must be real, substantial, and

[154] *Id.* § 112. The specification is concluded with a drafted set of either dependent or independent claims, which point out and distinctly claim the subject matter.

[155] 35 U.S.C. § 112.

[156] *Id.* This best mode requirement pertains to the best mode as contemplated by the inventor.

[157] *See* Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1022 (1989).

[158] 35 U.S.C. § 101.

[159] Utility Examination Guidelines, 66 Fed. Reg. 1092 (2001), *available at* http://www.USPTO.gov/web/offices/com/sol/notices/utilexmguide.pdf (last visited Feb. 19, 2004) [hereinafter Utility Examination Guidelines].

[160] EPC Art. 52(4).

[161] 64 Fed. Reg. 71,440 (1999).

[162] 65 Fed. Reg. 3425 (2000).

[163] Utility Examination Guidelines, *supra* note 159.

[164] *Id.* at 1094.

[165] *Id.*

[166] Nucleic acid hybridization is a process in which single-stranded nucleic acids fragments are joined together to form double-stranded molecules based on their complementary sequences following the pairing rules of nitrogenous bases pairing. This often is used to probe for known genes or sequences in nucleic acid samples. Allen C. Nunnally, *Commercialized Genetic Testing: The Role of Corporate Biotechnology in the New Genetic Age*, 8 B.U. SCI. & TECH. 306 n.88, *citing* WILLIAM PURVES ET AL., LIFE: THE SCIENCE OF BIOLOGY 258-59 (Sinauer Assocs., Inc. 1995).

[167] Utility Examination Guidelines, *supra* note 159, at 1094.

credible, meaning that the applicant must provide a specific function of the gene sequence.[168]

## IV. POLICY ISSUES—IMPACT ON ACCESS, COST, QUALITY, AND RESEARCH

### A. *Quality of Patient Health Care*

Increasingly, the appropriate treatment of an individual patient may include diagnostic genetic testing for BRCA mutations.[169] As a predictive genetic test, the BRCA test offers only the general estimated chances of developing breast cancer[170] and must take into account the influence of other genes and environmental factors.[171] In fact, the predictive power of the BRCA test is very low for women without a family history of breast cancer, meaning that many women who test positive for a BRCA1 mutation do not ever manifest symptoms of the disease.[172] A system of genetic counseling is an integral aspect of this process because it aids the individual patient in understanding the results of a predictive BRCA test.[173]

In addition to the generally low predictive value of predictive BRCA testing for the general population, the test offered by Myriad reportedly fails to detect ten to twenty percent of all expected mutations.[174] Scientists with the Institut Curie have discovered a deletion in the BRCA1 gene accounting for the predisposition to breast cancer of one U.S. family that the Myriad test fails to detect altogether.[175] The failure to detect such a large percentage of mutations in effect seriously jeopardizes the test quality and also significantly falls short of appropriate patient care when alternative, more effective tests, could be readily available to the patient. Because EP0705902 covers all diagnostics based on the BRCA1 genetic sequence, however, Myriad can prevent the marketing and use of tests derived by other research institutions that are more effective.[176]

The parties to the opposition also argue that allowing Myriad to exclusively supply genetic testing for hereditary breast cancer in effect dissociates actual testing from genetic counseling, high-risk patient care, and follow-up, all of which are essential to the European approach to medical care.[177] In European countries, healthcare workers follow a model that integrates biological research, clinical investigation, and patient care, especially considering the psychological aspects of diagnosis, both for the individual pa-

[168] *Id*. at 1098.

[169] According to the ELSI (Ethical, Legal, and Social Implications) Task Force, created and funded by the National Institutes of Health, the four main forces driving the expansion and availability of predictive genetic testing are: 1) the reward structures of science, which encourages immediate reporting of findings; 2) public demand for progress in the fight of disease; 3) biotechnology companies' objective of developing markets large enough to make testing profitable; and 4) media coverage of genetic discoveries. ELSI TASK FORCE ON GENETIC TESTING, INTERIM PRINCIPLES 2, at 2 (1996), *available at* http://www.genome.gov/10001754 (last accessed Mar. 9, 2004). A genetic test is the "analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes." N. HOLTZMAN & M. WATSON, EDS., PROMOTING SAFE AND EFFECTIVE GENETIC TESTING IN THE UNITED STATES: FINAL REPORT OF THE TASK FORCE ON GENETIC TESTING (Johns Hopkins Univ. Press 1999).

[170] Michael J. Malinowski & Robin J.R. Blatt, *Commercialization of Genetic Testing Services: The FDA, Market Forces, and Biological Tarot Cards*, 71 TUL. L. REV. 1211 n.12 (1997).

[171] *Id*.

[172] Wylie Burke, *Genetic Testing*, 347 NEW ENG. J. MED. 1867, 1872 (2002).

[173] Peterson, *supra* note 16.

[174] Stoppa-Lyonnet et al., *supra* note 60.

[175] *Id*.

[176] *See* Butler & Goodman, *supra* note 121, at 96.

[177] Joint Press Release, *supra* note 12, at 6.

tient and the patient's family.[178] In contrast, Myriad is accused of separating genetic testing from patient care in providing only the diagnostic BRCA test results without any significant follow-up individualized genetic counseling.[179] It is alleged that such dissociation seriously impedes the quality of patient care.[180]

For example, Myriad recently launched a direct-to-consumer advertising campaign for the BRCA diagnostic tests.[181] This type of advertising essentially bypasses physicians and directly targets the general population. Previously, the tests were marketed by Myriad exclusively to physicians, but Myriad plans to begin marketing tests in order to make them mainstream.[182] While Myriad has given assurances that they will train doctors to guide patients through the process, many insist that counseling should be undertaken only by genetic specialists without commercial interests tied to the corporation.[183] In fact, a genetics specialist who had been employed by Myriad as a consultant but resigned in 1999 because of the company's patent was quoted as stating, "I felt their interest in making money had completely subsumed their willingness to be reasonable and collegial."[184]

Many doctors and specialists fear that Myriad is pushing testing merely to increase profits and is disregarding the fact that mainstreaming the test could create unnecessary anxiety,[185] increase medical costs, and even induce a false sense of security in individuals not counseled on interpreting the results.[186] Some decry the direct-to-consumer marketing campaign as a blatant disregard for quality healthcare in furtherance of massive revenue.[187] And considering that only five to ten percent of breast cancer is hereditarily-based, there also is concern that mainstreaming the test is unnecessary because most doctors are aware of the testing and are best situated to discuss the option with their patients.

## B. *Access and Cost to Patients*

Another related argument against allowing patents on genetic diagnostics is grounded in the possibility of the test not being available to a patient for purposes of diagnosing a health problem, a result that hinders patient care and counters the goals of the healthcare

[178] *Id*.

[179] *Id*. at 10.

[180] *Id*.

[181] The advertising is focused on Atlanta, Georgia and Denver, Colorado and consists of television, print, and radio campaigns aimed at women between the ages of 25-54. *Breast Cancer: Myriad Launches Direct-to-Consumer Advertising Campaign for Breast Cancer Test*, HEALTH & MEDICINE WEEK, Oct. 21, 2002, at 12. *See also* Press Release, Myriad, Myriad Genetics Improves Patient Access to Predictive Medicine (Feb. 19, 2004) http://www.myriad.com/corporate/media_campaign.html (last visited Mar. 6, 2004).

[182] *Cancer Screening: Genetic Cancer Test Stirs Debate*, GENOMICS & GENETICS WEEKLY, July 5, 2002, at 7 [hereinafter *Cancer Screening*].

[183] *See* Theresa Agovino, *Myriad to Market Genetic Testing*, SALT LAKE TRIBUNE, June 6, 2002, at B4.

[184] Julian Borger, *Rush to Patent Genes Stalls Cures for Disease* (Dec. 15, 1999), *available at* http://www.organicconsumers.org/Patent/rushpatent.cfm (last visited Feb. 19, 2004).

[185] For a discussion of the psychological impact of BRCA genetic testing, see Murphy, *supra* note 18; A. Bredart et al., *Psychosocial Dimensions of BRCA Testing: An Overshadowed Issue*, 26 EUR. J. CANC. CARE 96-99 (2001).

[186] *Cancer Screening*, *supra* note 182. Women who obtain a negative test result for BRCA mutations actually have a normal population risk rather than a zero percent chance of developing breast cancer. Bennett et al., *supra* note 18, at 102.

[187] It is interesting that predictive genetic tests accounted for about half of Myriad's revenues in 2002 at $19.1 million, and the new marketing campaign is estimated to boost their revenues to $100 million by the year 2006. *Cancer Screening*, *supra* note 182.

system. One commercial aspect of diagnostic gene patents is that doctors must either obtain a license to provide such a test, which Myriad allegedly will not supply to any European laboratories,[188] or else charge the patient a fee for sending a sample to be tested at the corporation or research institution that holds the patent. In many situations, as evidenced by the Myriad controversy, this fee can be exorbitant. As an alternative to utilizing a patented procedure that may cost the patient, the insurance company, managed care organization, or the government a significant amount of money, the doctor may even choose to perform an inferior procedure, perhaps resulting in inaccurate results or even failure to screen for the specific disease.

Myriad requires that all BRCA1 and BRCA2 diagnostic testing in the United States be performed by their Utah laboratories at an average cost of about $2,760.[189] In European nations, Myriad charges 2,744 euros for BCRA testing services to be done solely at the Utah labs, which is three times the amount of the 914 euros that it costs French laboratories to do the tests on their own.[190] At the current exchange rate, this price in euros converts to roughly $2,912.[191] With such figures, the challengers project that Myriad's fees would create expenditures of 5.5 million euros a year ($5.83 million) as figured by a constant 1,500 tests per year,[192] and 110 million euros ($116.75 million) over the next twenty years in France alone.[193]

## C. *Research*

The challengers are concerned that the monopoly over testing inevitably will lead to a loss of expertise and information among researchers and physicians in Europe.[194] This arises from the fact that researchers and physicians are most often completely barred from using any gene or protein sequences claimed within the patent, and thus are prevented from undertaking or improving diagnostic technology relating to that particular gene.[195] The complete bar to use may have a deleterious effect on innovation and future research and ultimately may result in an intellectual standstill.[196] Because researchers and physicians are barred from the use of the BRCA1 gene itself, no improvements to the inaccuracies of the current testing mechanisms will be discovered.

Research and diagnosis undoubtedly have been hindered in the United States by exclusivity of genetic material essential to human disease detection. In the United States, 35% of geneticists report that even the sharing of basic data and research material has decreased substantially in the last decade,[197] and 21% claim that failure to access such data from another researcher has resulted in their abandonment of a promising line of research.[198] A survey of 200 genetic-testing laboratories offers that 25% of the labora-

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[188] Joint Press Release, *supra* note 12, at 4.

[189] Myriad SEC Report, *supra* note 17, at 10.

[190] Joint Press Release, *supra* note 12, at 6.

[191] Utilizing the Universal Currency Converter, *available at* http://www.xe.com/ucc (last visited Feb. 19, 2004), the exchange rate is 1 U.S. dollar = .9442224 euro. The result is a price in U.S. dollars of $2,912.26.

[192] This figure was calculated from year 2000 statistics for diagnostic breast cancer tests undertaken in France. Joint Press Release, *supra* note 12, at 6.

[193] *Id.*

[194] *Id. See also* Butler & Goodman, *supra* note 121, at 96.

[195] *Id.*

[196] For a discussion of the potential negative effect on research, see Heller & Eisenberg, *supra* note 10.

[197] Eric G. Campbell et al., *Data Withholding in Academic Genetics*, 287 JAMA 473, 473-80 (2002).

[198] *Id.* at 478.

tories have been prevented from offering a test due to the enforcement of a patent or license.[199] In addition, approximately 50% reported that they did not attempt to develop new tests because of commercial constraints brought on by a patent.[200] For example, beginning in 1998, SmithKline Beecham Clinical Laboratories sent letters to laboratories ordering them to stop performing or developing tests for the hemochromatosis (HFE) gene.[201] SmithKline had acquired the patent through an exclusive licensing deal with Progenitor, a corporation that had merged with Mercator Genetics, the entity that was issued three U.S patents on HFE testing.[202] As a result of SmithKline's letter, 30% of laboratories discontinued testing and/or ceased development of HFE testing services.[203]

Furthermore, the mandatory export of all tissue samples to Myriad for testing in the United States allows Myriad to build up the only genetic BRCA databank in the world, effectively giving Myriad total control over the key research materials relating to genes coding for breast cancer susceptibility.[204] With such an extensive tissue bank, Myriad can make further discoveries and file patent applications to the exclusion of all other nations and researchers.[205]

## V. POSSIBLE MECHANISMS FOR CHANGE

As a result of exclusive grants of rights over genetic material, there is a growing negative effect on an international scale on both patient care and research. The European opposition clearly illustrates the urgent problems that have resulted from the protection of patent law, both in the European Union and in the United States, for gene patents expressly covering sequences of human genetic material. How can the United States address the legal and policy issues presented by gene patents and make the application of patent law more uniform? There are a number of possibilities: a) an amendment to U.S. patent law through federal legislation; b) broadening of the common law research exception through case law; c) compulsory licensing, on either a federal or international level; or d) regulation through a specialized agency.

### A. *An Amendment to U.S. Patent Law*

One potential option to remedy the policy and legal concerns is through the adoption of specific federal legislation exempting genetic material from being the subject of an infringement action. In 1996, with the introduction of an amendment to 35 U.S.C. § 287(c)(1), the U.S. Congress created a patent law exception to patent infringement in the performance of medical surgical procedures.[206] The statute resulted from an in-

[199] M.K. CHO, PREPARING FOR THE MILLENNIUM: LABORATORY MEDICINE IN THE 21ST CENTURY 47-58 (2d ed. 1998).

[200] *Id*.

[201] Jon F. Merz et al., *Diagnostic Testing Fails the Test*, 415 NATURE 577, 577-78 (2002).

[202] *Id*. These were U.S. Pat. Nos. 5,712,098, 5,753,428, and 5,705,343. Shortly thereafter, the patent rights were sold to Bio-Rad Laboratories, which is allowing researchers to use the hemochromatosis test for a fee. *Id*.

[203] *Id*. at 578.

[204] Joint Press Release, *supra* note 12, at 4.

[205] *Id*.

[206] *See* 35 U.S.C. § 287(c)(1)-(2). Section 287(c)(1) reads:

> With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b) of this title, the provisions of sections 281, 283, 284, and 285 … of this title shall not apply against the medical practitioner or against a related healthcare entity with respect to such medical activity.

Note that this narrow exemption applies only to the medical practitioner or entity performing the activity, and patent holders may still go after the suppliers of any infringing medical devices used in the performance of the procedure.

fringement action brought by a doctor against a fellow physician for utilizing a cataract surgery technique for a "self-sealing" incision that was subject to patent protection.[207] In *Pallin v. Singer*, the court held that upon a reading of the clear, unambiguous language of 35 U.S.C. § 287(c), the defendant was not entitled to the grant of a motion to dismiss on the grounds that the alleged infringing use was a medical procedure.[208] The amendment that directly followed the troublesome outcome of this case provides that with respect to a medical practitioner's performance of a medical activity that would otherwise constitute an infringement under patent law, infringement actions "shall not apply against the medical practitioner or against a related healthcare entity with respect to such medical activity."[209]

Recently, legislation was introduced in the House of Representatives that would set out specific exemptions from infringement under U.S. patent law for both research and genetic diagnostic testing.[210] The Genomic Research and Diagnostic Accessibility Act of 2002, H.R. 3967, introduced by Lynn Rivers (D-MI) and David Weldon (R-FL), provides for the amendment of 35 U.S.C. § 271 through the addition of a subsection allowing the use of genetic sequence information for noncommercial research purposes.[211] The Act also provides for an amendment of 35 U.S.C. § 287(c)(2) to allow for the use of genetic sequence information for "performance of a genetic diagnosis, prognostic, or predictive test of a medical or surgical procedure."[212] In addition, it calls for public disclosure of genetic sequence information in federal and federally assisted patents within thirty days of filing for a patent application.[213]

Opponents of the Myriad BRCA patents praise this legislation as being fully in tune with the European initiative.[214] In her remarks upon introduction of the bill, Congressperson Rivers commented on the European challenge and the ramifications of the BRCA monopoly on patient healthcare.[215] As a mechanism to directly address the inherent problems present with gene patent protections, this type of federal act would remedy the problems of access, cost, and quality by creating another explicit exception to the present law in furtherance of healthcare objectives and scientific advancement.[216]

## B. *Case Law*

There always is the potential to strike down protection of patents that inhibit access and cost in diagnostics and research through case precedent imposing a research exception to patent law for the use of genetic material. The creation of such an exception

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[207] Pallin v. Singer, 1995 U.S. Dist. LEXIS 20824 (Dist. Vt. 1995).

[208] *Id*. at *13.

[209] 35 U.S.C. § 287(c)(1).

[210] The sister bill, the Genomic Science and Technology Innovation Act of 2002, calls for the imposition of a study to be conducted by the Director of the Office of Science and Technology Policy in order to assess the "impact of Federal policies on the innovation process for genomic technologies." Included in the study would be the investigation of a researcher's access to genomic materials, the impact of restricted access to genomic diagnostics, the quantification of the actual and reasonably expected effects of innovation policies on genomic science and innovation, and whether there are barriers to research created through the denial of use of a research tool, increased costs of licensing, and litigation costs. Genomic Science and Technology Act of 2002, H.R. 3966, 107th Cong. (2002).

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

[212] *Id*.

[213] *Id*.

[214] Joint Press Release, *supra* note 12, at 9.

[215] Rivers Remarks, *supra* note 5, at E354.

[216] For another example of a bill to amend 35 U.S.C. § 287(c) to require compulsory licensing of process patents to providers of clinical laboratory services, see Merz, *supra* note 14, at 328.

for research and diagnostics would allow protected gene sequences to be utilized for the furtherance of both scientific development and patient care. Relevant litigation may arise as a result of patent infringement allegations brought against a defendant for using a genetic test such as for BRCA1 without a license from the corporation that owns the rights over the genetic sequence. In raising a defense, the defendant may argue that the patent is invalid on the basis that the patent holder is completely restricting use of the gene and unduly harming research and scientific discovery, which are the touchstones of the initial constitutional provisions that serve as the foundation for the creation of a patent system.[217]

Precedent dictates that the use of the experimental use exception is reserved only for endeavors that are "solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry" and is not dependent on commercial implication.[218] A federal circuit case recently reiterated the "very narrow" and "strictly limited" experimental use exception in holding that the nonprofit, educational status of a university is irrelevant.[219] The court determined that the correct focus is on whether the act of infringement is in furtherance of legitimate business or merely for amusement, curiosity, or philosophical inquiry.[220] It found that Duke University, as a major research institution, often sanctions and funds projects that, arguably, have no commercial gain but do further business objectives of educating and enlightening faculty and staff, as well as increasing the school standing and monetary grants.[221] The court also noted that major research institutions of higher learning, like Duke University, actively pursue patents and establish licensing programs that derive substantial revenue.[222] The case is now on remand to the district court to determine whether that business fits the extremely narrow exception.[223]

This investigation fails to distinguish between the subject matter of the patent, however, thus ignoring that restrictions on genetic material impede downstream diagnostics, therapy, and medical products.[224] In broadening this narrow exception to allow for the use of genetic material for diagnostic testing and research, consideration could be given to the importance of patient care and the development of these new biotechnologies.

## C. *Compulsory Licensing*

Compulsory licensing of gene patents would involve the government granting licenses to physicians and researchers to use a patented gene sequence without the patent holder's permission in return for a reasonable fee paid directly to the patent holder.[225] The European Union already provides for such a system of licensing drugs in order to promote the interests of scientific research and patient healthcare.[226] When faced with European concerns over the BRCA gene patents in 2001, both the French Minister for Research, Roger-Gerard Schwartzenberg, and the French Minster for Health,

[217] *See* U.S. CONST., Art. I, § 8, cl. 8.

[218] Roche Prod. v. Bolar Pharm. Co., 733 F.2d 858 (Fed. Cir. 1984), *cert. denied*, 469 U.S. 856 (1984).

[219] Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002).

[220] *Id*.

[221] *Id*.

[222] *Id*. at 1363 n.7.

[223] *Id*. at 1363.

[224] Heller & Eisenberg, *supra* note 10.

[225] Lori B. Andrews, *The Gene Patent Dilemma: Balancing Commercial Incentives With Health Needs*, 2 HOUST. HEALTH L.& POL'Y 65, 103 (2002).

[226] Joint Press Release, *supra* note 12, at 8. Specifically, French regulation contains a provision that allows a drug to be the subject of an automatic license if the demands appear to be "contrary to the interest of public health." *Id*.

Bernard Kouchner, suggested extending the compulsory licensing system to protected genetic material in the interest of public health.[227] A similar provision could be adopted in the United States to include gene patents critical in diagnostic genetic testing and research.

International agreements to which the United States is a signatory reflect provisions regarding the compulsory licensing of gene patents. The United States is one of the 146 nations presently party to the Agreement on Trade-Related Aspects of Intellectual Property (TRIPS), concluded in 1994 as part of a multilateral trade agreement promulgated as an instrument of the World Trade Organization.[228] A portion of TRIPS addresses standards concerning the availability, scope, and use of patent rights, with special attention directed to exceptions to patent protection.[229] Article 30 provides that there are certain limited exceptions to the exclusive rights conferred by a patent, so long as the exception would not unreasonably prejudice the legitimate interests of the patent owner.[230]

Article 31 establishes requirements that must be met in the limited circumstances when allowing others to use the subject matter of a patent without the authorization of the patent holder.[231] Included are that the authorization must be considered on individual merits,[232] use may only be permitted if the proposed user made efforts to obtain authorization from the right holder on reasonable commercial terms,[233] the scope and duration shall be limited to the purpose for which it was authorized,[234] use shall be nonexclusive[235] and nonassignable,[236] the use is subject to termination,[237] and the right holder is entitled to adequate payment for use.[238] Through active negotiation within the World Trade Organization, TRIPS could be amended to make it explicit that compulsory licensing is possible for genetic material when deemed necessary for the public good, as in patient diagnosis and research. Such an amendment would be enforceable in all TRIPS signatory nations.

## D. *Independent Agency Regulation*

Another potential mechanism of ensuring quality test results and fair testing costs may be through independent agency regulation. Laboratories and corporations that offer genetic testing services to be performed in their facilities on a mail-in basis are not subject to any Food and Drug Administration (FDA) regulations that ensure safety and effectiveness.[239] If the kits are instead packaged and distributed by biotechnology corporations to outside laboratories and physicians, then FDA regulation is triggered.

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[227] Key Dates, *supra* note 73.

[228] Agreement on Trade-Related Aspects of Intellectual Property (TRIPS), *available at* http://www.wto.org/english/docs_e/legal_e/27-trips.pdf (last visited Feb. 19, 2004). The Uruguay Round agreement created the World Trade Organization (WTO) as a means to replace the General Agreement on Tariffs and Trade (GATT) to implement and administer the provisions of the agreement.

[229] *Id.* pt. II, sec. 5.

[230] *Id.* Art. 30.

[231] *Id.* Art. 31.

[232] *Id.* Art. 31(a).

[233] *Id.* Art. 31(b).

[234] *Id.* Art. 31(c).

[235] *Id.* Art. 31(d).

[236] *Id.* Art. 31(e).

[237] *Id.* Art. 31(g).

[238] *Id.* Art. 31(h).

[239] Abby Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555, 587 (1998).

Because Myriad performs all testing services within their own laboratory facilities in Salt Lake City, only the technical competence of their laboratory as measured by accuracy, reliability, and timeliness of patient test results is regulated under the Clinical Laboratory Improvement Amendments (CLIA).[240]

In order to remedy the issue of accurate test results as seen with the Myriad patent, where it has been reported that the BRCA1 test fails to identify ten to twenty percent of mutations, regulation could be performed by an independent agency. While it may be an overwhelming feat for FDA to provide such regulation in addition to its current role in drug and diagnostic kits, a new agency could be created with the requisite authority to administer review of genetic testing services and prices.

## VI. CONCLUSION

The growing debate and public discord regarding gene patent domination over both patient care and research illustrate the need for prompt modification of U.S. patent law. By examining the current opposition underway in the European Union regarding the monopoly over the BRCA genes, it is apparent that something must be done, and soon. Most promising would be the adoption of federal legislation providing a specific exemption from infringement claims for gene patents, both for research and diagnosis, as seen with the Rivers/Weldon Bill. But whether the adjustment comes through federal legislation amending U.S. patent law; creation of an exception through case law; a system of compulsory licensing to remedy problems of access, cost, and quality across the board; or creation of a specialized regulatory agency to develop quality and cost safeguards, there must be provisions in place to allow genetic material to be used in healthcare and research. To allow the exclusive monopoly over human genes to continue in dereliction of healthcare and scientific research runs contrary to the public interest and the goals of the patent system, both in Europe and in the United States.

[240] CLIA was introduced in 1988 as a means of establishing a minimum set of quality standards for laboratory testing services. Reviews for accuracy and reliability of results are conducted by the Centers for Medicare and Medicaid Services. A laboratory is defined under CLIA as "any facility which performs laboratory testing on specimens derived from humans for the purpose of providing information for the diagnosis, prevention, treatment of disease, or impairment of, or assessment of health." *See* http://www.cms.hhs.gov/clia/ (last visited Feb. 19, 2004).