UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK

ASSOCIATION FOR MOLECULAR PATHOLOGY; AMERICAN COLLEGE OF MEDICAL GENETICS; AMERICAN SOCIETY FOR CLINICAL PATHOLOGY; COLLEGE OF AMERICAN PATHOLOGISTS; HAIG KAZAZIAN, MD; ARUPA GANGULY, PhD; WENDY CHUNG, MD, PhD; HARRY OSTRER, MD; DAVID LEDBETTER, PhD; STEPHEN WARREN, PhD; ELLEN MATLOFF, M.S.; ELSA REICH, M.S.; BREAST CANCER ACTION; BOSTON WOMEN'S HEALTH BOOK COLLECTIVE; LISBETH CERIANI; RUNI LIMARY; GENAE GIRARD; PATRICE FORTUNE; VICKY THOMASON; KATHLEEN RAKER, Plaintiffs, v. UNITED STATES PATENT AND TRADEMARK OFFICE; MYRIAD GENETICS; LORRIS BETZ, ROGER BOYER, JACK BRITTAIN, ARNOLD B. COMBE, RAYMOND GESTELAND, JAMES U. JENSEN, JOHN KENDALL MORRIS, THOMAS PARKS, DAVID W. PERSHING, and MICHAEL K. YOUNG, in their official capacity as Directors of the University of Utah Research Foundation, Defendants.	Civil Action No. 09-4515 (RWS)

DECLARATION OF JOSEPH STRAUS

I, Joseph Straus, hereby declare that:

1. I am currently at the Max-Planck-Institute for Intellectual Property, Competition and Tax Law, Munich, as a Director Emeritus.

2. I studied law at the University of Ljubljana, Slovenia, receiving a law-diploma in 1962. I continued my studies at the University of Munich, Germany, receiving first a certificate in German private and public law in 1963 and a doctorate of juridical science in 1968. In 1986, I attained habilitation at the University of Ljubljana. I was awarded the honorary grades of a Doctor Honoris Causa by the University of Ljubljana in 2001 and by the University of Kragujevac, Serbia, in 2003.

3. From 1968 until 1977, but partly already before, I was in private practice. Since 1977, I have practiced at the Max-Planck-Institute for Foreign and International Patent, Copyright and Competition Law in Munich, which was renamed in 2002 as the Max-Planck-Institute for Intellectual Property, Competition and Tax Law. At that Institute, I was first the Head of the Department primarily responsible for patents and I have been a Director there since 2001 until my retirement as of end of 2008.

4. Between 2001 and 2004, I was the Managing Director of the Institute. Until the end of 2008, I was also the Chair of the Managing Board of the Munich Intellectual Property Law Center ("MIPLC"), which I co-founded in 2003. My main area of interest is patent law, and in particular, the field of chemical and biotech inventions.

5. The academic positions that I currently hold include Nominated Full Professor for Intellectual Property Law, University of Ljubljana (since 1986); Professor of Law, University of

Munich, where I have taught patent law since 1990; and Marshall B. Coyne Visiting Professor of International and Comparative Law, George Washington University School of Law, Washington D.C., where I teach a course on chemical and biotechnology related patents. Additionally, I am a Visiting Fellow at the Hoover Institution, Stanford University. I am also an Honorary Professor of several universities including Tongji University, Shanghai and Huazhong University for Science and Technology, Wuhan, China.

6. During my career, I have held a number of other academic positions and have been a Visiting Professor at several establishments including Cornell Law School, Ithaca, New York (1989-1998); Toronto University (Spring 2005), Renmin University, Beijing (Spring 2005); and George Washington University, Washington D.C. (2001-2004).

7. I act or have acted as consultant to over ten international organizations and national state authorities including the Organization for Economic Cooperation and Development ("OECD"), World Intellectual Property Organization ("WIPO"), the World Bank, the United Nations Industrial Development Organization, the European Commission, the European Patent Office, the Swiss Intellectual Property Institute, the German Government as well as the Swiss Government and the German Parliament. As an expert on the protection of biotechnological inventions, I have testified before the Committee on Legal Affairs and Citizen's Rights of the European Parliament, before the Committee on Legal Affairs of the German Parliament (Bundestag), and before a Special Committee of the Austrian Parliament.

8. Over my career, I have held positions in several committees or advisory bodies of international governmental as well as non-governmental organizations, including the Advisory Board of the WIPO Worldwide Academy; the Standing Advisory Committee before the

European Patent Organization ("SACEPO"); the Advisory Board of the Research Fund of the European Patent Office; the Programme Committee of the International Association for the Protection of Industrial Property (Chair, 1997-2006); the Intellectual Property Rights Committee of the Human Genome Organization (Chair 1995-2006); and the International Association for the Advancement of Teaching and Research in Intellectual Property (President, 1993-1995). At present, I am the Vice-president of the German Association for the Protection of Industrial Property and Copyright ("GRUR") and Chair of the Law Section of the Academia Europaea.

9. In 1999, I was elected Katz-Kiley Fellow of the Houston Law Center, Houston. In 2000, I was awarded the "Science Award 2000" of the Foundation for the German Science (Stifterverband für die Deutsche Wissenschaft) as the first non-scientist. In 2005, I was awarded the "Commander's Cross" of the Order of Merit of the Federal Republic of Germany (Großes Verdienstkreuz des Verdienstordens der Bundesrpublik Deutschland). From 2003-2006, I was selected as one of the 50 most influential people in intellectual property by the Journal "Managing Intellectual Property" and was made a Member of Honour of the International Association for the Protection of Industrial Property ("AIPPI") in 2006. I was inducted into the Intellectual Asset Management Magazine IP Hall of Fame in 2007. In that same year, I was also given the Venice Award for Intellectual Property for commitment to the promotion of intellectual property culture.

10. I am the author or co-author of some 300 publications in the field of intellectual property. A full list of my publications is provided in **Ex.** A. Details of the various advisory and academic positions I have held during my career is set out in the bibliography which is provided at **Ex.** A.

11. In the past, I have provided expert opinions in connection with various patent disputes in

Germany, Europe, the United States of America, Japan and Brazil for a great number of companies, including U.S., Europe and Japan based companies.

12. At present, I am acting as Consultant to a number of companies, however, entirely unrelated to the case at hand and to the parties involved.

13. In view of the subject matter at hand, I may in particular emphasize the following:

14. In 1985, I co-authored (with Prof. F.K. Beier und St.R. Crespi) a study published by OECD, entitled "Biotechnology and Patent Protection – An International Review," which was translated into French, German and Japanese language and which presented the very first study in the area of patenting biotechnological inventions at an international level. Also, in 1985, I prepared a study for WIPO entitled "Industrial Property Protection of Biotechnological Inventions. Analysis of Certain Basic Issues," (WIPO Document BIG/281), which was translated into French, German and Spanish language and which served as the basis for deliberations of a Special Committee of WIPO on the Protection of Biotechnological Inventions.

15. Between 1986 and 1988, I served as consultant to the European Commission in the preparation of the first draft for a Directive on the legal protection of biotechnological inventions. I was the sole drafter of the Explanatory Memorandum to that document. Later on, I assisted the EC Commission in the deliberations with the EU Council and testified before the Committee on Legal Affairs and Citizen's Rights of the European Parliament in the last hearing before adoption of the European Directive 98/44/EC (the "EU Directive"); **Ex.** B.

16. From 1995 to 2006, I was the Chair of the Intellectual Property Rights Committee of the Human Genome Organization ("HUGO"), whose members at that time were *inter alia* Professors Rebecca Eisenberg (Michigan State University), Eric Lander (MIT), Sir John Sulston

(Cambridge), David Cox (Stanford). In this capacity, I was co-responsible for a number of statements on issues of patentability of human DNA sequences, which were adopted and published by HUGO's Council.

17. It should be noted that in 1997, when I was acting as Chairman of HUGO's IPR Committee, we issued a statement on patenting issues related to the early release of raw sequence data ("HUGO 1997 Statement"). *See* **Ex.** C. This statement embodied the principles we adopted in the organization, and particularly set out to inform the scientific and legal community that HUGO did *not* oppose the "patenting of useful benefits derived from genetic information." **Ex.** C. Quite the contrary, HUGO was in favor of patenting isolated DNAs with a known function. What HUGO opposed was patents on express sequence tags ("EST")[1] which had no known function or utility. The United States adopted this standard, which has been the state of the law since *Fisher*. *See In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005) (affirming the USPTO's refusal to grant a patent on ESTs with unknown function or utility). I note that, Sir Sulston, Plaintiffs' declarant, contrary to the positions he has taken in this case (*See*, *e.g.*, Sulston Decl. ¶¶ 37-38.), was indeed not only a member of HUGO at this time, but also a signatory of the 1997 HUGO Statement.

18. Between 2004 and 2006, I chaired an OECD Expert Group which in 2006 successfully developed detailed principles and best practices for the licensing of genetic inventions in order to ensure that therapeutics, diagnostics and other products and services employing genetic inventions are made readily available on a reasonable basis.

[1] An EST (Expressed Sequence Tag) is a short sequence of the complementary DNA that was expressed by the full-length gene.

19. I have reviewed the following documents: Plaintiffs' Memorandum of Law in Support of Motion for Summary Judgment; Plaintiffs' Rule 56.1 Statement of Material Facts; Declaration of Sir John E. Sulston, Ph.D. of August 17, 2009; Declaration of Myles W. Jackson of August 18, 2009; and United States Patent Nos. 5,747,282 ("the '282 patent"); 5,837,492 ("the '492 patent"); 5,693,473 ("the '474 patent"); 5,710,001 ("the '001 patent"); 5,753,441 ("the '441 patent"); 6,033,857 ("the '857 patent"), (collectively "Myriad patents"); *Utility Examination Guidelines*, 66 Fed. Reg. 1092 (January 5, 2001), **Ex.** D ("2001 Guidelines"); Decision of June 6, 2007 of the Opposition Division in connection with the EP 0 705 903 patent (granted May 23, 2001), **Ex.** E; Board of Appeal Decision T 0666/05 of November 13, 2008 in connection with the EP 0 705 903 patent, **Ex.** F; Board of Appeal Decision T 1213/05 of September 27, 2007 in connection with the EP 0 705 902 (granted November 28, 2001), Ex. **G**; Straus et al., "Genetic Inventions and Patent Law – An Empirical Survey of Selected German R & D Institutions," Published by Max Planck Institute for Intellectual Property, Competition and Tax Law, Munich 2004, **Ex.** H; Walsh *et al.*, 2005, *Science*, "View from the Bench: Patents and Material Transfers," 309:2002-03, **Ex.** I ("Walsh 2005").

I. ISOLATED NUCLEIC ACID PATENTS – A EUROPEAN PERSPECTIVE

A. SCIENTIFIC BACKGROUND

20. Genes are to be understood as fundamental physical and functional units of heredity. Genes are located in a particular position on a particular chromosome. Genes encode specific functional products, such as a protein or RNA molecule. Genes are of double nature: On the one hand, they are chemical substances or molecules. On the other hand, they are physical carriers of information, *i.e.*, where the actual biological function of this information is coding for proteins. Thus, inherently genes are multifunctional.

21. Since the completion of the raw sequence of the human genome not only do we know that we only have some 20,000–25,000 genes, but also that some 40 per cent of the gene products are alternatively spliced. Therefore, genes encode for more than one protein, depending on the combination of exons read in an open reading frame, or even depending on the direction in which the exons are read. Thus, many genes are rendered multifunctional based on this splicing mechanism. Moreover, DNA molecules as physical carriers and information are multifunctional under another important aspect: they hybridize to other DNA molecules, a property I would like to describe as an actually non-biological function. Thus, by virtue of this property, DNA molecules can be used, for instance, as DNA probes, and diagnostic markers.

B. WHAT CONSTITUTES AN INVENTION IN THE CASE OF ISOLATED NUCLEIC ACID PATENTS - A COMPARATIVE ANALYSIS WITH OTHER PRODUCT INVENTIONS

22. Generally, product inventions relate to: synthetic molecules produced in a lab; chemical substances isolated from natural environment; and DNA molecules of human origin, respectively. I will discuss whether essential differences exist between these different forms of chemical compounds, and secondly, if there are such differences, whether they require different legal treatment.

1. Synthetic Molecules

23. Synthetically produced new chemical substances are molecules of an arbitrary formula. They are new in an absolute sense and are in principle without an actual biological function. Such molecules are producible in arbitrary – unlimited variations. Finding a first surprising property, for instance a therapeutic effect, of such new, *i.e.*, not pre-existing molecule, even if routinely produced or detected, justifies patent protection. In other words, the essence of the

invention is in "making the absolutely new substance available" to the public. The substance made available, in combination with the disclosure of the surprising therapeutic effect, opens up an entire new field for further research. Third parties can search for, for instance, further therapeutic uses, or they can experiment with the disclosed new formula, for instance, by adding, exchanging or deleting protection groups, in order to achieve other useful effects. To my understanding, in such circumstances "absolute" protection is justified and in line with the spirit and purpose of patent law. Without the new molecule and its "invented" property, others could not embark on further research.

2. Chemical Substances Isolated from the Natural Environment

24. In case of chemical substances isolated from the natural environment, the assessment is similar, although such substances are "new" only in the sense of not being previously available to the public. For example, Lovastatin, a cholesterol lowering agent was isolated from *Monascus rubber* and various species of *Aspergilus terreus*, a microorganism. In such microorganisms, Lovastin's function by no means is lowering cholesterol. Thus, Lovastatin, and many other natural products, in their natural environment, in principle, typically have no actual biological function or use. Alternatively, the function of the chemical substance as "isolated" is distinct from that as it exists in nature. Moreover, such substances are available in unlimited numbers in nature. Thus, a finding of a first surprising property, such as lowering the blood cholesterol level in the case of Lovastatin, justifies for the very same reason the same treatment as in the case of synthetically produced new chemical molecules. Once the formula of Lovastatin was disclosed, the research in the entire area of the class of statins was opened up and eventually ended in inventing a great number of other new cholesterol-lowering agents.

3. DNA Molecules

25. As indicated above, human genes are biochemical substances as well as physical carriers of information. They have one or more related or unrelated actual, pre-determined biological function(s). They code for various proteins, for instance receptors, structural or regulatory proteins, etc. They are available – producible – only in limited numbers. The actual goal of research in this area is aimed at identifying and deciphering their actual nucleotide sequences, *i.e.*, the exact location and sequence of the gene, in order to find and exploit its actual and pre-determined biological function(s). This information can be used to make primers and probes for use in diagnostics.

26. Once the actual nucleotide sequences, *i.e.*, the exact location and sequence of the gene, is identified and deciphered, the focus of the invention should be shifted from the "making available" of the DNA, to finding the surprising property(ies), function(s). The identification of a specific open reading frame of a gene will involve "inventive" activity. Thus, "making available of the sequence" is playing the same role as in the case of synthetic molecules and chemical substances isolated from their natural environment. Isolation of such DNA molecules can thus constitute an invention fulfilling all the patentability requirements and deserving "absolute" protection.

II. A UNIFORM WORLD-WIDE APPROACH TO PATENTING ISOLATED NUCLEIC ACIDS

27. Although the appropriateness of granting patents on isolated DNA and other isolated nucleic acids continues to be publicly debated, the position of the official patent authorities in OECD has been clear and consistent for some time. From the standpoint of patent offices in Europe, especially the European Patent Office ("EPO"), genetic material is not seen as a special

case requiring treatment different from chemical compounds and other products. This view is shared by the patent offices of the United States and Japan. Common ground between the EPO, the United States Patent and Trademark Office ("USPTO") and the Japanese Patent Office ("JPO") has already been reached with respect to patents on isolated nucleic acids.

28. Mere determination of a DNA sequence is not enough for patentability. But, where the inventor is the first to identify a gene and its useful function, to isolate and clone the nucleic acid of the gene and thereby make synthetic copies of the nucleic acid that are available for use in diagnosis or therapy, patent offices world-wide accept that this is the kind of invention for which a patent can be granted.

III. THE EUROPEAN APPROACH

29. Patenting of biotechnology inventions, including patenting DNA molecules corresponding to genes, has been contentious and involved, at times, heated public debate. All of such discussions influenced the debate concerning the implementation of the EU Directive of the European Parliament and the Council on the legal protections of biotechnological inventions. The EU Directive 98/44/EC was adopted in July 1998 after a tense and controversial debate.

30. According to the EU Directive, assuming that a DNA sequence is novel, *i.e.*, not previously publicly known or used, and that other criteria for patentability are met (*i.e.*, industrial applicability ~ utility, non-obviousness, sufficient disclosure), the isolated substance of the DNA itself is patentable. To be precise, the claims concern not the sequence as abstract information, but a molecule which has a defined chemical structure (as nucleotide sequence) and function. This type of product claim will often be qualified in some respect, *e.g.*, by the limitation of "isolated" or "purified", especially if the substance exists in nature.

31. Specifically, the approach adopted by the EU Directive is that a nucleic acid corresponding to a complete or part of a gene, even if its structure is identical to that of a natural element, may constitute a patentable invention, if isolated from the human body or otherwise technically produced. **Ex.** B at Article 5(2). Indeed, the natural pre-existence of biological material alone does not constitute a patentability obstacle. **Ex.** B at Article 3(2). The EU Directive established that no patent can cover a substance *in situ* in the human body. Rather, the patent must cover the isolated substance. It is my understanding that the United States Patent and Trademark Office has a similar policy, in that it requires product claims to genetic materials be limited to the purified and isolated material. 2001 Guidelines; **Ex.** D.

32. Apart from the above restriction, an isolated DNA can be claimed as the substance *per se*, without limitation to any particular process of purification or isolation and without any limitation as to its intended use. In patent parlance, this is known as a "product per se" claim and it confers "absolute product protection". Granting "product per se" patents for genetic inventions is consistent with the established practice for new pharmaceuticals and other chemical compounds. The trend in many countries over the years has been to allow such product claims, as against previous more restrictive policies of allowing claims only to the particular chemical processes described in the patent application for making end products. In fact, the World Trade Organization ("WTO") Trade Related Intellectual Property Rights ("TRIPS") Agreement requires patent protection to be available for process and product claims in all branches of technology, without discrimination. TRIPS Agreement at Article 27 (1)).

33. Under the EU Directive, the disclosure of a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention (EU Directive at Recital 23), even if the method of manufacture is indicated. On the other hand,

the industrial applicability of the isolated DNA, in other words its function, has to be specifically disclosed in the patent application as filed. EU Directive at Recital 22, last sentence, Article 5(3). Where the use of a sequence or partial sequence of a gene for making a protein is claimed, the protein or part protein and its function have to be specified. EU Directive at Recital 24. If therapeutic or diagnostic uses are claimed, the disorder to be diagnosed or treated must be specifically indicated. Thus, the European legislator has made the function of a claimed DNA molecule an integral part of the notion of an invention (inventive concept) of a chemical compound invention, at least in this area.

34. Under the EU Directive, protection of a product, which consists of or contains genetic information, *i.e.*, a gene sequence, extends to any product – except man – in which this product is incorporated and in which the genetic information is contained and performs its function. **Ex.** B at Article 9.

IV. MYRIAD'S COMPOSITION OF MATTER CLAIMS COMPLY WITH THE EP PATENT LAWS

35. I reviewed claims 1, 2, 5, 6, and 7 of the '282 patent; claim 1 of the '473 patent; claims 1, 6, and 7 of the '492 patent. These claims all relate to isolated DNA molecules comprising either the *BRCA*1 or *BRCA*2 DNA. For ease of reference, I will refer to such claims as the "isolated DNA" claims.

36. Under the EU Directive, the Implementing Regulations to the European Patent Convention ("EPC") and case law interpretation of it, "isolated and purified" DNA molecules are patent-eligible subject matter. Thus, Myriad's isolated DNA claims are patent-eligible. The European Patent Office ("EPO") and Supreme Courts of the EU Member States, to my knowledge, have never challenged the validity of patents granted by the EPO Boards of Appeal

for "isolated and purified" DNA based on the grounds of their eligibility for patent protection.

37. As I mentioned above, I reviewed the decision of June 6, 2007 of the Opposition Division in connection with the EP 0 705 903 patent; Board of Appeal Decision T 0666/05 of November 13, 2008, confirming the holding of the Opposition Division and maintaining the EP 0 705 903 patent, and the Board of Appeal Decision T 1213/05 of September 27, 2007, maintaining the EP 0 705 902 patent. **Exs.** E-G. It should be noted that all the arguments that Plaintiffs have raised in this case (*see* Plaintiffs' Statement of Material Facts) were also raised during the Opposition Proceedings of these counterpart EP patents. In each case, these arguments were rejected by the Boards of Appeal.

38. Indeed, as reiterated by the Board of Appeal, an independent judiciary body, there simply is no bar to the patenting of isolated human DNA. Like plaintiffs in the U.S. case, the opponents in Europe attempted to raise socio-economic consequences of patenting of the claimed subject matter as a basis for denying patentability of Myriad's invention. But, like the Courts in the United States, those in Europe have all repeatedly ruled that isolated nucleic acids such as those claimed in the Myriad patents constitute patent eligible subject matter. Any change in the law is not within the province of the EPO or the national courts of the states parties to the European Patent Convention ("EPC") – neither is it within the province of the U.S. courts. Anyone challenging the Myriad patents would need to access another vehicle – perhaps, the Legislature.

V. EFFECT OF ISOLATED NUCLEIC ACID PATENTS ON BASIC RESEARCH, MEDICAL AND CLINICAL RESEARCH, INNOVATION AND COMMERCIALIZATION

39. While many have criticized the impact of genetic invention patents on access to the information and technologies covered by DNA patents, the available evidence does not suggest a systematic breakdown in the research and development of genetic inventions, once a particular isolated nucleic acid corresponding to a gene is patented. To the extent there are any concerns

regarding the potential for over-fragmentation of patent rights, blocking patents, or abusive monopoly positions, they appear anecdotal and not supported by any actual studies. Below, I summarize the result of two such empirical studies that negate the misconception that biotechnology patents have slowed biomedical research.

A. An Empirical Study in Germany

40. In 2002, the German government commissioned a study on "Genetic Inventions and Patent Law," which I conducted while at the Max Planck Institute for Foreign and International Patent, Copyright and Competition Law. **Ex.** H. The purpose of the German survey was to gain information from an objective viewpoint concentrating on the challenges of potential patentees for patenting genetic inventions and to provide evidence about the licensing practices relating to genetic inventions. Furthermore, the German survey was aimed at elucidating whether specific problems arise from the application of patent law on genetic inventions, in particular from patents on isolated DNA. As I indicated in a presentation, which I offered on the Survey in a January 2002 workshop, entitled "Genetic Inventions, Intellectual Property Rights and Licensing Practices," jointly organized by the OECD and the German Federal Ministry for Education and Research in Berlin, the overall goal of the survey was to verify concerns expressed on negative impact of patents in genomics as set forth in the EU Directive 98/44. Interviews were carried out at 25 institutions, including large pharmaceutical companies, biotech start-ups, clinical institutions associated with universities and other publicly funded research institutes and clinical institutions involved in genetic testing.

41. The survey specifically investigated, *inter alia*, whether there was reluctance to enter particular research fields in which gene related patents have been granted. No such tendency

was observed. Interestingly, the great majority of those interviewed across the entire surveyed group clearly favored the so-called absolute product patent protection of isolated nucleic acids. Those surveyed opposed any discrimination of this area of research and development as compared with the protection which classical chemical inventions enjoy. Of all the groups surveyed, including clinical institutions associated with universities, no specific problems of licensing were reported. Only some of those interviewed indicated a reduced interest for research in further uses of inventions patented for third parties.

42. Indeed, my study showed that all institutions surveyed were able to cope with the patent system ***as is*** in a satisfactory manner. We could not detect any support for a special regime for protecting genetic inventions. It should also be added that for those interviewed, there is a possibility for applying for a compulsory license, available under Section 24 German Patent Act ("GPA") which allows the grant of such a license, if such a license would be in public interest. Alternatively, in cases of a dependent patent claiming an invention, which involves an important technical advance of considerable economic significance in relation to the invention covered by the dominant patent, so-called dependency compulsory license would be available under the GPA. To my knowledge, neither in Germany nor in any other EU Member State a compulsory license has ever been applied for any of Myriad patents.

43. Finally, my study also found that patents on research tools, including isolated DNA molecules, have not had a discernible effect on the cost or pace of research in Germany, and the survey results suggested several reasons for this. First, some research tools are staple goods, like enzymes, which can be purchased without declaring their intended use. Second, it is difficult to detect infringement of research tools which are used behind laboratory doors. While end products may be suspected of having been developed using a patented research tool, many

biotechnology companies do not yet have such commercialized products, making it difficult to claim infringement. Third, public research bodies claim that their staff are often unaware of the legal implications of using patented research tools. In short, many groups act as if an "informal research exemption" exists for the use of patented research tools.

B. An Empirical Study in the United States

44. In May 2006, I attended a Conference Organized by the OECD among other organizations entitled "Research Use of Patented Inventions," where I was also a presenter. This conference was organized, in part, to address the concerns in the scientific and legal communities in accessing biotechnology inventions that are protected through the patent system. One presenter of note at this conference was John P. Walsh, associate Professor of Sociology at the University of Illinois, Chicago. *CSIC/OECD/OEPM Conference*, Madrid, Spain, May 18-19, 2006; John P. Walsh, "Roadblocks to Accessing Biomedical Research."

45. Walsh's study consisted of interviews with executives and researchers at biotechnology and pharmaceutical firms and research personnel and administrators at several universities. The objective of the study was to evaluate whether the "tragedy of the anti-commons"[2] is indeed a reality in biomedicine and whether patent rights to certain research tools are retarding innovation. Specifically, Walsh examined the impact of patents and licensing on access to knowledge and material inputs for academic biomedical research; the limitations on subsequent discovery and improvements imposed by assertion of patent on upstream foundational discoveries, such as discovery of genes; and the effect patents on research productivity.

[2] The "tragedy of the anti-commons", a term coined by Heller and Eisenberg (1998), refers to a situation where there are numerous property right claims over the building blocks necessary for research and development.

46. Walsh reported the results from a survey of 1125 academic researchers (including university, non-profits and government labs), which yielded 414 responses (adjusted response rate of 40%).

47. Walsh's results showed that there was little evidence so far of breakdowns in negotiations over patent rights or evidence that biomedical research has slowed as a result of biotechnology patents, including gene patents. Indeed, firms and research organizations in the United States reported "working solutions" which allow them to continue to innovate relatively unimpeded. Solutions included license negotiations where necessary or the avoidance of patent obstacles by working around the claims. Firms also chose to ignore or infringe patents, to challenge patents and litigate, to move offshore or to put innovations in the public domain. Thus, it would appear that access to patented technology has rarely, if ever, been blocked.

48. Further, in a 2005 article published in the journal *Science*, John P. Walsh and colleagues report the findings from a survey conducted on 414 biomedical researchers in universities, government, and nonprofit institutions to determine the effect of patents on biomedical research and material transfers. **Ex.** I at 2002. The researchers found that "few academic bench scientists currently pay much attention to the others' patents." *Id.* Moreover, of the "32 respondents who were aware of relevant IP, four reported changing their research approach and five delayed completion of an experiment by more than one month. No one reported abandoning a line of research. Thus, of 381 academic scientists . . . none were stopped by the existence of patents, and even modifications or delays were rare." *Id.*

49. I declare, pursuant to 28 U.S.C. § 1746, under penalty of perjury under the laws of the United States, that the foregoing is true and correct to the best of my knowledge and believe.

Executed on: December 22, 2009

Joseph Straus

APPENDIX 1

LIST OF EXHIBITS

Exhibit No.	Title
Ex. A	*Curriculum vitae* and Bibliography of Dr. Joseph Straus
Ex. B	European Directive 98/44/EC
Ex. C	HUGO 1997 Statement
Ex. D	*Utility Examination Guidelines*, 66 Fed. Reg. 1092 (January 5, 2001)
Ex. E	Decision of June 6, 2007 of the Opposition Division in connection with the EP 0 705 903 patent (granted May 23, 2001)
Ex. F	Board of Appeal Decision T 0666/05 of November 13, 2008 in connection with the EP 0 705 903 patent
Ex. G	Board of Appeal Decision T 1213/05 of September 27, 2007 in connection with the EP 0 705 902 patent
Ex. H	Straus et al., "Genetic Inventions and Patent Law – An Empirical Survey of Selected German R & D Institutions," Published by Max Planck Institute for Intellectual Property, Competition and Tax Law, Munich 2004
Ex. I	Walsh et al., 2005, "View from the Bench: Patents and Material Transfers," *Science*, 309:2002-03

CERTIFICATE OF SERVICE

This is to certify that on December 23, 2009, a true and correct copy of the foregoing document has been served on all counsel of record via the court's ECF system.

/s/ Brian M. Poissant
Brian M. Poissant

EXHIBIT A

C. V.

Joseph Straus (Dr. jur, Dres. jur. h.c.), Professor of Law (Universities of Munich and Ljubljana); Marshall B. Coyne Visiting Professor of International and Comparative Law, George Washington University Law School, Washington D.C.; Honorary Director of the Intellectual Property Institute of the Tongji University, Shanghai, Honorary Professor Tongji University, Shanghai; Honorary Professor Huazhong University for Science and Technology, Wuhan; Honorary Director of the Chinese-German Institute for Intellectual Property, Huazhong University, Wuhan; Honorary Professor, University of Xiamen; Visiting Professor, Graduate Institute of Intellectual Property, Taipei; Visiting Fellow, Hoover Institution, Stanford University.

Director Emeritus of the Max Planck Institute for Intellectual Property, Competition and Tax Law, Munich (2001-2009); Former Chairman, Managing Board of the Munich Intellectual Property Law Center (MIPLC) (2003-2009)

Born: 1938 in Trieste, Italy, received Law-Diploma 1962 from University of Ljubljana, Slovenia, and 1968 Dr. jur. (SJD) from University in Munich. Habilitation in 1986 at University of Ljubljana. Private practise from 1968 to 1977, since then with the Max Planck Institute. Nominated Full Professor of Intellectual Property Law, University of Ljubljana (1986-). Visiting Professor of Law, Cornell Law School, Ithaca, N.Y. (between 1989 and 1998); Distinguished Visiting Professor of Law, Faculty of Law, Toronto University (Spring 2005). Author or co-author of more than 300 publications in the field of intellectual property law, especially in the field of the protection of biotechnological inventions.

Consultant to OECD, WIPO, UNCTAD, UNIDO, EC-Commission, World Bank, Scientific Services of the German Bundestag (Federal Parliament) and the German Government, as well as the European Parliament, the European Patent Organisation, the Swiss Government and the Swiss Federal Institute for Intellectual Property.

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154. Latest Developments in Biotechnology - Gene Modification Techniques As They Relate to IPRs, Workshop "Intellectual Property Rights and Their Special Impact on Biotechnology, " Tufts University European Center, Talloires, France, May 19, 1998

155. Biodiversity and Intellectual Property, Workshop V “Genetic Diversity and Intellectual Property”, XXXVIIth Congress of the International Association for the Protection of Industrial Property, Rio de Janeiro, May 28, 1998

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158. The Legal Protection of Biological Material, General Report, XVth International Congress of Comparative Law, International Academy of Comparative Law, Bristol, July 28, 1998

159. Wem gehört das Genom, 120. Versammlung der Deutschen Gesellschaft der Naturforscher und Ärzte (GDNÄ), Berlin, September 21, 1998

160. Legal and Ethical Problems of Patenting Human Genes, VIth World Congress on Psychiatric Genetics, University of Bonn, Bonn, October 10, 1998

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163. Der Schutz des geistigen Eigentums in der Welthandelsorganisation: Konsequenzen des TRIPs für die EG und ihre Mitgliedstaaten, Tagung "Die europäische Gemeinschaft in der Welthandelsorganisation - Europa und die Globalisierung -" des Arbeitskreises Europäische Integration e.V. in Verbindung mit dem Institut für deutsches und europäisches Gesellschafts- und Wirtschaftsrecht der Universität Heidelberg, Academy of Sciences Heidelberg, January 30, 1999

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165. Life as a subject of Patenting, Workshop 11.2, BioGenTec Forum NRW 1999, International Meeting Biotechnology, Cologne, March 16, 1999

166. Wem gehört das Genom? Kein Patent auf Leben, fwf-Wissenschaftsforum (Who owns the genome? No patent on life, Austrian Research Foundation), Vienna, March 19, 1999

167. On the Need for Harmonization of Patents and Plant Breeders Rights, Workshop 2C, International Life Sciences Forum, bioVision, Lyon, March 27, 1999

168. Clinical Trials: The Situation in Germany, Studiedag on "Octrooirecht en geneesmiddelen", Centre for Intellectual Property Rights of the University Leuven, April 29, 1999

169. Genome Sequencing and Intellectual Property - The European Situation, Annual Meeting on Genome Mapping, Sequencing and Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, May 21, 1999

170. The Legal Foundation for Biotechnology Patenting, PLA Round Table 5 "Patent & Technology Management Forum", Dresden, May 31, 1999

171. Patenting Genes and Gene Therapy - Legal and Ethical Aspects, Novartis Foundation 50th Anniversary Symposium "From Genome to Therapy: Integrating New Technologies with Drug Development," Basel, June 24, 1999

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175. Patent Litigation in Europe: Setting the Scene, Patinnova '99 Congress, Thessaloniki/Chalkidiki, October 18, 1999

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179. Patents for Protecting Biotechnology Inventions, Marie Curie Fellowship Association Symposium "Key Technologies, Products and Patents", Munich, November 18, 1999

180. Gewerblicher Rechtsschutz und Gentechnologie, Symposium Gentechnologiebericht, Berlin-Brandenburgische Akademie der Wissenschaften, Berlin, November 20, 1999

181. Die Regelung der Neuheitsschonfrist - ein rechtsvergleichender Überblick, Workshop des Bundesministeriums für Bildung und Forschung, Wissenschaftszentrum Bonn, December 16, 1999

182. Inventions Based on the Use of Human Tissue Samples - Patent Aspects, Workshop of Industrial Association for the Promotion of Human Genome Research (FV) on "Correlation of Genetic Data with Clinical Data and Use of Human Tissue in Research - Ethical and Legal Requirements," Schloss Hohenkammer, near Munich, January 26, 2000

183. The Contemporary Evolution of Intellectual Property in Biotechnology, Rockefeller Foundation Bellagio Meeting on Intellectual Property and Developing World Biotechnology, Bellagio, March 28, 2000

184. Intellectual Property Rights and Genomics - Opening Comments, Wellcome Trust Conference IPR in Genomics, Hinxton Hall, Cambridge, June 7, 2000

185. Intellectual Property in Structural Genomics, OECD Global Science Forum Workshop: International Cooperation on Structural Genomics, Aula Magna, University of Florence, June 9, 2000

186. Patentrecht als Bindeglied zwischen wissenschaftlichem Fortschritt und globalisierter Wirtschaft (Lecture delivered on the occasion of the Science Award), Harnack House of the Max-Planck Gesellschaft, Berlin, June 21, 2000

187. Legal Problems Related to Gene Patents, Colloquium "Life Sciences, Ethics, Economy and Society," of the French Ministry of Research and the French Academy of Sciences, University of Bordeaux, June 23, 2000

188. Gibt es Patente auf Leben?, Studentenschaft Suevia, Munich, July 6, 2000

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190. Rethinking the Grace Period in Europe, CASRIP High Technology Protection Summit 2000, University of Washington School of Law, Seattle, July 22, 2000

191. The Impact of Gene Patenting on Research Activity, Gene Patenting Seminar, Laboratory of Molecular Biology of the British Medical Research Council, Cambridge, September 27, 2000

192. The Importance of Intellectual Property Rights for Academic Research, Meeting of Slovenian Scientists, Slovenian World Congress, Bled, September 29, 2000

193. Patenting in Genomics, Nestlé Research Center Genomics Conference, Lausanne, October 11, 2000

194. Life Sciences and Intellectual Property Rights, Forum Discussion Life Sciences and Technologies, 75th Session of the Committee for Scientific and Technological Policy of the OECD, Berlin, October 12, 2000

195. Basic Principles of the European Patent System, Post Graduate Course on European Law, University of Sarajevo, Sarajevo, October 20, 2000

196. Present State of Patenting in the Field of Biotechnology - An International Review, Executive Board of the International Council for Science (ICSU), Paris, October 25, 2000

197. The Need for Patents, Genetics in Europe Open Day 2000 - GEOD, organized by Progress Educational Trust, HUGO, European Genetics Foundation, Instituto de Recerca Oncologica and EMBO, Kennedy Lecture Theatre, Institute of Child Health, London, November 8, 2000

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199. The Use of Stem Cell Technology, Legal and Patent Law Aspects, Schering Foundation "Kamingespräch," Berlin, November 16, 2000

200. Biopatente auf dem Weg von Innovationsgrundlage zum Forschungshinderniss?, Conference "Wissenschaft zwischen Geld und Geist" of the Max-Planck-Institute for the History of Science, Berlin, November 17, 2000

201. Should a "Grace Period" be Introduced in the European Patent Convention?, Administrative Council of the European Patent Organization, Munich, December 6, 2000

202. Patentierung von Leben, CDU Bioethik-Kongress "Auch in Zukunft menschenwürdig leben - Ethik und Gentechnologie im 21. Jahrhundert", Berlin, December 13, 2000

203. Internationales Patentrecht - Monopolisierung des Wissens?, Ringvorlesung "Global Governance und die Zukunft der Entwicklungspolitik", Veranstaltungsreihe der Johann Wolfgang Goethe Universität in Zusammenarbeit mit der Gesellschaft für Technische Zusammenarbeit (GTZ), der KfW (Kreditanstalt für Wiederaufbau) und der Society for International Development (SID), Frankfurt/Main, December 19, 2000

204. Patentrechtliche Probleme der DNA-Chiptechnologie, Plenary Lecture, DECHEMA Status Seminar Chiptechnolgien: von Genom zum Proteom, Frankfurt/Main, January 22, 2001

205. Patent Protection for Inventions in Plants, KWS SAAT Colloquium "Modern Plant Breeding and Intellectual Property Rights," Einbeck, January 26, 2001

206. Biodiversity and Intellectual Property - Convention on Biodiversity, TRIPS Agreement and FAO Draft International Undertaking, International Symposium on Biodiversity and Intellectual Property of the Japanese National Group of AIPPI, Tokyo, February 2, 2001

207. Intellectual Property Issues for Structural Genomics, 2nd International Structural Genomics Meeting organized by National Institutes of Health, National Institute for General Medical Sciences, Airlie House, Warrenton, Virginia, April 5, 2001

208. Patent Protection for Bio-Genetic Inventions, A Comparison Between the US and European Law, Duke University School of Law, Durham, North Carolina, April 13, 2001

209. The Grace Period in Patent Law: A Look at Europe, Fordham University School of Law 9th Annual Conference on Intellectual Property Law and Policy, Fordham University School of Law, New York, April 20, 2001

210. Points to Consider When Patenting Results of Structural Genomics Research, National Institute for General Medical Sciences, Bethesda, M.D., April 25, 2001

211. Grace Period in Patent Systems: Impact on Information, Conference on "Scientific Information and Intellectual Property - Problems and Opportunities", organized by the International Council for Scientific and Technical Information (ICSTI), Munich, May 4, 2001

212. Recent Developments and Challenges in the Protection of Intellectual Property Rights, International Conference on Intellectual Property, The Internet, Electronic Commerce and Traditional Knowledge, organized under the auspices of his Excellency Mr. Petar Stojanov, President of the Republic of Bulgaria by the World Intellectual Property Organization (WIPO) in corporation with the National Intellectual Property Association of Bulgaria, Boyana Government Residence Sofia, May 29-31, 2001

213. Gene und Patente- Rechtliche Patentsituation: USA und Europa im Vergleich, Seance de réflexion "Gene und Patente", organized by Gen Suisse, Berne, June 6, 2001

214. Kommerzielle und patentrechtliche Aspekte der Genomforschung, Ringvorlesung Forschen und tun was möglich ist? "Humangenomprojekt und Ethik", Veranstaltungsreihe der Technischen Universität Carolo-Wilhelmina zu Braunschweig, Braunschweig, June 13, 2001

215. Genetic Inventions, IPRs and Licensing Practices - A Planned Empirical Study of the Max-Planck-Institute for Foreign and International Patent, Copyright and Competition Law in Munich, OECD Steering Group on Genetic Inventions, IPRs and Licensing Practices, Paris, June 18, 2001

216. Patentierung gentechnischer Erfindungen, life Science live, Münchner Wissenschaftstage, organized by Verband Deutscher Biologen und biowissenschaftlicher Fachgesellschaften e.V. Technical University Munich, June 26, 2001

217. Reform des Gesetzes über Arbeitnehmererfindung - Die deutsche Regelung im europäischen Umfeld, Infineons Technology Lunch, Berlin, June 27, 2001

218. Patent Law and Regulatory Environment for Biotechnological Inventions - EU-US Comparison, Expert Meeting “The Patenting of Genes - Legal and Socio-Economic Issues for Science and Technology Policy,” organized by DG RTD Life Science Directorate under the Auspices of the Life Science High Level Group of the European Union, Brussels July 5, 2001

219. Macro- und mikroökonomische Aspekte der Patentierung von softwarebezogenen Erfindungen, Introductory talk, Workshop “Economic Implications of Software Patenting,” organized by the Federal Ministry of Economics and Technology, Berlin July 10, 2001

220. Stoffschutz für DNA-Sequenzen - eine aktuelle Herausforderung des Patentrechts, Festvortrag aus Anlass des 40-jährigen Bestehens des Bundespatentgerichts (keynote speech on the occasion of the 40th Anniversary of the Federal Patent Court), Munich July12, 2001

221. Patentierung genetischer Erfindungen, Bonner Patenttage - Verwertung von Schutzrechten aus den Hochschulen der Region Aachen/Bonn/Köln/Ahrweiler, organized by Rheinische Friedrich-Weilhelms Universität Bonn, Bonn July 16, 2001

222. Regulation of Gene Technology in Legislation, Workshop: Gene Technology - The Impact on the Human Dimension, Joint meeting organized by the European Academy of Sciences and Arts and the Institute of Medicine of the National Academies of the United States of America, Salzburg, August 31, 2001

223. Ethische und rechtliche Aspekte der Patentierung genetischer Erfindungen - Generalbericht, 28. Tagung der Gesellschaft für Rechtsvergleichung, Universität Hamburg, September 21, 2001

224. Legal and Ethical Issues of Patenting Human DNA-Sequences, 22. Symposium of the AGNP - Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie, Universität Erlangen-Nürnberg, September 28, 2001

225. Reversal of the Burden of Proof, The Principle of "Fair and Equitable Procedures" and Preliminary Injunction Under the TRIPS Agreement, Seminar "Hungarian and International Tendencies in Enforcement of Patent Law," Organized by World Jurist Association (WJA), Supreme Court of the Republic of Hungary, Budapest, October 8, 2001

226. Product Patents on DNA Sequences and Possible Solutions for Reducing Dependencies Under the EU Biotech Directive of 1998, Second International Conference on Intellectual Property Rights and Biotechnology, Jointly organized by Intellectual Property Office, Ministry of Economic Affairs of Taiwan and The Graduate Institute of Technology and Innovation Management, National Chengchi University and the Asia Foundation in Taiwan, College of Commerce, National Chengchi University, Taipei, November 16, 2001

227. Importance of the Patent for the Universities: A Special Aspect, The Grace Period, Conference "A Community Patent for Europe," organized by the Ministry of Economic Affairs of the Belgian Presidency of the European Union, Liège, November 29, 2001

228. Genetic Inventions and Patents - A German Empirical Survey, BMBF & OECD Workshop "Genetic Inventions, Intellectual Property Rights and Licensing Practices", Berlin, January 24, 2002

229. Gene Patenting and Developing Countries, Conference "How Intellectual Property Rights Could Work Better for Developing Countries and Poor People", organized by the United Kingdom Commission on Intellectual Property Rights, The Royal Society, London, February 22, 2002

230. Pre-Grant Appeal and Post-Grant Review in the Field of Patents - From a European Perspective, 2nd International Patent Appeal Examination Symposium organized by the Japanese Patent Office, Tokyo, March 7, 2002

231. Die Diskussion um die Neuheitsschonfrist in Europa, Fachgespräch zur Neuheitsschonfrist veranstaltet vom Bundesministerium für Bildung und Forschung, Wissenschaftszentrum Bonn-Bad Godesberg, March 12, 2002

232. A Pleading Pro Grace Period, Conference ”Pros and Cons on Grace Period”, The Royal Society, London, March 14, 2002

233. Novelty Based on Discoveries, Indications and Technical Features in EPO Practice, Back to Basics - Novelty and Technical Character in Patents, International Symposium organised by the Finish National Group of AIPPI, Helsinki, March 18, 2002

234. Patents and Health Issues, WIPO Conference on International Patent System, Geneva, March 25, 2002

235. Product Patent on DNA-Sequences - An Obstacle for Implementing the EU Biotech Directive of 1998?, Colloquium on ”Human Genome Project, Patenting Genetic Products”, Washington University, School of Law and School of Medicine, St. Louis, April 12, 2002

236. Novelty and Inventive Step as Patentability Requirements, Direct Applicability of the TRIPS Agreement and Provisional Measures Under Article 50 TRIPS, Patent Seminar of the "Deutsche Stiftung für internationale rechtliche Zusammenarbeit," Supreme Court of the Republic of Slovenia, Ljubljana, May 13, 2002

237. The Right to Protect Intellectual Property in Plant Science and How to Communicate This With the Public, Syngenta Lecture, Syngenta AG, Basel, May 23, 2002

238. Produktpatente auf DNA Sequenzen, Jahrestagung der Deutschen Vereinigung für gewerblichen Rechtschutz und Urheberrecht, Munich, May 30, 2002

239. Basic Principles of the EU-Directive 98/44/EC on the Legal Protection of Biotechnological Inventions - State and Problems of its Implementation into National Laws of the EU-Member States, Symposium ”Genomics and Public Policy” of the Policy Research Initiative Canada, Toronto, June 7, 2002

240. Patentierung in der Tierzucht - Rechtsfragen und Auswirkungen auf die Züchter in Deutschland und in Entwicklungsländern, Tierwissenschaftliches Seminar, Institut für Tierproduktion in den Tropen und Subtropen, Universität Hohenheim, July 1, 2002

241. Produktpatente auf DNA Sequenzen, Ethikbeirat der Novartis AG, Basel, July 3, 2002

242. Wissensproduktion und Aneignung des Wissens – Zur neuen Rolle der Hochschule als Innovationskraft in der globalisierten Wirtschaft – 5. Steinheimer Gespräche des Fonds der chemischen Industrie im Verband der chemischen Industrie e.V., Hanau-Steinheim, July 6, 2002

243. Ethical Issues in Patent Law - Biotechnology and Research Ethics - A European Perspective –, CASRIP 2002 High Technology Protection Summit, University of Washington, School of Law, Seattle July 20, 2002

244. An Updating Concerning the Protection of Biotechnological Inventions, Including the Scope of Patents for Genes, 11th European Patent Judges Symposium, Copenhagen, September 19, 2002

245. Die Kontroverse um Biopatente – Gründe und Auswirkungen, Landeskuratorium Hamburg/Schleswig-Holstein des Stifterverbandes für die Deutsche Wissenschaft, Hamburg, September 25, 2002

246. The Future of the European Patent System, Keynote lecture, Opening Ceremony of IXth Magister Lucentinus, University of Alicante, October 2, 2002

247. Measures Necessary for the Balanced Co-existence of Patents and Plant Breeders' Rights – A Predominantly European View, WIPO-UPOV Symposium on the Co-existence of Patents and Plant Breeders' Rights in the Promotion of Biotechnological Developments, organized by the World Intellectual Property Organization (WIPO) and the International Union for the Protection of New Varieties of Plants (UPOV), Geneva, October 25, 2002

248. The Role of Intellectual Property in the Global Knowledge Based Society (Slov.), Workshop "Intellectual Property as Opportunity, Challenge and Necessity on the Occasion of Entering into EU," Chamber of Commerce of the Republic of Slovenia, Ljubljana, November 15, 2002

249. The European and the International Patent System – Principles and Examples (Slov.), Workshop "Intellectual Property as Opportunity, Challenge and Necessity on the Occasion of Entering into EU," Chamber of Commerce of the Republic of Slovenia, Ljubljana, November 15, 2002

250. Protection of Computer-Related and Business Model Inventions, Opening Address "International Forum: Protection of Computer-Related and Business Model Inventions," organized by the European Patent Office in co-operation with the Max Planck Institute and the European Patent Institute, European Patent Office, Munich, November 21, 2002

251. Topical Issues in Patent Law, Max Planck Legal Forum Workshop, Schloss Elmau, November 22, 2002

252. Our New LL.M. Program in IP Law at the Max Planck Institute, Conference "Get a Global Competence in IP Profession – Human Resource Development Necessary for the IP-Based Economy," co-organized by the Research Center for Advanced Science and Technology (RCAST), the University of Tokyo and The Intellectual Property Association of Japan, Academy Hall, Tokyo, November 28, 2002

253. The Ethics of Patenting DNA, Discussion Paper by the Nuffield Council on Bioethics, Genomics Momentum 2002 Conference, organized by the Netherlands Genomics Initiative, The Hague, December 4, 2002

254. Academia New Powerful Player in Innovation, Descartes-Prize 2002 Award Ceremony, organized by the European Commission, European Patent Office, Munich, December 5, 2002

255. The EU-Directive 98/44 and its Implementation in the Member States, European Forum for Innovation 2002, organized by European Grand Prix Commission, Monte-Carlo, December 7, 2002

256. Patentschutz durch TRIPS-Abkommen; Ausnahmeregelungen und Praktiken und ihre Bedeutung, insbesondere hinsichtlich pharmazeutischer Produkte, 41. Bitburger Gespräche, organized by the Stiftung Gesellschaft für Rechtspolitik, Bitburg, January 10, 2003

257. Science as Generator and User of Intellectual Property Rights, OECD Global Science Forum, Workshop on Best Practices in International Scientific Cooperation jointly organized by OECD and Japanese Ministry of Education, Tokyo, February 13, 2003

258. TRIPS Agreement and Access to Medicines, Symposium on Recent Trends of Intellectual Property, jointly organized by Intellectual Property Association of Japan and Japan Bio-Industry Association, Tokyo, February 14,2003

259. The Aftermath of Doha – Patents an Obstacle to Access Drugs, Virginia School of Law, Charlottesville, April 4, 2003

260. Patents on Biomaterials. A New Colonialism?, Spring Conference "Bioethics in a Small World", Europäische Akademie zur Erforschung von Folgen wissenschaftlich-technischer Entwicklungen, Bad-Neuenahr, April 12, 2003

261. European Models of Research Exemption, Workshop „Exploring Options for Establishing a Research Exemption", American Association for the Advancement of Science (AAAS), Washington, D.C., April 24, 2003

262. Patents on Genes – What Constitutes the Invention?, 1st European Conference in Functional Genomics and Disease, organized by the European Science Foundation (ESF), Prague, May 16, 2003

263. Compulsory Licensing as a Result of Abuse of Dominant Market Position, Conference Competition and Intellectual Property: Transatlantic Perspectives, Covington & Burling, Brussels, June 12, 2003

264. Geistiges Eigentum und Welthandelsrecht – Vernunftehe auf Zeit?, Symposium „Zukunftsfragen des Welthandelsrechts" des Max-Planck-Instituts für Geistiges Eigentum, Wettbewerbs- und Steuerrecht, Munich, June 27, 2003

265. The Munich Intellectual Property Law Center – A New Player in Teaching IP, Workshop „IP Teaching and IP Training Materials," organized by the European Patent Office International Academy and Ministero delle Attività Produttive, Torino, July 3, 2003

266. Der Beitrag Deutschlands zur Entwicklung des internationalen gewerblichen Rechtsschutzes, Festvortrag im Rahmen des Festakts "100 Jahre Beitritt Deutschlands zur Pariser Verbandsübereinkunft zum Schutz des gewerblichen Eigentums", Veranstaltet vom Deutschen Patent- und Markenamt, dem Europäischen Patentamt und der Deutschen Vereinigung für Gewerblichen Rechtsschutz und Urheberrecht, Munich, July 14, 2003

267. Statutory Research Exemption – Experience of European Countries, CASRIP 2003 High Technology Protection Summit, University of Washington School of Law, Seattle, July 25, 2003

268. TRIPS Agreement and Access to Medicines, CASRIP 2003 High Technology Protection Summit, University of Washington School of Law, Seattle, July 25, 2003

269. The New LL.M. Programme in IP Law at the Munich Intellectual Property Law Center, ATRIP Annual Conference, Tokyo, August 6, 2003

270. Present and Future of the German Employees' Inventions Law, Symposium "Truly International Perspective for Current IP Issues", co-organized by Research Center for Advanced Science and Technology (RCAST) of the University of Tokyo and by International Association for the Advancement of Teaching and Research in Intellectual Property (ATRIP), Tokyo, August 7, 2003

271. Patents and Access to Medicines – From a Developed Country Perspective, Symposium "Truly International Perspective for Current IP Issues", co-organized by Research Center for Advanced Science and Technology (RCAST) of the University of Tokyo and by International Association for the Advancement of Teaching and Research in Intellectual Property (ATRIP), Tokyo, August 7, 2003

272. Stellungnahme zum Gesetzesentwurf der Bundesregierung "Entwurf eines Gesetzes zur Reform des Geschmacksmusterrechts (Geschmacksmusterreformgesetz) BT-Drucksache 15/1075, Öffentliche Anhörung im Rechtsausschuss des Deutschen Bundestages, Berlin, September 24, 2003

273. On the Role of Patents in the Globalized „Knowledge Based" Economy (in Serb), lecture given on the occasion of the Award of a Honorary Doctorate, University of Kragujevac, Kragujevac, September 26, 2003

274. European Trends in Access and Benefit-Sharing Policy From an Intellectual Property Rights Perspective, International Symposium on Commercial Prospects of Access to and Benefit-Sharing of Genetic Resources, jointly organized by the United Nations University Institute of Advanced Studies and Japan Bioindustry Association, Tokyo, September 30, 2003

275. Patenting New Technologies – Recent Developments, "Patinnova-03 Conference", jointly organized by the EU-Commission and the European Patent Office, Luxembourg, November 12, 2003

276. Intellectual Property and Investment in Research, "3% Workshop" organized by the Committee on Industry and External Trade, Research and Energy, European Parliament, Brussels, December 2, 2003

277. Patenting in the Area of Genomics and Proteomics – Brief Status Report on the EU and US Law, Patent Facilitating Center, Indian Department of Science and Technology, New Delhi, January 20, 2004, and International Center for Genetic Engineering and Biotechnology, New Delhi, January 21, 2004

278. Panelist, Session "What Happens When the US Stops Discovering Drugs?" together with H.A. McKinell (CEO, Pfizer Inc.) M. McClellan (Commissioner, US Federal Drug Agency), A. Piramal (Chairman, Piramal, India), F.S. Collins (Director, National Human Genome Center), G. Moore (Managing Partner, TCG Advisors), World Economic Forum, Davos, January 22, 2004

279. Can all items be owned?, Session "What is this Thing Called Ownership?", World Economic Forum, Davos, January 22, 2004

280. Legal Framework for Protecting Human Stem Cell Technology, Private Dialogue on "Ethical Questions Related to Embryonic Human Stem Cell Research," World Economic Forum, Davos, January 23, 2004

281. On the New Role of Intellectual Property Rights in the Globalized Economy, Intellectual Property Academy of the National University of Singapore, Singapore, February 20, 2004

282. Intellectual Property and Science – A Complex Partnership, General Assembly of All European Academies (ALLEA), Belgian Royal Academy of Sciences, Brussels, March 25, 2004

283. International IP Standards for Protecting Inventions in Stem Cell Technology, 2nd International Meeting Stem Cell Network North Rhine Westphalia, Bonn-Bad Godesberg, April 2, 2004

284. Protection of Inventions in Plants and Plant Varieties – A European Perspective, Conference "Seeds of Change: Intellectual Property for Agricultural Biotechnology", University of Illinois at Urbana-Champaign, April 9, 2004

285. European patent, Community patent and Europe of Technologies, Seminar on "Il futuro dell'Europa delle technolgie," organized by the Universitá Ca' Foscari di Venezia, Venice, May 7, 2004

286. One Hundred Years of Japan Institute of Invention and Innovation, Address at Precentennial Celebration for the Commemorative Ceremony and International Symposium in Commemoration of the 100th Anniversary of the JIII, Tokyo, May 24, 2004

287. The Role of Intellectual Property Culture as Contributing to Social Stability, International Symposium held on the occasion of the 100th Anniversary of Japan Institute of Invention and Innovation, Tokyo, May 25, 2004

288. Intellectual Property Rights, Human Rights and the Public Domain, International Conference "TRIPS Agreement 10 Years Later," organized by the EU-Commission, Brussels, June 24, 2004

289. Intellectual Property and Human Rights, 2004 CASRIP High Technology Protection Summit, University of Washington School of Law, Seattle, July 16, 2004

290. Genetic Inventions and Patents, Results of a German Empirical Survey, 2004 CASRIP High Technology Protection Summit, University of Washington School of Law, Seattle, July 17, 2004

291. Employees' Inventions and the Innovation Law – An International Perspective, XXIV National Seminar on Intellectual Property: Economic Growth with Social Responsibility, organized by Associaçao Brasileira da Propriedade Intelectual, Brasilia, August 17, 2004

292. Protection of Further Medical Uses and the Research Exemption – As Means Serving Medical Progress, XXIV National Seminar on Intellectual Property: Economic Growth with Social Responsibility, organized by Associaçao Brasileira da Propriedade Intelectual, Brasilia, August 18, 2004

293. Driving Investment: The Critical Link Between Intellectual Property Protection and Private Sector Investment, EuroScience Open Forum 2004, Stockholm, August 26, 2004

294. Zur Neuen Rolle des Geistigen Eigentums in der globalisierten Wirtschaft – Ist Europa gerüstet? Kodifikation, Europäisierung und Harmonisierung des Privatrechts, Internationale Wissenschaftliche Konferenz VIII, Dies Luby Iurisprudentiae Stefan Luby Stiftung, Universität Trnava, Smolenice, September 16, 2004

295. Future Perspectives for the Protection of Intellectual Property and How to Deal with it in Teaching and Research, Seminar: Intellectual Property Research: The Future, Law Faculty, Cambridge University, October 1, 2004

296. On the New Role of Intellectual Property Rights in the Globalized Economy, The First Tongji IP Forum, Tongji University & IP Office of Shanghai, Municipality Shanghai, October 8, 2004

297. New Rules for Protecting Inventions in the Area of Genomics, Proteomics and Stem Cells in Europe, Sino-German Seminar: Science, Technology and Intellectual Property Protection in the 21st Century, Beijing, October 9, 2004

298. On the New Role of Intellectual Property Rights in the Globalized Economy, Gran Forum of the Most Honourable Jurists, Renmin University of China Law School, Beijing, October 10, 2004

299. Intellectual Property and Investment in Research, Conference "New Science, New Industry – The Challenges for the New Europe", Accademia nazionale dei lincei and Fondazione Edison, Rome, October 13, 2004

300. La portata del brevetto biotecnologico Situazione e prospettiva nelle Unione Europea, Seminario "Biotecnologie e brevetti", Libera Università Internazionale degli Studi Sociali Guido Carli, Rome, October 14, 2004

301. Zur Patentierbarkeit von humanen embryonalen Stammzellen – Ein internationaler Vergleich, Ethikbeirat des Robert-Koch-Instituts, Berlin, November 17, 2004

302. Biowissenschaftliche Eigentumsrechte - Belange der Entwicklungsländer, Kongress der Konrad-Adenauer-Stiftung e.V. „Biowissenschaften und ihre völkerrechtlichen Herausforderungen", November 22, 2004, Königswinter

303. Intellectual Property and Competition, SIPCon 2004, of the Siemens AG, Miesbach, December 2, 2004

304. GATT and TRIPS, Inseparable Guarantors of the Globalized Economy, The 2004 Shanghai International IP Forum: Intellectual Property & City's Competitiveness, organized by Shanghai Intellectual Property Administration, Shanghai, December 10, 2004

305. The Role of GATT and TRIPS for the Globalized Economy, Cornell University Law School, Ithaca, N.Y., April 11, 2005

306. Basic Issues of Patenting DNA Sequences and Human Embryonic Stem Cells, Slovenian Academy of Science and Art, Ljubljana, April 25, 2005

307. The New Circumstances of IP Protection and its Developing Tendencies and Hotspots, lecture delivered on the occasion of an award of Honorary Professorship, Huazhong University of Science and Technology, Wuhan, May 9, 2005

308. The Impact of GATT and TRIPS on Economic Development of China, Zhongnan University of Economics and Law, Wuhan, May 9, 2005

309. Protecting Inventions in the Area of Biotechnology and Software in Europe, Huazhong University of Science and Technology, Wuhan, May 10, 2005

310. Protecting Biotechnological Inventions in Europe – Statutory Rules and Case Law, Tongji University, Shanghai, May 19, 2005

311. IP and Economic Development and other World Issues in IP, International Association for the Protection of Intellectual Property (AIPPI) Australian Group, Melbourne, May 26, 2005

312. Community Patents and Central Patent Enforcement in Europe, Annual Conference of Licensing Executive Society (LES), Munich, June 14, 2005

313. Challenges Faced by Academic Institutions in Teaching of Intellectual Property and Carrying out Intellectual Property Research, International Symposium on Intellectual Property (IP) Education and Research, World Intellectual Property Organization, Geneva, June 30, 2005

314. Compound (DNA-Sequence) Protection Eroded? – An Academic Point of View, Seminar "Compound Protection and its Erosion in Germany: How Stable is it Elsewhere? – An International Assessment", organized by Vossius & Partner, Munich, July 1, 2005

315. TRIPS, TRIPS-plus or TRIPS-minus – Remarks on the Future of International Protection of Intellectual Property Rights, The 22nd Congress on the Law of the World, "The Rule of Law and Harmony of International Society", organized by the Supreme Court of China, Beijing, September 6, 2005

316. Disclosure of Origin or Source of Genetic Resources & Associated Traditional Knowledge in Patent Application – Proposal of the European Community and its Member States, Conference BioJapan 2005, Yokohama, September 7, 2005

317. IP Rights as Means of Appropriation and Distribution of Knowledge, World Science Forum “Knowledge, Ethics and Responsibility”, Hungarian Academy of Sciences, Budapest, November 10, 2005

318. The Concept and Meaning of Quality in the European Patent System – An Academic View supported but by own thoughts – Conference on Quality in the European Patent System, European Patent Office, The Hague, November 21, 2005

319. Patentierung von humanen Stammzellen nach EU-Recht und in der Praxis des EPA, Tagung "Perspektiven und Risiken der Stammzelltherapie" der Europäischen Akademie der Wissenschaften und Künste, München, 20. Januar 2006

320. Patenting of Genes and Life Forms, and the Impact of Patenting on Upstream Science, WIPO Open Forum on the Draft SPLT, Geneva, March 3, 2006

321. Grace Period – First Real Chance after 70 Years, WIPO Open Forum on the Draft SPLT, Geneva, March 3, 2006

322. Justifying Intellectual Property in the Society of Knowledge, Conference "Markets and Innovation in the Society of Knowledge", Center for Research on Markets, Innovation and Technology, Department of Private Law, Faculty of Law, University of Oslo, Oslo, May 15, 2006

323. How Effective are Research Exemptions in Patent Law? The German Experience, Research Use of Patented Inventions CSIC/OECD/OEPM Conference, Madrid, May 17, 2006

324. The Impact of the New World Order on Economic Development, Conference on the Role of the United States in World Intellectual Property Law, The John Marshall Law School Chicago, May 25, 2006

325. Patents and Biotechnology Development in Europe, Conference Biotechnology Patents and Policy: What's the Evidence, University of Alberta, Banff, Alberta, Canada, May 26, 2006

326. The Impact of GATT and TRIPS on Economic Development, First CEI International Conference on Transfer in Life Sciences, A North-South Dialogue, Trieste, June 12-14, 2006

327. Stem Cell Research and Stem Cell Patenting in Europe, 2nd EuroScience Open Forum, Munich, July 18, 2006

328. Schränkt der Patentschutz für Gensequenzen die Freiheit der Forschung ein?, Diskussionsabend der Stiftung "Forschung für Leben", Collegium Helveticum, Zürich, August 24, 2006

329. Panel Quality Issues in the Patent System, 1st EPIP Conference of the EPIP Association on "Policy, Law and Economics of Intellectual Property," European Patent Office, Munich, September 7, 2006

330. Chairman Session Intellectual Property Rights to Work for All, Science and Technology in Society (STS) Forum, Kyoto, September 10-12, 2006

331. Der Einfluss von GATT und TRIPS auf die wirtschaftliche Entwicklung, Bird & Bird Patentseminar, Düsseldorf, September 21, 2006

332. Harmonisierung des internationalen Patentrechts, Symposium "25 Jahre Deutsch-Chinesische Zusammenarbeit auf dem Gebiet des Geistigen Eigentums", Deutsches Patent- und Markenamt, München, 22. September 2006

333. Patents on God's Creation – To Whose Benefit?, "Analysis, Exploitation and Conservation of Biodiversity," Annual Meeting 2006 of the German Association for Gene Diagnostics (AGD e.V.), Cologne, September 22, 2006

334. The Role of IPRs in the New World Economic Order, 40th Congress of the International Association for the Protection of Intellectual Property (AIPPI), Gothenburg, October 11, 2006

335. Patentierung von humanen embryonalen Stammzellen – ein rechtsvergleichender Überblick, Symposium "Patentierbarkeit der Forschungsergebnisse im Zusammenhang mit humanen embryonalen Stammzellen", Chungnam National University Research Center for Intellectual Property, Daejon, Korea, Oktober 27-28, 2006

336. Intellectual Property and Development: Innovation, IP Law and its Impact on Social, Cultural and Economic Development: Perspectives from India, Europe and WIPO, International Seminar on Intellectual Property Education and Research, NALSAR University of Law, Hyderabad, November 16-17, 2006

337. On the Role of Law and Ethics in the Globalized Economy, Brainstorming Meeting of EASA Members, Munich, December 15, 2006

338. Flexibilities in the Patent System, Colloquium on Selected Patent Issues, World Intellectual Property Organization, Geneva, February 16, 2007

339. China and India – The Two New Players in the Intellectual Property Game, George Washington University Law School, Washington D.C., March 27, 2007

340. The Impact of GATT 94 and TRIPS on Economic Development – Not on Development Agenda, European Patent Forum, European Patent Office, April 18-19, 2007

341. Intellectual Property Rights, Innovation and Public Goods, at Reconciling National Security and Economic Development – A Challenge for the G8, The German Marshall Fund of the United States and Alfred Herrhausen Society's Conference, Berlin, May 24, 2007

342. Patentierung von humanen embryonalen Stammzellen – Gegenwärtiger Stand, 30. Sitzung der Zentralen Ethik-Kommission für Stammzellenforschung (ZES), Robert-Koch-Institut, Berlin, 13. Juni 2007

343. The Role of Law and Ethics in the Globalized Economy, Senate of the European Academy of Sciences and Arts, Salzburg, July 6, 2007

344. Patenting of Genes and Exploiting as Well as Enforcing such Patents in Europe as Compared with the US, Session on Gene Patents and Licensing Practices, Secretary's Advisory Committee on Genetics, Health and Society, US Department of Health, Washington DC, July 10, 2007

345. The Impact of TRIPS on Global Economics, European Patent Academy Public Seminar: "The Industrial Property Business", European Patent Office, Munich, July 12, 2007

346. Ethical Issues in Patenting Human Embryonic Stem Cells – A European Problem? CASRIP High Technology Protection Summit, Seattle, July 21, 2007

347. Patents on Human Embryonic Stem Cells and on Transgenic Plants - What have they in Common? Discussion of some European Dilemmas, Seminar at Scuola Superiore di Catania, Catania, September 19, 2007

348. Patents on Human Embryonic Stem Cells and on Transgenic Plants - What have they in Common? Discussion of some European Dilemmas, University for Law and Economics, Wuhan, October 25, 2007

349. IP Infrastructures in Asia's Emerging Markets, The Industrial Property Perspective, The 5th Shanghai International IP Forum: The Impact of WTO TRIPS Agreement on the Economic Development of Asian Countries, Shanghai October 26, 2007

350. Intellectual Property/Academic Freedom? A complex Relationship within the Innovation Ecosystem, International Symposium "The University in the Market Place" organized by Academia Europaea and Wenner-Gren Foundation, Stockholm, November 2, 2007

351. Patents and Biotechnology, WIPO International Seminar on the Strategic Use of Intellectual Property for Economic and Social Development, organized by World Intellectual Property Organization (WIPO) in cooperation with The Slovenian Intellectual Property Office (SIPO), Ljubljana, November 15, 2007

352. Intellectual Property Rights and Competition Policy, WIPO International Seminar on the Strategic Use of Intellectual Property for Economic and Social Development, organized by World Intellectual Property Organization (WIPO) in cooperation with The Slovenian Intellectual Property Office (SIPO), Ljubljana, November 15, 2007

353. Is There a "Global Warming of Patents"?, "Managing, Financing and Protecting Innovation", International Conference on the Occasion of the Fourth Venice Award for Intellectual Property Culture, jointly organized by The European Patent Office , the Italian Patent and Trademark Office and Venice International University, San Servolo Island/Venice, November 22, 2007

354. The Strategic Importance of Patenting after TRIPS in Europe and Beyond, Seminar "The Importance of Intellectual Property for Companies", Università IULM Feltre, January 30, 2008

355. The Strategic Importance of Patenting after TRIPS in Europe and Beyond, Seminar "Patent Policy in Europe and Turkey", University of Ankara Law School, January 31, 2008

356. Bilaterale Verträge und bessere Koordination als Mittel der TRIPS-Fortschreibung, Internationales Fachhearing „Der Schutz Geistigen Eigentums in einer Globalisierten Welt", jointly organized by the Bavarian State Government and the Munich Intellectual Property Law Center (MIPLC), Munich, February 29, 2008

357. International Protection of Intellectual Property Beyond TRIPS, Cornell University School of Law, Ithaca, New York, April 7, 2008

358. Patenting and Licensing in Genetic Testing, Workshop of the European Society of Human Genetics, Royal Belgium Academy of Sciences, Brussels, April 24, 2008

359. Opening of the Conference "The Role of Law and Ethics in the Globalized Economy", Bavarian Academy of Sciences and Humanities, Munich, May 22/23, 2008,

360. Internationale Harmonisierung des Patentrechts: Möglichkeiten – Vor- und Nachteile für Wirtschaft und Wissenschaft, Expertengespräch „Schutz und Nutzungsrechte in Forschungskooperationen zwischen Wirtschaft und Wissenschaft", Stifterverband für die Deutsche Wissenschaft, Berlin, 28. Mai 2008

361. The Strategic Importance of Patenting After TRIPS in Europe and Beyond, Conference "Intellectual Property and Development", SWISSCAM Brazil, Swiss-Brazilian Chamber of Commerce, Sao Paulo, June 9, 2008, Rio de Janeiro, June 10, 2008, and Brasilia, June 11, 2008

362. Biomedicine and Patents, The European Approach, Conference "Law Meets Industry: Biosciences Patents", University of Haifa, June 16, 2008

363. Exhaustion of Patent Rights – Recent Developments in Europe, CASRIP High Technology Summit 2008, University of Washington, Seattle, July 25, 2008

364. Development and Development Agenda Anomalies or Complements? SFIR & AIPPI Sweden 100 Years Centennial Celebration, Stockholm, August 27, 2008

365. Definition of Novelty, Novelty Criteria & Other Issues, EU-China Workshop on the Chinese Patent Law, Harbin, September 24, 2008

366. Compulsory Licensing – Introduction to the Role and Limitations, EU-China Workshop on the Chinese Patent Law, Harbin, September 25, 2008

367. Abuse of Patents and Forfeiture of Claims, Counter Claims for Damages for Malicious Litigation, EU-China Workshop on the Chinese Patent Law, Harbin, September 25, 2008

368. Perspectives on Biotechnology Patents: Laws and Regulations in Europe, Biolatina 2008 - Biotechnology in Latin America, 8th Latin-American Congress - Fair on Biotechnology, 4th Brazilian Congress on Biotechnology, Sao Paulo, October 1, 2008

369. Zur Rolle des Rechts und der Ethik in der Globalisierten Wirtschaft, Münchener Wissenschaftstage, Ludwig-Maximilians Universität, Munich, October 21, 2008

370. The Importance of IP Teaching in Universities, Conference Disseminating IP Knowledge in Universities, European Patent Office, The Hague, December 2, 2008

371. Biotechnology and Patents from a European Perspective, Salzburg Global Seminar – New Models of Intellectual Property: Predictability and Openness as Spurs to Innovation, Salzburg, December 7, 2008

372. Clouds on European IP Sky & The (Weather) Forecast, Conference on EU IP Enforcement: Present and Future, Waseda Law School, Tokyo, January 17, 2009

373. Legal Protection of Biotech Inventions and Medicines in the USA and Europe, keynote speech, International Conference on Biotech Medicines Innovations in Developing Countries: IP Protection and Regulations for Safety and Efficacy, National Graduate Institute for Policy Studies, Tokyo, February 12, 2009

374. The Role of Intellectual Property in the Globalized Economy, Grinnell College, Grinnell, Iowa, March 31, 2009

375. Patenting of Human Embryonic Stem Cells in Europe after the WARF Decision of the Enlarged Board of Appeal of the European Patent Office, ESTOOLS Open Symposium on Stem Cell Science, Accademia Nazionale dei Lincei, Rome, May 27, 2009

376. Patents on Biomaterial, Department for Mercantile Law of the University of South Africa, Pretoria, July 2, 2009

377. Promoting Access to Medicines Through Balancing Patent Rights and Responsibilities, WIPO Conference on Intellectual Property and Public Policy Issues, Geneva, July 14, 2009

378. Patent Law Harmonization - Do We Need a New International Patent Law? Session: Intellectual Property Rights, Patents and Standards in Global Markets, 4th Transatlantic Market Conference - Transatlantic Cooperation for Growth and Employment, Washington, D.C., July 20, 2009

379. Scholarly Contribution to Comparative Patent Law by Martin Adelman, Patent System as Stimulus for Economy, 2009 High Technology Protection Summit, CASRIP, Seattle, July 24, 2009

380. Business in the Global Eco-System: Initiatives to Foster Innovation (keynote speech), Conference "Trading Ideas": The Future of IP in Asia and Pacific, organized by the Intellectual Property Office of Singapore, Singapore, July 30, 2009

381. The Role and Task of Science & Technology for Sustainable Development - an IP Lawyer's Point of View -, METI-JETRO Symposium 2009 "Boosting Science and Technology Through Industrial Collaboration 2009", Tokyo, October 7, 2009

382. Patent Application as an Abuse of Dominant Market Position under Article 82 EC Treaty? Session "New Frontiers in Antitrust Liability: Abuses of Patent Settlements and Standard-Making", Congress of International League of Competition Law, Vienna, October 24, 2009

383. Laudatio for Sir Professor Roger Elliott, Oxford, ALLEA, Hungarian Patent Office and the World Science Forum Symposium in Honour of Sir Roger Elliott, Hungarian Patent Office, Budapest, November 4, 2009

384. Does Stem Cell Research in Europe Use Human Embryos for Industrial or Commercial Purposes? A Comment of EBA G 02/06 Decision, ALLEA/Hungarian IP Office/World Science Forum Symposium "Intellectual Property rights in the European Research Area: Grand Challenges and New Opportunities", Budapest, November 4, 2009

385. Strategic Tasks of ALLEA Standing Committee on Intellectual Property Rights, ALLEA Extraordinary Strategy Meeting, Royal Netherlands Academy of Arts and Science, Amsterdam, November 17, 2009

386. Does Stem Cell Research in Europe Use Human Embryos for Industrial or Commercial Purposes?, Meeting of the Novartis Advisory Board on Ethics, Basel, November 24, 2009

387. Promoting Access to Medicines Through Balancing Patent Rights and Responsibilities, Inaugural Ceremony of the Intellectual Property Institute of Renmin University of China, Beijing, November 26, 2009

388. Application of European Intellectual Property Experience in Emerging Countries, Conference "Intellectual Property Protection and Management", Peking University, Beijing, November 27, 2009

389. Intellectual Property Protection in Europe, The Third Tongji International Intellectual Property Forum, Tongji University, Shanghai, December 2, 2009

II. Membership in Scientific Organizations, Professional Associations

1. International Association for the Advancement of Teaching and Research in Intellectual Property (ATRIP), President (1993-1995), President Elect (1991-1993), Treasurer (1987-1991)

2. International Association for the Protection of Industrial Property (AIPPI). Programme Committee (Member 1992-1994, Deputy Chairman 1994-1997, Chairman 1997-), Co-Chairman of Special Committee Q 144 - Publications (1998); Chairman of the Special Committee Q 114 - Biotechnology (1992-1998). Member of the Executive Committee since 1982; Member of the Board of the German National Group (1990-)

3. Human Genome Organisation (HUGO), Chairman of the Intellectual Property Rights Committee (1995-2006)

4. German Association for the Protection of Industrial Property and Copyright [Vice-President (2005-)], Member of the Executive Board (2001-) and Member of the Committee for Plant Breedings (1986) and of the Committee for Patent- and Utility Models Law (1992-)

5. Association Littéraire et Artistique International (ALAI)

6. Association for Comparative Law.

7. Member of the Standing Committee "Intellectual Property Rights" of the All European Academies - ALLEA (1998-)

III. Membership in Advisory Bodies

1. Member of the Standing Advisory Committee before the European Patent Office

2. Member of the Research Advisory Board of the Research Fund of the European Patent Organisation

3. Member of the Senate Commission on Basic Issues of Gene Research of the German Research Foundation (Senatskommission für Grundsatzfragen der Genforschung der DFG) 1993-1999

4. Member of Advisory Board of the Worldwide Academy of the World Intellectual Property Organisation (WIPO)

5. Member of the Advisory Board of the Intellectual Property Office of the Republic of Slovenia

6. Member of the Administrative Council, Center for International Industrial Property Studies (CEIPI), Université Robert Schuman

7. Member of the Executive Council, Center for Advanced Study and Research on Intellectual Property (CASRIP), University of Washington School of Law, Seattle

8. Member of the International Board of Assessors, Intellectual Property Research Center, University of Melbourne

9. Member of the Advisory Council of the McCarthy Institute for Intellectual Property and Technology Law, University of San Francisco School of Law

10. Member of the Advisory Board of the Ifo Institute für Wirtschaftsforschung, Munich

11. Member of the Advisory Board of Intellectual Property Rights Annual Journal, Peking

12. Member Advisory Board, Creative and Innovative Economy Center, The George Washington University Law School, Washington D.C.

IV. Consulting Activities

1. Member EU Commission's Expert Group on Biotechnological Inventions (2002-)

2. Consultant to the OECD, Paris, on Biotechnology and Patent Protection, 1982-1985; 1991, 1995, 1996, 1999, 2000; Chair Expert Group on Guidelines for Licensing of Genetic Inventions (2004 -)

3. Consultant to World Intellectual Property Organization (WIPO), Geneva, on Questions of Industrial Property Protection of Biotechnological Inventions, 1985, 1986 and 1999

4. Consultant to the Commission of the European Economic Community for the preparation of the Draft for a Council Directive on the Legal Protection of Biotechnological Inventions, 1987-1989; On the Future European Patent System, 1995-1996; and on "Strategic Dimensions of Intellectual Property Rights in the Context of Technology Policy" (ETAN Working Group) (1998-1999)

5. Consultant to the Scientific Service of the German Bundestag (Parliament), 1996

6. Consultant to the European Patent Organisation on the Introduction of a Grace Period, 2000

7. Consultant to the German Federal Ministry of Justice, 2000

8. Consultant to the United Nations Conference on Trade and Development (UNCTAD), Geneva, on the Impact of technological and commercial changes on policies and legislation affecting the creation and transfer of technologies, 1987/1988

9. Consultant to the United Nations Industrial Development Organization (UNIDO), Vienna, 1989

10. Consultant to the World Bank, Washington D.C., 1991

11. Member of the Advisory Panel for the Human Genome Project and Patenting DNA Sequences, Office of Technology Assessment (OTA), Congress of the United States, 1993-1994

12. Consultant to the Ministry for Science and Technology of the Republic of Slovenia on the legislation in the field of employees' inventions, 1993-1994

13. Member of the Working Group of the Conference of the Presidents of German Universities (Deutsche Hochschulrektorenkonferenz) for the Preparation of Recommendations aimed to Incent Patent Applications from Universities and other Institutions of Higher Professional Education in Germany (Präsidial-Arbeitsgruppe zur Vorbereitung von Empfehlungen zur Förderung der Patentanmeldungen aus den Universitäten und Fachhochschulen in Deutschland) 1996

14. Member of the Working Group on Bio-Sciences of the Technology Council of The German Federal Chancellor (Bundeskanzler) 1996

15. Testified as Expert before the "Committee on Legal Affairs and Citizen's Rights", European Parliament, Brussels, June 10, 1996

16. Testified as Expert (”Auskunftsperson”) before the Special Committee on ”Gentechnik-Volksbegehren” of the Austrian Parliament, Vienna, October 24, 1997

17. Arbitrator with the Arbitration Court of the International Chamber of Commerce in Paris

18. Member of the WIPO Arbitration and Mediation Center’s List of Neutrals

V. Educational Work

1. Lecturing of Industrial Property at the Faculty of Law, University of Ljubljana, 1986-

2. Visiting Professor of Intellectual Property Law, Fall Semester 1989 and 1992, Spring Semester 1994, Fall 1996, Spring 1998, Cornell Law School, Cornell University, Ithaca, New York

3. Distinguished Visiting Professor of Law (Spring Semester 2001, 2002, 2003, 2004, 2006, 2007), Marshall B. Coyne Professor of International and Comparative Law (2004-), George Washington University School of Law, Washington, D.C.

4. Distinguished Visiting Professor of Law, University of Toronto, Faculty of Law, Spring 2005

5. Lecturing of German and European Patent Law, Faculty of Law, University of Munich, 1990-

6. Lecturing in the frame work of Post Diploma Studies on Intellectual Property, Federal Institute of Technology (Eidgenössische Technische Hochschule - ETH), Zürich, 1996-2000

7. Lecturing of Conflict of Laws Aspects in Intellectual Property, Postgraduate Studies, Faculty of Law, University of Zürich, 1996-1997

8. Co-director of the course on 'Intellectual Property Rights' at the Inter-University Center of Post Graduate Studies, Dubrovnik, 1988-1990

9. Permanent collaboration in the Seminar of the Max Planck Institute

10. Supervision of national and foreign doctorands in the Max Planck Institute

11. Lecturing in the Framework of the Summer Academy of the "Studienstiftung des Deutschen Volkes"

12. Member of Ph.D. Committees at Faculty of Law, University New Delhi; Faculty of Law, Erasmus University, Rotterdam; Faculty of Law, University of Tasmania, Hobart; Faculty of Law, University of Witwatersrand, Johannesburg; Faculty of Law, University of Ljubljana; Faculty of Law, Catholic University of Louvain, Louvain-la-Neuve, Brussels

13. Foreign Member of Promotion Committees at the Department of Agricultural Economics, Cornell University, Ithaca, N.Y.; Faculty of Law, University of Texas, Houston; Duke University, School of Law, Durham; Faculty of Law, University of Basel; University of Washington School of Law, Seattle; Swiss Federal Technical Institute (ETH), Zürich; McGill University Law School, Montreal

14. Visiting Professor of Law, Graduate Institute of Intellectual Property, National Chengchi University, Taipei

VI. Awards and Honors

1. Doctor Honoris Causa (Dr. jur. h.c.), University of Ljubljana (2001)

2. Doctor Honoris Causa (Dr. jur. h.c.), University of Kragujevac (2003)

3. Member of the Academia Europaea (2001-), Chair Law Section (2009-)

4. Member of the European Academy of Sciences and Arts (2001-), Dean Class of Social Sciences Law and Economics (2005-)

5. Slovenian Academy of Sciences and Arts, Corresponding Member (1995-)

6. Science Award 2000, upon proposal of the Max-Planck Society for the Advancement of Science, of the Foundation for the German Science (Stifterverband für die Deutsche Wissenschaft)

7. Honorary Director of the Intellectual Property Institute of the Tongji University, Shanghai (2004-)

8. Honorary Professor Tongji University, Shanghai (2004-)

9. Grand Cross of Merits of the Order of Merits of the Federal Republic of Germany by the President of the Federal Republic of Germany (Großes Verdienstkreuz des Verdienstordens der Bundesrepublik Deutschland) (2005)

10. Distinguished Visiting Professor of Law, Faculty of Law University of Toronto (2005)

11. Honorary Director of the German-Chinese Institute for Intellectual Property, Department of Management, Huazhong University of Science and Technology (HUST), Wuhan (2005-)

12. Honorary Professor, Huazhong University of Science and Technology (HUST), Wuhan (2005-)

13. Visiting Professor, Graduate Institute of Intellectual Property, Taipei (2005-)

14. Honorary Professor, Xiamen University, Xiamen, 2009

15. Inducted into IAM IP Hall of Fame 2007

16. Venice IP Award 2007 ("Premio Venezia per la Proprietà Intellettuale")

17. Katz-Kiley Fellow 1999 of the University of Houston Law Center

18. Member of Honour, International Association for the Protection of Intellectual Property (AIPPI), 2006

19. Medal of Merits, International Association for the Protection of Industrial Property (AIPPI), 1997

20. Diploma of Merits, International Association for the Advancement of Teaching and Research in Intellectual Property (ATRIP), 1991

EXHIBIT B

DIRECTIVE 98/44/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 6 July 1998

on the legal protection of biotechnological inventions

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 100a thereof,

Having regard to the proposal from the Commission [1],

Having regard to the opinion of the Economic and Social Committee [2],

Acting in accordance with the procedure laid down in Article 189b of the Treaty [3],

(1) Whereas biotechnology and genetic engineering are playing an increasingly important role in a broad range of industries and the protection of biotechnological inventions will certainly be of fundamental importance for the Community's industrial development;

(2) Whereas, in particular in the field of genetic engineering, research and development require a considerable amount of high-risk investment and therefore only adequate legal protection can make them profitable;

(3) Whereas effective and harmonised protection throughout the Member States is essential in order to maintain and encourage investment in the field of biotechnology;

(4) Whereas following the European Parliament's rejection of the joint text, approved by the Conciliation Committee, for a European Parliament and Council Directive on the legal protection of biotechnological inventions [4], the European Parliament and the Council have determined that the legal protection of biotechnological inventions requires clarification;

(5) Whereas differences exist in the legal protection of biotechnological inventions offered by the laws and practices of the different Member States; whereas such differences could create barriers to trade and hence impede the proper functioning of the internal market;

(6) Whereas such differences could well become greater as Member States adopt new and different legislation and administrative practices, or whereas national case-law interpreting such legislation develops differently;

(7) Whereas uncoordinated development of national laws on the legal protection of biotechnological inventions in the Community could lead to further disincentives to trade, to the detriment of the industrial development of such inventions and of the smooth operation of the internal market;

(8) Whereas legal protection of biotechnological inventions does not necessitate the creation of a separate body of law in place of the rules of national patent law; whereas the rules of national patent law remain the essential basis for the legal protection of biotechnological inventions given that they must be adapted or added to in certain specific respects in order to take adequate account of technological developments involving biological material which also fulfil the requirements for patentability;

(9) Whereas in certain cases, such as the exclusion from patentability of plant and animal varieties and of essentially biological processes for the production of plants and animals, certain concepts

[1] OJ C 296, 8.10.1996, p. 4 and OJ C 311, 11.10.1997, p. 12.
[2] OJ C 295, 7.10.1996, p. 11.
[3] Opinion of the European Parliament of 16 July 1997 (OJ C 286, 22.9.1997, p. 87). Council Common Position of 26 February 1998 (OJ C 110, 8.4.1998, p. 17) and Decision of the European Parliament of 12 May 1998 (OJ C 167, 1.6.1998). Council Decision of 16 June 1998.
[4] OJ C 68, 20.3.1995, p. 26.

in national laws based upon international patent and plant variety conventions have created uncertainty regarding the protection of biotechnological and certain microbiological inventions; whereas harmonisation is necessary to clarify the said uncertainty;

(10) Whereas regard should be had to the potential of the development of biotechnology for the environment and in particular the utility of this technology for the development of methods of cultivation which are less polluting and more economical in their use of ground; whereas the patent system should be used to encourage research into, and the application of, such processes;

(11) Whereas the development of biotechnology is important to developing countries, both in the field of health and combating major epidemics and endemic diseases and in that of combating hunger in the world; whereas the patent system should likewise be used to encourage research in these fields; whereas international procedures for the dissemination of such technology in the Third World and to the benefit of the population groups concerned should be promoted;

(12) Whereas the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPs) [1] signed by the European Community and the Member States, has entered into force and provides that patent protection must be guaranteed for products and processes in all areas of technology;

(13) Whereas the Community's legal framework for the protection of biotechnological inventions can be limited to laying down certain principles as they apply to the patentability of biological material as such, such principles being intended in particular to determine the difference between inventions and discoveries with regard to the patentability of certain elements of human origin, to the scope of protection conferred by a patent on a biotechnological invention, to the right to use a deposit mechanism in addition to written descriptions and lastly to the option of obtaining non-exclusive compulsory licences in respect of interdependence between plant varieties and inventions, and conversely;

(14) Whereas a patent for invention does not authorise the holder to implement that invention, but merely entitles him to prohibit third parties from exploiting it for industrial and commercial purposes; whereas, consequently, substantive patent law cannot serve to replace or render superfluous national, European or international law which may impose restrictions or prohibitions or which concerns the monitoring of research and of the use or commercialisation of its results, notably from the point of view of the requirements of public health, safety, environmental protection, animal welfare, the preservation of genetic diversity and compliance with certain ethical standards;

(15) Whereas no prohibition or exclusion exists in national or European patent law (Munich Convention) which precludes *a priori* the patentability of biological matter;

(16) Whereas patent law must be applied so as to respect the fundamental principles safeguarding the dignity and integrity of the person; whereas it is important to assert the principle that the human body, at any stage in its formation or development, including germ cells, and the simple discovery of one of its elements or one of its products, including the sequence or partial sequence of a human gene, cannot be patented; whereas these principles are in line with the criteria of patentability proper to patent law, whereby a mere discovery cannot be patented;

(17) Whereas significant progress in the treatment of diseases has already been made thanks to the existence of medicinal products derived from elements isolated from the human body and/or otherwise produced, such medicinal products resulting from technical processes aimed at obtaining elements similar in structure to those existing naturally in the human body and whereas, consequently, research aimed at obtaining and isolating such elements valuable to medicinal production should be encouraged by means of the patent system;

(18) Whereas, since the patent system provides insufficient incentive for encouraging research into and production of biotechnological medicines which are needed to combat rare or 'orphan' diseases, the Community and the Member States have a duty to respond adequately to this problem;

[1] OJ L 336, 23.12.1994, p. 213.

(19) Whereas account has been taken of Opinion No 8 of the Group of Advisers on the Ethical Implications of Biotechnology to the European Commission;

(20) Whereas, therefore, it should be made clear that an invention based on an element isolated from the human body or otherwise produced by means of a technical process, which is susceptible of industrial application, is not excluded from patentability, even where the structure of that element is identical to that of a natural element, given that the rights conferred by the patent do not extend to the human body and its elements in their natural environment;

(21) Whereas such an element isolated from the human body or otherwise produced is not excluded from patentability since it is, for example, the result of technical processes used to identify, purify and classify it and to reproduce it outside the human body, techniques which human beings alone are capable of putting into practice and which nature is incapable of accomplishing by itself;

(22) Whereas the discussion on the patentability of sequences or partial sequences of genes is controversial; whereas, according to this Directive, the granting of a patent for inventions which concern such sequences or partial sequences should be subject to the same criteria of patentability as in all other areas of technology: novelty, inventive step and industrial application; whereas the industrial application of a sequence or partial sequence must be disclosed in the patent application as filed;

(23) Whereas a mere DNA sequence without indication of a function does not contain any technical information and is therefore not a patentable invention;

(24) Whereas, in order to comply with the industrial application criterion it is necessary in cases where a sequence or partial sequence of a gene is used to produce a protein or part of a protein, to specify which protein or part of a protein is produced or what function it performs;

(25) Whereas, for the purposes of interpreting rights conferred by a patent, when sequences overlap only in parts which are not essential to the invention, each sequence will be considered as an independent sequence in patent law terms;

(26) Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law;

(27) Whereas if an invention is based on biological material of plant or animal origin or if it uses such material, the patent application should, where appropriate, include information on the geographical origin of such material, if known; whereas this is without prejudice to the processing of patent applications or the validity of rights arising from granted patents;

(28) Whereas this Directive does not in any way affect the basis of current patent law, according to which a patent may be granted for any new application of a patented product;

(29) Whereas this Directive is without prejudice to the exclusion of plant and animal varieties from patentability; whereas on the other hand inventions which concern plants or animals are patentable provided that the application of the invention is not technically confined to a single plant or animal variety;

(30) Whereas the concept 'plant variety' is defined by the legislation protecting new varieties, pursuant to which a variety is defined by its whole genome and therefore possesses individuality and is clearly distinguishable from other varieties;

(31) Whereas a plant grouping which is characterised by a particular gene (and not its whole genome) is not covered by the protection of new varieties and is therefore not excluded from patentability even if it comprises new varieties of plants;

(32) Whereas, however, if an invention consists only in genetically modifying a particular plant variety, and if a new plant variety is bred, it will still be excluded from patentability even if the genetic modification is the result not of an essentially biological process but of a biotechnological process;

(33) Whereas it is necessary to define for the purposes of this Directive when a process for the breeding of plants and animals is essentially biological;

(34) Whereas this Directive shall be without prejudice to concepts of invention and discovery, as developed by national, European or international patent law;

(35) Whereas this Directive shall be without prejudice to the provisions of national patent law whereby processes for treatment of the human or animal body by surgery or therapy and diagnostic methods practised on the human or animal body are excluded from patentability;

(36) Whereas the TRIPs Agreement provides for the possibility that members of the World Trade Organisation may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect *ordre public* or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law;

(37) Whereas the principle whereby inventions must be excluded from patentability where their commercial exploitation offends against *ordre public* or morality must also be stressed in this Directive;

(38) Whereas the operative part of this Directive should also include an illustrative list of inventions excluded from patentability so as to provide national courts and patent offices with a general guide to interpreting the reference to *ordre public* and morality; whereas this list obviously cannot presume to be exhaustive; whereas processes, the use of which offend against human dignity, such as processes to produce chimeras from germ cells or totipotent cells of humans and animals, are obviously also excluded from patentability;

(39) Whereas *ordre public* and morality correspond in particular to ethical or moral principles recognised in a Member State, respect for which is particularly important in the field of biotechnology in view of the potential scope of inventions in this field and their inherent relationship to living matter; whereas such ethical or moral principles supplement the standard legal examinations under patent law regardless of the technical field of the invention;

(40) Whereas there is a consensus within the Community that interventions in the human germ line and the cloning of human beings offends against *ordre public* and morality; whereas it is therefore important to exclude unequivocally from patentability processes for modifying the germ line genetic identity of human beings and processes for cloning human beings;

(41) Whereas a process for cloning human beings may be defined as any process, including techniques of embryo splitting, designed to create a human being with the same nuclear genetic information as another living or deceased human being;

(42) Whereas, moreover, uses of human embryos for industrial or commercial purposes must also be excluded from patentability; whereas in any case such exclusion does not affect inventions for therapeutic or diagnostic purposes which are applied to the human embryo and are useful to it;

(43) Whereas pursuant to Article F(2) of the Treaty on European Union, the Union is to respect fundamental rights, as guaranteed by the European Convention for the Protection of Human Rights and Fundamental Freedoms signed in Rome on 4 November 1950 and as they result from the constitutional traditions common to the Member States, as general principles of Community law;

(44) Whereas the Commission's European Group on Ethics in Science and New Technologies evaluates all ethical aspects of biotechnology; whereas it should be pointed out in this connection that that Group may be consulted only where biotechnology is to be evaluated at the level of basic ethical principles, including where it is consulted on patent law;

(45) Whereas processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit in terms of research, prevention, diagnosis or therapy to man or animal, and also animals resulting from such processes, must be excluded from patentability;

(46) Whereas, in view of the fact that the function of a patent is to reward the inventor for his creative efforts by granting an exclusive but time-bound right, and thereby encourage inventive activities,

the holder of the patent should be entitled to prohibit the use of patented self-reproducing material in situations analogous to those where it would be permitted to prohibit the use of patented, non-self-reproducing products, that is to say the production of the patented product itself;

(47) Whereas it is necessary to provide for a first derogation from the rights of the holder of the patent when the propagating material incorporating the protected invention is sold to a farmer for farming purposes by the holder of the patent or with his consent; whereas that initial derogation must authorise the farmer to use the product of his harvest for further multiplication or propagation on his own farm; whereas the extent and the conditions of that derogation must be limited in accordance with the extent and conditions set out in Council Regulation (EC) No 2100/94 of 27 July 1994 on Community plant variety rights [1];

(48) Whereas only the fee envisaged under Community law relating to plant variety rights as a condition for applying the derogation from Community plant variety rights can be required of the farmer;

(49) Whereas, however, the holder of the patent may defend his rights against a farmer abusing the derogation or against a breeder who has developed a plant variety incorporating the protected invention if the latter fails to adhere to his commitments;

(50) Whereas a second derogation from the rights of the holder of the patent must authorise the farmer to use protected livestock for agricultural purposes;

(51) Whereas the extent and the conditions of that second derogation must be determined by national laws, regulations and practices, since there is no Community legislation on animal variety rights;

(52) Whereas, in the field of exploitation of new plant characteristics resulting from genetic engineering, guaranteed access must, on payment of a fee, be granted in the form of a compulsory licence where, in relation to the genus or species concerned, the plant variety represents significant technical progress of considerable economic interest compared to the invention claimed in the patent;

(53) Whereas, in the field of the use of new plant characteristics resulting from new plant varieties in genetic engineering, guaranteed access must, on payment of a fee, be granted in the form of a compulsory licence where the invention represents significant technical progress of considerable economic interest;

(54) Whereas Article 34 of the TRIPs Agreement contains detailed provisions on the burden of proof which is binding on all Member States; whereas, therefore, a provision in this Directive is not necessary;

(55) Whereas following Decision 93/626/EEC [2] the Community is party to the Convention on Biological Diversity of 5 June 1992; whereas, in this regard, Member States must give particular weight to Article 3 and Article 8(j), the second sentence of Article 16(2) and Article 16(5) of the Convention when bringing into force the laws, regulations and administrative provisions necessary to comply with this Directive;

(56) Whereas the Third Conference of the Parties to the Biodiversity Convention, which took place in November 1996, noted in Decision III/17 that 'further work is required to help develop a common appreciation of the relationship between intellectual property rights and the relevant provisions of the TRIPs Agreement and the Convention on Biological Diversity, in particular on issues relating to technology transfer and conservation and sustainable use of biological diversity and the fair and equitable sharing of benefits arising out of the use of genetic resources, including the protection of knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity',

[1] OJ L 227, 1.9.1994, p. 1. Regulation as amended by Regulation (EC) No 2506/95 (OJ L 258, 28.10.1995, p. 3).

[2] OJ L 309, 31.12.1993, p. 1.

HAVE ADOPTED THIS DIRECTIVE:

CHAPTER I

Patentability

Article 1

1. Member States shall protect biotechnological inventions under national patent law. They shall, if necessary, adjust their national patent law to take account of the provisions of this Directive.

2. This Directive shall be without prejudice to the obligations of the Member States pursuant to international agreements, and in particular the TRIPs Agreement and the Convention on Biological Diversity.

Article 2

1. For the purposes of this Directive,

(a) 'biological material' means any material containing genetic information and capable of reproducing itself or being reproduced in a biological system;

(b) 'microbiological process' means any process involving or performed upon or resulting in microbiological material.

2. A process for the production of plants or animals is essentially biological if it consists entirely of natural phenomena such as crossing or selection.

3. The concept of 'plant variety' is defined by Article 5 of Regulation (EC) No 2100/94.

Article 3

1. For the purposes of this Directive, 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.

2. Biological 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.

Article 4

1. The following shall not be patentable:

(a) plant and animal varieties;

(b) essentially biological processes for the production of plants or animals.

2. Inventions which concern plants or animals shall be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety.

3. Paragraph 1(b) shall be without prejudice to the patentability of inventions which concern a microbiological or other technical process or a product obtained by means of such a process.

Article 5

1. The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions.

2. An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element.

3. The industrial application of a sequence or a partial sequence of a gene must be disclosed in the patent application.

Article 6

1. Inventions shall be considered unpatentable where their commercial exploitation would be contrary to *ordre public* or morality; however, exploitation shall not be deemed to be so contrary merely because it is prohibited by law or regulation.

2. On the basis of paragraph 1, the following, in particular, shall be considered unpatentable:

(a) processes for cloning human beings;

(b) processes for modifying the germ line genetic identity of human beings;

(c) uses of human embryos for industrial or commercial purposes;

(d) processes for modifying the genetic identity of animals which are likely to cause them suffering without any substantial medical benefit to man or animal, and also animals resulting from such processes.

Article 7

The Commission's European Group on Ethics in Science and New Technologies evaluates all ethical aspects of biotechnology.

CHAPTER II

Scope of protection

Article 8

1. The protection conferred by a patent on a biological material possessing specific characteristics as a result of the invention shall extend to any biological material derived from that biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics.

2. The protection conferred by a patent on a process that enables a biological material to be produced possessing specific characteristics as a result of the invention shall extend to biological material directly obtained through that process and to any other biological material derived from the directly obtained biological material through propagation or multiplication in an identical or divergent form and possessing those same characteristics.

Article 9

The protection conferred by a patent on a product containing or consisting of genetic information shall extend to all material, save as provided in Article 5(1), in which the product in incorporated and in which the genetic information is contained and performs its function.

Article 10

The protection referred to in Articles 8 and 9 shall not extend to biological material obtained from the propagation or multiplication of biological material placed on the market in the territory of a Member State by the holder of the patent or with his consent, where the multiplication or propagation necessarily results from the application for which the biological material was marketed, provided that the material obtained is not subsequently used for other propagation or multiplication.

Article 11

1. By way of derogation from Articles 8 and 9, the sale or other form of commercialisation of plant propagating material to a farmer by the holder of the patent or with his consent for agricultural use implies authorisation for the farmer to use the product of his harvest for propagation or multiplication by him on his own farm, the extent and conditions of this derogation corresponding to those under Article 14 of Regulation (EC) No 2100/94.

2. By way of derogation from Articles 8 and 9, the sale or any other form of commercialisation of breeding stock or other animal reproductive material to a farmer by the holder of the patent or with his consent implies authorisation for the farmer to use the protected livestock for an agricultural purpose. This includes making the animal or other animal reproductive material available for the purposes of pursuing his agricultural activity but not sale within the framework or for the purpose of a commercial reproduction activity.

3. The extent and the conditions of the derogation provided for in paragraph 2 shall be determined by national laws, regulations and practices.

CHAPTER III

Compulsory cross-licensing

Article 12

1. Where a breeder cannot acquire or exploit a plant variety right without infringing a prior patent, he may apply for a compulsory licence for non-exclusive use of the invention protected by the patent inasmuch as the licence is necessary for the exploitation of the plant variety to be protected, subject to payment of an appropriate royalty. Member States shall provide that, where such a licence is granted, the holder of the patent will be entitled to a cross-licence on reasonable terms to use the protected variety.

2. Where the holder of a patent concerning a biotechnological invention cannot exploit it without infringing a prior plant variety right, he may apply for a compulsory licence for non-exclusive use of the plant variety protected by that right, subject to payment of an appropriate royalty. Member States shall provide that, where such a licence is granted, the holder of the variety right will be entitled to a cross-licence on reasonable terms to use the protected invention.

3. Applicants for the licences referred to in paragraphs 1 and 2 must demonstrate that:

(a) they have applied unsuccessfully to the holder of the patent or of the plant variety right to obtain a contractual licence;

(b) the plant variety or the invention constitutes significant technical progress of considerable economic interest compared with the invention claimed in the patent or the protected plant variety.

4. Each Member State shall designate the authority or authorities responsible for granting the licence. Where a licence for a plant variety can be granted only by the Community Plant Variety Office, Article 29 of Regulation (EC) No 2100/94 shall apply.

CHAPTER IV

Deposit, access and re-deposit of a biological material

Article 13

1. Where an invention involves the use of or concerns biological material which is not available to the public and which cannot be described in a patent application in such a manner as to enable the invention to be reproduced by a person skilled in the art, the description shall be considered inadequate for the purposes of patent law unless:

(a) the biological material has been deposited no later than the date on which the patent application was filed with a recognised depositary institution. At least the international depositary authorities which acquired this status by virtue of Article 7 of the Budapest Treaty of 28 April 1977 on the international recognition of the deposit of micro-organisms for the purposes of patent procedure, hereinafter referred to as the 'Budapest Treaty', shall be recognised;

(b) the application as filed contains such relevant information as is available to the applicant on the characteristics of the biological material deposited;

(c) the patent application states the name of the depository institution and the accession number.

2. Access to the deposited biological material shall be provided through the supply of a sample:

(a) up to the first publication of the patent application, only to those persons who are authorised under national patent law;

(b) between the first publication of the application and the granting of the patent, to anyone requesting it or, if the applicant so requests, only to an independent expert;

(c) after the patent has been granted, and notwithstanding revocation or cancellation of the patent, to anyone requesting it.

3. The sample shall be supplied only if the person requesting it undertakes, for the term during which the patent is in force:

(a) not to make it or any material derived from it available to third parties; and

(b) not to use it or any material derived from it except for experimental purposes, unless the applicant for or proprietor of the patent, as applicable, expressly waives such an undertaking.

4. At the applicant's request, where an application is refused or withdrawn, access to the deposited material shall be limited to an independent expert for 20 years from the date on which the patent application was filed. In that case, paragraph 3 shall apply.

5. The applicant's requests referred to in point (b) of paragraph 2 and in paragraph 4 may only be made up to the date on which the technical preparations for publishing the patent application are deemed to have been completed.

Article 14

1. If the biological material deposited in accordance with Article 13 ceases to be available from the recognised depositary institution, a new deposit of the material shall be permitted on the same terms as those laid down in the Budapest Treaty.

2. Any new deposit shall be accompanied by a statement signed by the depositor certifying that the newly deposited biological material is the same as that originally deposited.

CHAPTER V

Final provisions

Article 15

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive not later than 30 July 2000. They shall forthwith inform the Commission thereof.

When Member States adopt these measures, they shall contain a reference to this Directive or shall be accompanied by such reference on the occasion of their official publication. The methods of making such reference shall be laid down by Member States.

2. Member States shall communicate to the Commission the text of the provisions of national law which they adopt in the field covered by this Directive.

Article 16

The Commission shall send the European Parliament and the Council:

(a) every five years as from the date specified in Article 15(1) a report on any problems encountered with regard to the relationship between this Directive and international agreements on the protection of human rights to which the Member States have acceded;

(b) within two years of entry into force of this Directive, a report assessing the implications for basic genetic engineering research of failure to publish, or late publication of, papers on subjects which could be patentable;

(c) annually as from the date specified in Article 15(1), a report on the development and implications of patent law in the field of biotechnology and genetic engineering.

Article 17

This Directive shall enter into force on the day of its publication in the *Official Journal of the European Communities*.

Article 18

This Directive is addressed to the Member States.

Done at Brussels, 6 July 1998.

For the European Parliament	*For the Council*
The President	*The President*
J. M. GIL-ROBLES	R. EDLINGER

EXHIBIT C

HUGO INTELLECTUAL PROPERTY COMMITTEE STATEMENT ON PATENTING ISSUES RELATED TO EARLY RELEASE OF RAW SEQUENCE DATA

May 1997

HUGO, having reviewed recent developments in the field and, in particular, having taken note of the Principles agreed at the International Strategy Meetings on Human Genome Sequencing*[1] in Bermuda in February 1996 and February 1997, and of the practice of the U.S. Patent and Trademark Office (PTO) on granting patents on Expressed Sequence Tags (ESTs) as recently reported in Science 275: 1056:

- **reaffirms** its Statements on Patenting of DNA Sequences of 1992 and 1995, clarifying the fact that HUGO does not oppose patenting of useful benefits derived from genetic information, but does explicitly oppose the patenting of short sequences from randomly isolated portions of genes encoding proteins of uncertain functions;

- **regrets** the decision of some patent offices, such as the U.S. PTO, to grant patents on ESTs based on their utility "as probes to identify specific DNA sequences , urging these offices to rescind these decisions and, pending this, to strictly limit their claims to specified uses, since it would be untenable to make all subsequent innovation in which EST sequence would be involved in one way or other dependent on such patents;

- **urges** all large-scale sequencing centres and their funding agencies to adopt the policy of immediate release, without privileged access for any party, of all human genome sequence information in order to secure an optimal functioning of the international network, as well as to avoid unfair distortions of the system;

- **stresses** that only the policy of rapid publication and free availability of human genomic sequence information will secure further international co-operation of large-scale sequencing centres;

- **ephasises** the differences between the U.S. patent law, which provides for a so-called one year "grace period , allowing the authors of published data to subsequently file patent applications for inventions based on such information, and the patent laws of practically all other countries, which do not contain such a provision and where therefore no protection for, or based on, published data can be acquired;

- **calls upon** the law makers to enter negotiations aimed at reaching an agreement on the introduction of a "grace period along the lines of the U.S. law, which should precede the Paris Convention Union priority term, and which will eventually provide conditions putting all participants in the international network on an equal footing;

- **expresses** the hope that the free availability of raw sequence data, although forming part of the relevant state of the art, will not unduly prevent the protection of genes as new drug targets, which is essential for securing adequate high risk investments in biology, and will not result in a shift of activities of the pharmaceutical industry to searching for compounds that give marginal advantages against known targets rather than taking risks with new targets.

This Statement was prepared by the Intellectual Property Rights Committee of HUGO and approved for release by the Council of HUGO, May 1997

Members of HUGO's Intellectual Property Rights Committee:
Prof. David R Cox
Dr Peter N Goodfellow
Dr Tim J R Harris
Prof. Eric Lander
Dr Kate H Murashige
Prof. Richard M Myers
Dr Hatsushi Shimizu
Prof. Joseph Straus (Chair)
Dr John Sulston
Maitre Jacques Warcoin

[1] Sponsored by The Wellcome Trust

EXHIBIT D

DEPARTMENT OF COMMERCE

National Oceanic and Atmospheric Administration

Fair Market Value Analysis for a Fiber Optic Cable Permit in National Marine Sanctuaries

AGENCY: Office of National Marine Sanctuaries (ONMS), National Ocean Service (NOS), National Oceanic and Atmospheric Administration (NOAA), Department of Commerce (DOC).

ACTION: Notice of availability.

SUMMARY: Notice is hereby given that NOAA is requesting comments on the report ''Fair Market Value Analysis for a Fiber Optic Cable Permit in National Marine Sanctuaries'' and two peer reviews of this report. The report and peer reviews are available for download at http://www.sanctuaries.nos.noaa.gov/news/newsbboard/newsbboard.html or by requesting an electronic or hard copy. Requests can be made by sending an email to submarine.cables@noaa.gov (subject line ''Request for Fair Market Value Analysis'') or by calling Matt Brookhart at (301) 713–3125 x140.

DATES: Comments on this notice must be received by January 18, 2001.

ADDRESSES: Address all comments regarding this notice to Matt Brookhart, Conservation Policy and Planning Branch, Office of National Marine Sanctuaries, 1305 East-West Highway, 11th Floor, Silver Spring, MD 20910, Attention: Fair Market Value Analysis. Comments may also be submitted by email to: *submarine.cables@noaa.gov,* subject line ''Fair Market Value Analysis.''

FOR FURTHER INFORMATION CONTACT: Helen Golde, (301) 713–3125 x152.

SUPPLEMENTARY INFORMATION: The Office of National Marine Sanctuaries has issued several special-use permits to companies seeking to install fiber optic cables in National Marine Sanctuaries. The Sanctuary statute allows ONMS to permit the presence of cables on the sanctuaries' seafloor should it decide to do so. If an application is approved, ONMS may collect certain administrative and monitoring fees. In addition, ONMS is entitled to receive fair market value for the permitted use of sanctuary resources.

The report ''Fair Market Value Analysis for a Fiber Optic Cable Permit in National Marine Sanctuaries'' presents an assessment of fair market value for the use of National Marine Sanctuary resources for a fiber optic cable. Proper stewardship of sanctuary resources and open and equitable relations with telecommunication industry interests require a clear and consistent policy in this matter. The content of this report is based on dozens of industry and government sources and draws on the collaboration and review of numerous experts in the business, legal and technical arenas.

Once finalized, the fee structure proposed in this report will be used to assess fees (as stated in their respective special use permits) for cables already installed in the Olympic Coast and Stellwagen Bank National Marine Sanctuaries. In addition, this structure will provide the basis for future fair market value assessment of submarine cable permit applications in National Marine Sanctuaries. Comments on the report and peer reviews should focus on the methodology employed and the conclusions that it reached.

Dated: December 29, 2000.

John Oliver,

Chief Financial Officer, National Ocean Service.

[FR Doc. 01–387 Filed 1–4–01; 8:45 am]

BILLING CODE 3510–08–P

DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

[Docket No. 991027289–0263–02]

RIN 0651–AB09

Utility Examination Guidelines

AGENCY: United States Patent and Trademark Office, Commerce.

ACTION: Notice.

SUMMARY: The United States Patent and Trademark Office (USPTO) is publishing a revised version of guidelines to be used by Office personnel in their review of patent applications for compliance with the ''utility'' requirement of 35 U.S.C. 101. This revision supersedes the Revised Interim Utility Examination Guidelines that were published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136 (2000); and correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67 (2000).

DATES: The Guidelines are effective as of January 5, 2001.

FOR FURTHER INFORMATION CONTACT: Mark Nagumo by telephone at (703) 305–8666, by facsimile at (703) 305–9373, by electronic mail at ''mark.nagumo@uspto.gov,'' or by mail marked to his attention addressed to the Office of the Solicitor, Box 8, Washington, DC 20231; or Linda Therkorn by telephone at (703) 305–9323, by facsimile at (703) 305–8825, by electronic mail at ''linda.therkorn@uspto.gov,'' or by mail marked to her attention addressed to Box Comments, Commissioner for Patents, Washington, DC 20231.

SUPPLEMENTARY INFORMATION: As of the publication date of this notice, these Guidelines will be used by USPTO personnel in their review of patent applications for compliance with the ''utility'' requirement of 35 U.S.C. 101. Because these Guidelines only govern internal practices, they are exempt from notice and comment rulemaking under 5 U.S.C. 553(b)(A).

I. Discussion of Public Comments

The Revised Interim Utility Examination Guidelines published at 64 FR 71440, Dec. 21, 1999; 1231 O.G. 136, Feb. 29, 2000, with a correction at 65 FR 3425, Jan. 21, 2000; 1231 O.G. 67, Feb. 15, 2000, requested comments from the public. Comments were received from 35 individuals and 17 organizations. The written comments have been carefully considered.

Overview of Comments

The majority of comments generally approved of the guidelines and several expressly stated support for the three utility criteria (specific, substantial, and credible) set forth in the Guidelines. A few comments addressed particular concerns with respect to the coordinate examiner training materials that are available for public inspection at the USPTO website, *www.uspto.gov.* The comments on the training materials will be taken under advisement in the revision of the training materials. Consequently, those comments are not specifically addressed below because they do not impact the content of the Guidelines. Comments received in response to the request for comments on the ''Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1 'Written Description' Requirement,'' 64 FR 71427, Dec. 21, 1999; 1231 O.G. 123, Feb. 29, 2000, which raised issues pertinent to the utility requirement are also addressed below.

Responses to Specific Comments

(1) *Comment:* Several comments state that while inventions are patentable, discoveries are not patentable. According to the comments, genes are discoveries rather than inventions. These comments urge the USPTO not to issue patents for genes on the ground that genes are not inventions. *Response:* The suggestion is not adopted. An inventor can patent a discovery when the patent application satisfies the statutory requirements. The U.S.

Constitution uses the word ''discoveries'' where it authorizes Congress to promote progress made by inventors. The pertinent part of the Constitution is Article 1, section 8, clause 8, which reads: ''The Congress shall have power * * * To 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.''

When Congress enacted the patent statutes, it specifically authorized issuing a patent to a person who ''invents or discovers'' a new and useful composition of matter, among other things. The pertinent statute is 35 U.S.C. 101, which reads: ''Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.'' Thus, an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state and processed through purifying steps that separate the gene from other molecules naturally associated with it.

If a patent application discloses only nucleic acid molecular structure for a newly discovered gene, and no utility for the claimed isolated gene, the claimed invention is not patentable. But when the inventor also discloses how to use the purified gene isolated from its natural state, the application satisfies the ''utility'' requirement. That is, where 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.

(2) *Comment:* Several comments state that a gene is not a new composition of matter because it exists in nature, and/or that an inventor who isolates a gene does not actually invent or discover a patentable composition because the gene exists in nature. These comments urge the USPTO not to issue patents for genes on the ground that genes are products of nature. Others state that naturally occurring DNAs are part of our heritage and are not inventions. Another comment expressed concern that a person whose body includes a patented gene could be guilty of patent infringement. *Response:* The comments are not adopted. A patent claim directed to an isolated and purified DNA molecule could cover, *e.g.,* a gene excised from a natural chromosome or a synthesized DNA molecule. An isolated and purified DNA molecule that has the same sequence as a naturally occurring gene is eligible for a patent because (1) an excised gene is eligible for a patent as a composition of matter or as an article of manufacture because that DNA molecule does not occur in that isolated form in nature, or (2) synthetic DNA preparations are eligible for patents because their purified state is different from the naturally occurring compound.

Patenting compositions or compounds isolated from nature follows well-established principles, and is not a new practice. For example, Louis Pasteur received U.S. Patent 141,072 in 1873, claiming ''[y]least, free from organic germs of disease, as an article of manufacture.'' Another example is an early patent for adrenaline. In a decision finding the patent valid, the court explained that compounds isolated from nature are patentable: ''even if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it [adrenaline] available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.'' *Parke-Davis & Co.* v. *H. K. Mulford Co.,* 189 F. 95, 103 (S.D.N.Y. 1911) (J. Learned Hand).

In a more recent case dealing with the prostaglandins PGE_2 and PGE_3, extracted from human or animal prostate glands, a patent examiner had rejected the claims, reasoning that ''inasmuch as the 'claimed compounds are naturally occurring' * * * they therefore 'are not 'new' within the connotation of the patent statute.' '' *In re Bergstrom,* 427 F.2d 1394, 1397, 166 USPQ 256, 259 (CCPA 1970). The Court reversed the Patent Office and explained the error: ''what appellants claim—pure PGE_2 and PGE_3—is not 'naturally occurring.' Those compounds, as far as the record establishes, do not exist in nature in pure form, and appellants have neither merely discovered, nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse, albeit unknown, or what has previously been known to exist.'' *Id.* at 1401, 166 USPQ at 261–62. Like other chemical compounds, DNA molecules are eligible for patents when isolated from their natural state and purified or when synthesized in a laboratory from chemical starting materials.

A patent on a gene covers the isolated and purified gene but does not cover the gene as it occurs in nature. Thus, the concern that a person whose body ''includes'' a patented gene could infringe the patent is misfounded. The body does not contain the patented, isolated and purified gene because genes in the body are not in the patented, isolated and purified form. When the patent issued for purified adrenaline about one hundred years ago, people did not infringe the patent merely because their bodies naturally included unpurified adrenaline.

(3) *Comment:* Several comments suggested that the USPTO should seek guidance from Congress as to whether naturally occurring genetic sequences are patentable subject matter. *Response:* The suggestion is not adopted. Congress adopted the current statute defining patentable subject matter (35 U.S.C. 101) in 1952. The legislative history indicates that Congress intended ''anything under the sun that is made by man'' to be eligible for patenting. S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952). The Supreme Court interprets the statute to cover a ''nonnaturally occurring manufacture or composition of matter—a product of human ingenuity.'' *Diamond* v. *Chakrabarty,* 447 U.S. 303, 309, 206 USPQ 193, 197 (1980). Thus, the intent of Congress with regard to patent eligibility for chemical compounds has already been determined: DNA compounds having naturally occurring sequences are eligible for patenting when isolated from their natural state and purified, and when the application meets the statutory criteria for patentability. The genetic sequence data represented by strings of the letters A, T, C and G alone is raw, fundamental sequence data, i.e., nonfunctional descriptive information. While descriptive sequence information alone is not patentable subject matter, a new and useful purified and isolated DNA compound described by the sequence is eligible for patenting, subject to satisfying the other criteria for patentability.

(4) *Comment:* Several comments state that patents should not issue for genes because the sequence of the human genome is at the core of what it means to be human and no person should be able to own/control something so basic. Other comments stated that patents should be for marketable inventions and not for discoveries in nature. *Response:* The comments are not adopted. Patents do not confer ownership of genes, genetic information, or sequences. The patent system promotes progress by securing a complete disclosure of an invention to the public, in exchange for the inventor's legal right to exclude other people from making, using, offering for sale, selling, or importing

the composition for a limited time. That is, a patent owner can stop infringing activity by others for a limited time.

Discoveries from nature have led to marketable inventions in the past, but assessing the marketability of an invention is not pertinent to determining if an invention has a specific, substantial, and credible use. ''[D]evelopment of a product to the extent that it is presently commercially salable in the marketplace is not required to establish 'usefulness' within the meaning of § 101.'' *In re Langer,* 503 F.2d 1380, 1393, 183 USPQ 288, 298 (CCPA 1974). Inventors are entitled to patents when they have met the statutory requirements for novelty, nonobviousness and usefulness, and their patent disclosure adequately describes the invention and clearly teaches others how to make and use the invention. The utility requirement, as explained by the courts, only requires that the inventor disclose a practical or real world benefit available from the invention, i.e., a specific, substantial and credible utility. As noted in a response to other comments, it is a long tradition in the United States that discoveries from nature which are transformed into new and useful products are eligible for patents.

(5) *Comment:* Several comments state that the Guidelines mean that anyone who discovers a gene will be allowed a broad patent covering any number of possible applications even though those uses may be unattainable and unproven. Therefore, according to these comments, gene patents should not be issued. *Response:* The comment is not adopted. When a patent claiming a new chemical compound issues, the patentee has the right to exclude others from making, using, offering for sale, selling, or importing the compound for a limited time. The patentee is required to disclose only one utility, that is, teach others how to use the invention in at least one way. The patentee is not required to disclose all possible uses, but promoting the subsequent discovery of other uses is one of the benefits of the patent system. When patents for genes are treated the same as for other chemicals, progress is promoted because the original inventor has the possibility to recoup research costs, because others are motivated to invent around the original patent, and because a new chemical is made available as a basis for future research. Other inventors who develop new and nonobvious methods of using the patented compound have the opportunity to patent those methods.

(6) *Comment:* One comment suggests that the USPTO should not allow the patenting of ESTs because it is contrary to indigenous law, because the Supreme Court's *Diamond* v. *Chakrabarty* decision was a bare 5-to-4 decision, because it would violate the Thirteenth Amendment of the U.S. Constitution, because it violates the novelty requirement of the patent laws, because it will exacerbate tensions between indigenous peoples and western academic/research communities and because it will undermine indigenous peoples' own research and academic institutions. The comment urges the USPTO to institute a moratorium on patenting of life forms and natural processes. *Response:* The comments are not adopted. Patents on chemical compounds such as ESTs do not implicate the Thirteenth Amendment. The USPTO must administer the patent statutes as the Supreme Court interprets them. When Congress enacted § 101, it indicated that ''anything under the sun that is made by man'' is subject matter for a patent. S. Rep. No. 1979, 82d Cong., 2d Sess., 5 (1952); H.R. Rep. No. 1923, 82d Cong., 2d Sess., 6 (1952). The Supreme Court has interpreted § 101 many times without overturning it. *See, e.g., Diamond* v. *Diehr,* 450 U.S. 175, 209 USPQ 1 (1981) (discussing cases construing section 101). Under United States law, a patent applicant is entitled to a patent when an invention meets the patentability criteria of title 35. Thus, ESTs which meet the criteria for utility, novelty, and nonobviousness are eligible for patenting when the application teaches those of skill in the art how to make and use the invention.

(7) *Comment:* Several comments state that patents should not issue for genes because patents on genes are delaying medical research and thus there is no societal benefit associated with gene patents. Others state that granting patents on genes at any stage of research deprives others of incentives and the ability to continue exploratory research and development. Some comment that patentees will deny access to genes and our property (our genes) will be owned by others. *Response:* The comments are not adopted. The incentive to make discoveries and inventions is generally spurred, not inhibited, by patents. The disclosure of genetic inventions provides new opportunities for further development. The patent statutes provide that a patent must be granted when at least one specific, substantial and credible utility has been disclosed, and the application satisfies the other statutory requirements. As long as one specific, substantial and credible use is disclosed and the statutory requirements are met, the USPTO is not authorized to withhold the patent until another, or better, use is discovered. Other researchers may discover higher, better or more practical uses, but they are advantaged by the starting point that the original disclosure provides. A patent grants exclusionary rights over a patented composition but does not grant ownership of the composition. Patents are not issued on compositions in the natural environment but rather on isolated and purified compositions.

(8) *Comment:* Several comments stated that DNA should be considered unpatentable because a DNA sequence by itself has little utility. *Response:* A DNA sequence—*i.e.,* the sequence of base pairs making up a DNA molecule—is simply one of the properties of a DNA molecule. Like any descriptive property, a DNA sequence itself is not patentable. A purified DNA *molecule* isolated from its natural environment, on the other hand, is a chemical compound and is patentable if all the statutory requirements are met. An isolated and purified DNA molecule may meet the statutory utility requirement if, *e.g.,* it can be used to produce a useful protein or it hybridizes near and serves as a marker for a disease gene. Therefore, a DNA molecule is not *per se* unpatentable for lack of utility, and each application claim must be examined on its own facts.

(9) *Comment:* One comment states that the disclosure of a DNA sequence has inherent value and that possible uses for the DNA appear endless, even if no single use has been worked out. According to the comment, the ''basic social contract of the patent deal'' requires that such a discovery should be patentable, and that patenting should be ''value-blind.'' *Response:* The comment is not adopted. The Supreme Court did not find a similar argument persuasive in *Brenner* v. *Manson,* 383 U.S. 519 (1966). The courts interpret the statutory term ''useful'' to require disclosure of at least one available practical benefit to the public. The Guidelines reflect this determination by requiring the disclosure of at least one specific, substantial, and credible utility. If no such utility is disclosed or readily apparent from an application, the Office should reject the claim. The applicant may rebut the Office position by showing that the invention does have a specific, substantial, and credible utility that would have been recognized by one of skill in the art at the time the application was filed.

(10) *Comment:* Several comments stated that the scope of patent claims directed to DNA should be limited to applications or methods of using DNA, and should not be allowed to

encompass the DNA itself. *Response:* The comment is not adopted. Patentable subject matter includes both ''process[es]'' and ''composition[s] of matter.'' 35 U.S.C. 101. Patent law provides no basis for treating DNA differently from other chemical compounds that are compositions of matter. If a patent application claims a composition of matter comprising DNA, and the claims meet all the statutory requirements of patentability, there is no legal basis for rejecting the application.

(11) *Comment:* Several comments stated that DNA patent claim scope should be limited to uses that are disclosed in the patent application and that allowing patent claims that encompass DNA itself would enable the inventor to assert claims to ''speculative'' uses of the DNA that were not foreseen at the time the patent application was filed. *Response:* The comment is not adopted. A patent on a composition gives *exclusive* rights to the composition for a limited time, even if the inventor disclosed only a single use for the composition. Thus, a patent granted on an isolated and purified DNA composition confers the right to exclude others from *any* method of using that DNA composition, for up to 20 years from the filing date. This result flows from the language of the statute itself. When the utility requirement and other requirements are satisfied by the application, a patent granted provides a patentee with the right to exclude others from, *inter alia,* ''using'' the patented composition of matter. *See* 35 U.S.C. 154. Where a new use is discovered for a patented DNA composition, that new use may qualify for its own process patent, notwithstanding that the DNA composition itself is patented.

By statute, a patent is required to disclose one practical utility. If a well-established utility is readily apparent, the disclosure is deemed to be implicit. If an application fails to disclose one specific, substantial, and credible utility, and the examiner discerns no well-established utility, the examiner will reject the claim under section 101. The rejection shifts the burden to the applicant to show that the examiner erred, or that a well-established utility would have been readily apparent to one of skill in the art. The applicant cannot rebut the rejection by relying on a utility that would not have been readily apparent at the time the application was filed. *See, e.g., In re Wright,* 999 F.2d 1557, 1562–63, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993) (''developments occurring after the filing date of an application are of no significance regarding what one skilled in the art believed as of the filing date'').

(12) *Comment:* Several comments stated that DNA should be freely available for research. Some of these comments suggested that patents are not necessary to encourage additional discovery and sequencing of genes. Some comments suggested that patenting of DNA inhibits biomedical research by allowing a single person or company to control use of the claimed DNA. Another comment expressed concern that patenting ESTs will impede complete characterization of genes and delay or restrict exploration of genetic materials for the public good. *Response:* The scope of subject matter that is eligible for a patent, the requirements that must be met in order to be granted a patent, and the legal rights that are conveyed by an issued patent, are all controlled by statutes which the USPTO must administer. ''Whoever invents or discovers any new and useful * * * composition of matter * * * may obtain a patent therefor.'' 35 U.S.C. 101. Congress creates the law and the Federal judiciary interprets the law. The USPTO must administer the laws as Congress has enacted them and as the Federal courts have interpreted them. Current law provides that when the statutory patentability requirements are met, there is no basis to deny patent applications claiming DNA compositions, or to limit a patent's scope in order to allow free access to the use of the invention during the patent term.

(13) *Comment:* Several comments suggested that DNA sequences should be considered unpatentable because sequencing DNA has become so routine that determining the sequence of a DNA molecule is not inventive. *Response:* The comments are not adopted. A DNA sequence is not patentable because a sequence is merely descriptive information about a molecule. An isolated and purified DNA molecule may be patentable because a molecule is a ''composition of matter,'' one of the four classes of invention authorized by 35 U.S.C. 101. A DNA molecule must be *nonobvious* in order to be patentable. Obviousness does not depend on the amount of work required to characterize the DNA molecule. *See* 35 U.S.C. 103(a) (''Patentability shall not be negatived by the manner in which the invention was made.''). As the nonobviousness requirement has been interpreted by the U.S. Court of Appeals for the Federal Circuit, whether a claimed DNA molecule would have been obvious depends on whether a molecule having the particular *structure* of the DNA would have been obvious to one of ordinary skill in the art at the time the invention was made. *See, e.g., In re Deuel,* 51 F.3d 1552, 1559, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995) (''[T]he existence of a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious.''); *see also, In re Bell,* 991 F.2d 781, 26 USPQ2d 1529 (Fed. Cir. 1993).

(14) *Comment:* One comment suggested that genes ought to be patentable only when the complete sequence of the gene is disclosed and a function for the gene product has been determined. *Response:* The suggestion is not adopted. To obtain a patent on a chemical compound such as DNA, a patent applicant must adequately describe the compound and must disclose how to make and use the compound. 35 U.S.C. 101, 112. ''An adequate written description of a DNA * * * requires a precise definition, *such as* by structure, formula, chemical name, or physical properties.'' *Univ. of California* v. *Eli Lilly & Co.,* 119 F.3d 1559, 1556, 43 USPQ2d 1398, 1404 (Fed. Cir. 1997) (emphasis added, internal quote omitted). Thus, describing the complete chemical structure, *i.e.,* the DNA sequence, is one method of describing a DNA molecule but it is not the only method. In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, *e.g.,* it hybridizes near a disease-associated gene or it has a gene-regulating activity.

(15) *Comment:* One comment stated that the specification should ''disclose the invention,'' including why the invention works and how it was developed. *Response:* The comment is not adopted. The comment is directed more to the requirements imposed by 35 U.S.C. 112 than to those of 35 U.S.C. 101. To satisfy the enablement requirement of 35 U.S.C. 112, ¶ 1, an application must disclose the claimed invention in sufficient detail to enable a person of ordinary skill in the art to make and use the claimed invention. To satisfy the written description requirement of 35 U.S.C. 112, ¶ 1, the description must show that the applicant was in possession of the claimed invention at the time of filing. If all the requirements under 35 U.S.C. 112, ¶1, are met, there is no statutory basis to require disclosure of why an invention works or how it was developed. ''[I]t is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works.'' *Newman* v. *Quigg,*

877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989).

(16) *Comment:* One comment suggested that patents should ''allow for others to learn from and improve the invention.'' The comment suggested that claims to patented plant varieties should not prohibit others from using the patented plants to develop improved varieties. The comment also stated that uses of plants in speculative manners should not be permitted. *Response:* By statute, a patent provides the patentee with the right to exclude others from, *inter alia,* making and using the claimed invention, although a limited research exemption exists. *See* 35 U.S.C. 163, 271(a), (e). These statutory provisions are not subject to revision by the USPTO and are not affected by these Guidelines. Where a plant is claimed in a utility patent application, compliance with the statutory requirements for utility under 35 U.S.C. 101 only requires that a claimed invention be supported by at least one specific, substantial and credible utility. It is somewhat rare for academic researchers to be sued by commercial patent owners for patent infringement. Most inventions are made available to academic researchers on very favorable licensing terms, which enable them to continue their research.

(17) *Comment:* Two comments suggested that although the USPTO has made a step in the right direction in raising the bar in the Utility Guidelines, there is still a need to apply stricter standards for utility. *Response:* The USPTO is bound by 35 U.S.C. 101 and the case law interpreting § 101. The Guidelines reflect the USPTO's understanding of § 101.

(18) *Comment:* Several comments addressed specific concerns about the examiner training materials. *Response:* The comments received with respect to the training materials will be taken under advisement as the Office revises the training materials. Except for comments with regard to whether sequence homology is sufficient to demonstrate a specific and substantial credible utility, specific concerns about the training materials will not be addressed herein as they will not impact the language of the guidelines.

(19) *Comment:* Several comments suggested that the use of computer-based analysis of nucleic acids to assign a function to a given nucleic acid based upon homology to prior art nucleic acids found in databases is highly unpredictable and cannot form a basis for an assignment of function to a putatively encoded protein. These comments also indicate that even in instances where a general functional assignment may be reasonable, the assignment does not provide information regarding the actual biological activity of an encoded protein and therefore patent claims drawn to such nucleic acids should be limited to method of use claims that are explicitly supported by the as-filed specification(s). These comments also state that if homology-based utilities are acceptable, then the nucleic acids, and proteins encoded thereby, should be considered as obvious over the prior art nucleic acids. On the other hand, one comment stated that homology is a standard, art-accepted basis for predicting utility, while another comment stated that any level of homology to a protein with known utility should be accepted as indicative of utility. *Response:* The suggestions to adopt a *per se* rule rejecting homology-based assertions of utility are not adopted. An applicant is entitled to a patent to the subject matter claimed unless statutory requirements are not met (35 U.S.C. 101, 102, 103, 112). When the USPTO denies a patent, the Office must set forth at least a *prima facie* case as to why an applicant has not met the statutory requirements. The inquiries involved in assessing utility are fact dependent, and the determinations must be made on the basis of scientific evidence. Reliance on the commenters' *per se* rule, rather than a fact dependent inquiry, is impermissible because the commenters provide no scientific evidence that homology-based assertions of utility are inherently unbelievable or involve implausible scientific principles. *See, e.g., In re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (rejection of claims improper where claims did ''not suggest an inherently unbelievable undertaking or involve implausible scientific principles' and where ''prior art * * * discloses structurally similar compounds to those claimed by the applicants which have been proven * * * to be effective'').

A patent examiner must accept a utility asserted by an applicant unless the Office has evidence or sound scientific reasoning to rebut the assertion. The examiner's decision must be supported by a preponderance of all the evidence of record. *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). More specifically, when a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion. ''[A] 'rigorous correlation' need not be shown in order to establish practical utility; 'reasonable correlation' is sufficient.'' *Fujikawa* v. *Wattanasin,* 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed. Cir. 1996). The Office will take into account both the nature and degree of the homology.

When a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein. If the preponderance of the evidence of record, or of sound scientific reasoning, casts doubt upon such an asserted utility, the examiner should reject the claim for lack of utility under 35 U.S.C. 101. For example, where a class of proteins is defined by common structural features, but evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific, substantial, and credible utility to a new member of the class. When there is a reason to doubt the functional protein assignment, the utility examination may turn to whether or not the asserted protein encoded by a claimed nucleic acid has a well-established use. If there is a well-established utility for the protein and the claimed nucleic acid, the claim would meet the requirements for utility under 35 U.S.C. 101. If not, the burden shifts to the applicant to provide evidence supporting a well-established utility. There is no *per se* rule regarding homology, and each application must be judged on its own merits.

The comment indicating that if a homology-based utility could meet the requirements set forth under 35 U.S.C. 101, then the invention would have been obvious, is not adopted. Assessing nonobviousness under 35 U.S.C. 103 is separate from analyzing the utility requirements under 35 U.S.C. 101. When a claim to a nucleic acid supported by a homology-based utility meets the utility requirement of section 101, it does not follow that the claimed nucleic acid would have been *prima facie* obvious over the nucleic acids to which it is homologous. ''[S]ection 103 requires a fact-intensive comparison of the [claim] with the prior art rather than the mechanical application of one or another *per se* rule.'' *In re Ochiai,* 71 F.3d 1565, 1571, 37 USPQ2d 1127, 1132 (Fed. Cir. 1995). Nonobviousness must be determined according to the analysis

in *Graham* v. *John Deere,* 383 U.S. 1, 148 USPQ 459 (1966). *See also, In re Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (in banc) (''structural similarity between claimed and prior art subject matter, * * * *where the prior art gives reason or motivation to make the claimed compositions,* creates a prima facie case of obviousness'') (emphasis added). Where ''the prior art teaches a specific, structurally-definable compound [] the question becomes whether the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention.'' *In re Deuel,* 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1214 (Fed. Cir. 1995).

(20) *Comment:* Several comments indicated that in situations where a well-established utility is relied upon for compliance with 35 U.S.C. 101, the record should reflect what that utility is. One comment stated that the record should reflect whether the examiner accepted an asserted utility or relied upon a well-established utility after dismissing all asserted utilities. Another comment stated that when the examiner relies on a well-established utility not explicitly asserted by the applicant, the written record should clearly identify this utility and the rationale for considering it specific and substantial. *Response:* The comments are not adopted. Only one specific, substantial and credible utility is required to satisfy the statutory requirement. Where one or more well-established utilities would have been readily apparent to those of skill in the art at the time of the invention, an applicant may rely on any one of those utilities without prejudice. The record of any issued patent typically reflects consideration of a number of references in the prior art that the applicant or the examiner considered material to the claimed invention. These references often indicate uses for related inventions, and any patents listed typically disclose utilities for related inventions. Thus, even when the examiner does not identify a well-established utility, the record as a whole will likely disclose readily apparent utilities. Just as the examiner without comment may accept a properly asserted utility, there is no need for an examiner to comment on the existence of a well-established utility. However, the Guidelines have been revised to clarify that a well-established utility is a specific, substantial, and credible utility that must be readily apparent to one skilled in the art. Most often, the closest prior art cited and applied in the course of examining the application will demonstrate a well-established utility for the invention.

(21) *Comment:* Several comments stated that the Guidelines erroneously burden the examiner with proving that a person of skill in the art would not be aware of a well-established utility. One comment states that this requires the examiner to prove a negative. Another comment states that the Guidelines should direct examiners that if a specific utility has not been disclosed, the applicant should be required to identify a specific utility. *Response:* The comments have been adopted in part. The Guidelines have been revised to indicate that where the applicant has not asserted a specific, substantial, and credible utility, and the examiner does not perceive a well-established utility, a rejection under § 101 should be entered. That is, if a well-established utility is not readily apparent and an invention is not otherwise supported by an asserted specific, substantial, and credible utility, the burden will be shifted to applicant to show either that the specification discloses an adequate utility, or to show that a well-established utility exists for the claimed invention. Again, most often the search of the closest prior art will reveal whether there is a well-established utility for the claimed invention.

(22) *Comment:* Several comments suggested that further clarification was required with regard to the examiner's determination that there is an adequate nexus between a showing supporting a well-established utility and the application as filed. The comments indicated that the meaning of this ''nexus'' was unclear. *Response:* The Guidelines have been modified to reflect that evidence provided by an applicant is to be analyzed with regard to a concordance between the showing and the full scope and content of the claimed invention as disclosed in the application as filed. In situations where the showing provides adequate evidence that the claim is supported by at least one asserted specific, substantial, and credible or well-established utility, the rejections under 35 U.S.C. 101 and 112, first paragraph, will be withdrawn. However, the examiner is instructed to consider whether or not the specification, in light of applicant's showing, is enabled for the use of the full scope of the claimed invention. Many times prior patents and printed publications provided by applicant will clearly demonstrate that a well-established utility exists.

(23) *Comment:* One comment states that the Office is using an improper standard in assessing ''specific'' utility. According to the comment, a distinction between ''specific'' and ''general'' utilities is an overreaching interpretation of the specificity requirement in the case law because ''unique'' or ''particular'' utilities have never been required by the law. The comment states that the specificity requirement concerns sufficiency of disclosure, *i.e.,* teaching how to make and use a claimed invention, not the utility requirement. The comment states that the specificity requirement is to be distinguished from the ''substantial'' utility requirement, and that the *Brenner* v. *Manson* decision concerned only a ''substantial'' utility issue, not specificity. *Response:* The comment is not adopted. The disclosure of only a general utility rather than a particular utility is insufficient to meet statutory requirements. Although the specificity requirement is relevant to § 112, it is not severable from the utility requirement.

> [S]urely Congress intended § 112 to presuppose *full satisfaction* of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention. As this court stated in *Diederich,* quoting with approval from the decision of the board:
>
> 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.' As the Supreme Court said in Brenner v. Manson:
>
> '* * * a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.'
>
> *In re Kirk,* 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967) (affirming rejections under §§ 101 and 112) (emphasis in original).

II. Guidelines for Examination of Applications for Compliance With the Utility Requirement

A. Introduction

The following Guidelines establish the policies and procedures to be followed by Office personnel in the evaluation of any patent application for compliance with the utility requirements of 35 U.S.C. 101 and 112. These Guidelines have been promulgated to assist Office personnel in their review of applications for compliance with the utility

requirement. The Guidelines do not alter the substantive requirements of 35 U.S.C. 101 and 112, nor are they designed to obviate the examiner's review of applications for compliance with all other statutory requirements for patentability. The Guidelines do not constitute substantive rulemaking and hence do not have the force and effect of law. Rejections will be based upon the substantive law, and it is these rejections which are appealable. Consequently, any perceived failure by Office personnel to follow these Guidelines is neither appealable nor petitionable.

B. Examination Guidelines for the Utility Requirement

Office personnel are to adhere to the following procedures when reviewing patent applications for compliance with the ''useful invention'' (''utility'') requirement of 35 U.S.C. 101 and 112, first paragraph.

1. Read the claims and the supporting written description.

(a) Determine what the applicant has claimed, noting any specific embodiments of the invention.

(b) Ensure that the claims define statutory subject matter (*i.e.,* a process, machine, manufacture, composition of matter, or improvement thereof).

(c) If at any time during the examination, it becomes readily apparent that the claimed invention has a well-established utility, do not impose a rejection based on lack of utility. An invention has a well-established utility (1) if a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (*e.g.,* properties or applications of a product or process), and (2) the utility is specific, substantial, and credible.

2. Review the claims and the supporting written description to determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible:

(a) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (*i.e.,* it has a ''specific and substantial utility'') and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility.

(1) A claimed invention must have a specific and substantial utility. This requirement excludes ''throw-away,'' ''insubstantial,'' or ''nonspecific'' utilities, such as the use of a complex invention as landfill, as a way of satisfying the utility requirement of 35 U.S.C. 101.

(2) Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.,* test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

(b) If no assertion of specific and substantial utility for the claimed invention made by the applicant is credible, and the claimed invention does not have a readily apparent well-established utility, reject the claim(s) under § 101 on the grounds that the invention as claimed lacks utility. Also reject the claims under § 112, first paragraph, on the basis that the disclosure fails to teach how to use the invention as claimed. The § 112, first paragraph, rejection imposed in conjunction with a § 101 rejection should incorporate by reference the grounds of the corresponding § 101 rejection.

(c) If the applicant has not asserted any specific and substantial utility for the claimed invention and it does not have a readily apparent well-established utility, impose a rejection under § 101, emphasizing that the applicant has not disclosed a specific and substantial utility for the invention. Also impose a separate rejection under § 112, first paragraph, on the basis that the applicant has not disclosed how to use the invention due to the lack of a specific and substantial utility. The §§ 101 and 112 rejections shift the burden of coming forward with evidence to the applicant to:

(1) Explicitly identify a specific and substantial utility for the claimed invention; and

(2) Provide evidence that one of ordinary skill in the art would have recognized that the identified specific and substantial utility was well established at the time of filing. The examiner should review any subsequently submitted evidence of utility using the criteria outlined above. The examiner should also ensure that there is an adequate nexus between the evidence and the properties of the now claimed subject matter as disclosed in the application as filed. That is, the applicant has the burden to establish a probative relation between the submitted evidence and the originally disclosed properties of the claimed invention.

3. Any rejection based on lack of utility should include a detailed explanation why the claimed invention has no specific and substantial credible utility. Whenever possible, the examiner should provide documentary evidence regardless of publication date (*e.g.,* scientific or technical journals, excerpts from treatises or books, or U.S. or foreign patents) to support the factual basis for the *prima facie* showing of no specific and substantial credible utility. If documentary evidence is not available, the examiner should specifically explain the scientific basis for his or her factual conclusions.

(a) Where the asserted utility is not specific or substantial, a *prima facie* showing must establish that it is more likely than not that a person of ordinary skill in the art would not consider that any utility asserted by the applicant would be specific and substantial. The *prima facie* showing must contain the following elements:

(1) An explanation that clearly sets forth the reasoning used in concluding that the asserted utility for the claimed invention is not both specific and substantial nor well-established;

(2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

(b) Where the asserted specific and substantial utility is not credible, a *prima facie* showing of no specific and substantial credible utility must establish that it is more likely than not that a person skilled in the art would not consider credible any specific and substantial utility asserted by the applicant for the claimed invention.

The *prima facie* showing must contain the following elements:

(1) An explanation that clearly sets forth the reasoning used in concluding that the asserted specific and substantial utility is not credible;

(2) Support for factual findings relied upon in reaching this conclusion; and

(3) An evaluation of all relevant evidence of record, including utilities taught in the closest prior art.

(c) Where no specific and substantial utility is disclosed or is well-established, a *prima facie* showing of no specific and substantial utility need only establish that applicant has not asserted a utility and that, on the record before the examiner, there is no known well-established utility.

4. A rejection based on lack of utility should not be maintained if an asserted utility for the claimed invention would be considered specific, substantial, and credible by a person of ordinary skill in the art in view of all evidence of record.

Office personnel are reminded that they must treat as true a statement of fact made by an applicant in relation to

an asserted utility, unless countervailing evidence can be provided that shows that one of ordinary skill in the art would have a legitimate basis to doubt the credibility of such a statement. Similarly, Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered.

Once a *prima facie* showing of no specific and substantial credible utility has been properly established, the applicant bears the burden of rebutting it. The applicant can do this by amending the claims, by providing reasoning or arguments, or by providing evidence in the form of a declaration under 37 CFR 1.132 or a patent or a printed publication that rebuts the basis or logic of the *prima facie* showing. If the applicant responds to the *prima facie* rejection, the Office personnel should review the original disclosure, any evidence relied upon in establishing the *prima facie* showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained.

If the applicant satisfactorily rebuts a *prima facie* rejection based on lack of utility under § 101, withdraw the § 101 rejection and the corresponding rejection imposed under § 112, first paragraph.

Dated: December 29, 2000.

Q. Todd Dickinson,

Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office.

[FR Doc. 01–322 Filed 1–4–01; 8:45 am]

BILLING CODE 3510–16–U

DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

[Docket No. 991027288–0264–02]

RIN 0651–AB10

Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, ''Written Description'' Requirement

AGENCY: United States Patent and Trademark Office, Commerce.

ACTION: Notice.

SUMMARY: These Guidelines will be used by USPTO personnel in their review of patent applications for compliance with the ''written description'' requirement of 35 U.S.C. 112, ¶ 1. These Guidelines supersede the ''Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 'Written Description' Requirement'' that were published in the **Federal Register** at 64 FR 71427, Dec. 21, 1999, and in the Official Gazette at 1231 O.G. 123, Feb. 29, 2000. These Guidelines reflect the current understanding of the USPTO regarding the written description requirement of 35 U.S.C. 112, ¶ 1, and are applicable to all technologies.

DATES: The Guidelines are effective as of January 5, 2001.

FOR FURTHER INFORMATION CONTACT: Stephen Walsh by telephone at (703) 305–9035, by facsimile at (703) 305–9373, by mail to his attention addressed to United States Patent and Trademark Office, Box 8, Washington, DC 20231, or by electronic mail at ''stephen.walsh@uspto.gov''; or Linda Therkorn by telephone at (703) 305–8800, by facsimile at (703) 305–8825, by mail addressed to Box Comments, Commissioner for Patents, Washington, DC 20231, or by electronic mail at ''linda.therkorn@uspto.gov.''

SUPPLEMENTARY INFORMATION: As of the publication date of this notice, these Guidelines will be used by USPTO personnel in their review of patent applications for compliance with the ''written description'' requirement of 35 U.S.C. 112, ¶ 1. Because these Guidelines only govern internal practices, they are exempt from notice and comment rulemaking under 5 U.S.C. 553(b)(A).

Discussion of Public Comments

Comments were received from 48 individuals and 18 organizations in response to the request for comments on the ''Revised Interim Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 'Written Description' Requirement'' published in the **Federal Register** at 64 FR 71427, Dec. 21, 1999, and in the Official Gazette at 1231 O.G. 123, Feb. 29, 2000. The written comments have been carefully considered.

Overview of Comments

The majority of comments favored issuance of final written description guidelines with minor revisions. Comments pertaining to the written description guidelines are addressed in detail below. A few comments addressed particular concerns with respect to the associated examiner training materials that are available for public inspection at the USPTO web site (www.uspto.gov). Such comments will be taken under advisement in the revision of the training materials; consequently, these comments are not specifically addressed below as they do not impact the content of the Guidelines. Several comments raised issues pertaining to the patentability of ESTs, genes, or genomic inventions with respect to subject matter eligibility (35 U.S.C. 101), novelty (35 U.S.C. 102), or obviousness (35 U.S.C. 103). As these comments do not pertain to the written description requirement under 35 U.S.C. 112, they have not been addressed. However, the aforementioned comments are fully addressed in the ''Discussion of Public Comments'' in the ''Utility Examination Guidelines'' Final Notice, which will be published at or about the same time as the present Guidelines.

Responses to Specific Comments

(1) *Comment:* One comment stated that the Guidelines instruct the patent examiner to determine the correspondence between what applicant has described as the essential identifying characteristic features of the invention and what applicant has claimed, and that such analysis will lead to error. According to the comment, the examiner may decide what applicant should have claimed and reject the claim for failure to claim what the examiner considers to be the invention. Another comment suggested that the Guidelines should clarify what is meant by ''essential features of the invention.'' Another comment suggested that what applicant has identified as the ''essential distinguishing characteristics'' of the invention should be understood in terms of *Fiers* v. *Revel*, 984 F.2d 1164, 1169, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993) (''Conception of a substance claimed *per se* without reference to a process requires conception of its structure, name,

EXHIBIT E

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Date: 17-07-2009

Reference	Application No./Patent No.
OPPO 06	95305605.8 - 2405 / 0705903

Applicant/Proprietor: The University of Utah Research Foundation

Decision to maintain the European patent in amended form (Art. 101(3)(a) EPC)

European Patent No. : **0705903**
Filing date : 11.08.95
Priority claimed : 12.08.94/ USA 289221
02.09.94/ USA 300266
16.09.94/ USA 308104
29.11.94/ USA 348824
24.03.95/ USA 409305
07.06.95/ USA 480784
07.06.95/ USA 483553

Designated States and
Patent proprietor(s) : AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
The University of Utah Research Foundation
615 Arapeen Drive, Suite 310
Salt Lake City,
Utah 84108/US

is maintained as amended.

Registered letter
EPO Form 2329 12.07 10.07.09

to EPO postal service: 10.07.09

Maintenance is based on the documents as specified and notified previously.

The announcement that the European patent is being maintained as amended will be published in the European Patent Bulletin 09/33 on 12.08.09.

Your attention is drawn to the communication of 16.03.09, regarding the requirements and time limits for submitting translations of the new European Patent Specification in the designated Contracting States.

Opposition division

1st Examiner:	2nd Examiner:	Chairman:	Legally qualified member:
Stolz B	Sprinks M	Isert B	Treichel P

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Datum/Date 09.06.05

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
K27090PP(EP)S3	95305605.8-2405/0705903

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
THE UNIVERSITY OF UTAH RESEARCH FOUNDATION

INTERLOCUTORY DECISION IN OPPOSITION PROCEEDINGS (ARTICLES 102(3) AND 106(3) EPC)

The Opposition Division - at the oral proceedings dated 24./25.01.05
- has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.
[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

POSSIBILITY OF APPEAL:
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

OPPOSITION DIVISION:

ISERT B Chairman	STOLZ B 1st Examiner
SPRINKS M T 2nd Examiner	TREICHEL P E Legally qualified examiner

Enclosures: Reasons for the decision (Form 2916, 16 pages)
Text of Articles 106-108 EPC (Form 2019)
Documents relating to the amended text (Form 2339.4)
[ ] Minutes of oral proceedings

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Datum/Date
09.06.05

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
E18565-BF OPPO 01-03	95305605.8-2405/0705903

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
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The Opposition Division - at the oral proceedings dated 24., 25.01.05 - has decided:

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Datum/Date

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
K1873EP OPPO 04	95305605.8-2405/0705903

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
THE UNIVERSITY OF UTAH RESEARCH FOUNDATION

INTERLOCUTORY DECISION IN OPPOSITION PROCEEDINGS (ARTICLE 106(3) EPC)

The Opposition Division - at the oral proceedings dated 24., 25.01.05
- has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.
[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

POSSIBILITY OF APPEAL:
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

OPPOSITION DIVISION:

ISERT B	STOLZ B
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2nd Examiner	Legally qualified examiner

Enclosures: Reasons for the decision (Form 2916, 16 pages)
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Datum/Date 09.06.05

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./Brevet n°.
BZ718BSW/CS OPPO 05	95305605.8-2405/0705903

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
THE UNIVERSITY OF UTAH RESEARCH FOUNDATION

INTERLOCUTORY DECISION IN OPPOSITION PROCEEDINGS (ARTICLE 106(3) EPC)

The Opposition Division - at the oral proceedings dated 24.25.01.05
- has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.
[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

POSSIBILITY OF APPEAL:
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

OPPOSITION DIVISION:

ISERT B Chairman	STOLZ B 1st Examiner
SPRINKS M T 2nd Examiner	TREICHEL P E Legally qualified examiner

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Datum/Date
09.06.05

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr ./Patent No./Brevet n°.
OPPO 06	95305605.8-2405/0705903

Anmelder/Applicant/Demandeur/Patentinhaber/Proprietor/Titulaire
THE UNIVERSITY OF UTAH RESEARCH FOUNDATION

INTERLOCUTORY DECISION IN OPPOSITION PROCEEDINGS (ARTICLE 106(3) EPC)

The Opposition Division - at the oral proceedings dated 24.,25.01.05
- has decided:

Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the Convention.
[ ] Additional decision:

The reasons for the decision together with Form 2339 relating to the documents on which it is based are enclosed.

POSSIBILITY OF APPEAL:
This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 EPC.

OPPOSITION DIVISION:

ISERT B Chairman	STOLZ B 1st Examiner
SPRINKS M T 2nd Examiner	TREICHEL P E Legally qualified examiner

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[ ] Minutes of oral proceedings

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Facts and Submissions

1. European Patent No. 705903 is based on European Patent application No. 95305605. The filing date is 11.08.1995. Mention of the grant was published on 23.05.2001 in Bulletin 2001/21.

2. Oppositions have been filed by the following parties and on the following dates:

O1:	Institut Curie, Paris, France	22.02.2002
O2:	Assistance Publique, Hopitaux de Paris, France	22.02.2002
O3:	Institut Gustave Roussy, Villejuif, France	22.02.2002
O4:	Vereniging van Stichtingen Klinische Genetica Leiden, The Netherlands, et al.	25.02.2002
O5:	De Staat der Nederlanden	22.02.2002
O6:	Greenpeace e.V., Hamburg, Deutschland	22.02.2002

Oppositions were filed under Art. 100(a), 100(b) and 100(c) EPC, i.e. for lack of novelty (Art.54 EPC), inventive step (Art. 56 EPC), non-patentability of subject matter (Art. 52(2) EPC), lack of industrial applicability (Art. 57 EPC), insufficiency of disclosure (Art. 83 EPC), and extension of scope (Art. 123(2) EPC). In support of the submissions by the opponents, a large number of documents has been cited.

All opponents requested revocation of the patent in its entirety.

3. In a letter dated 10.12.2002, the Patentee (P) presented his position and submitted a new set of claims as well as several documents. He presented a consolidated list of the documents cited (D1-D97) (the list, including also later filed documents, is shown as Annex). He requested maintenance of the patent on the basis of the new set of claims.

4. Third party observations (Art. 115 EPC) were filed on 24.02.2003. Their contents appeared however to be directed to the copending opposition against EP 705902. The submissions went in any case not beyond the submissions already filed by other opposing parties.

5. A summons to attend oral proceedings together with a preliminary opinion of the

Opposition Division (OD) was issued on 26.04.04. The deadline for written submissions was set to 24.11.2004.

6. With letter dated 20.10.2004, the P requested postponement of the oral proceedings or as an auxiliary measure to set the deadline for written submissions to 24.12.2004. The OD did not follow this request (cf. communication of 09.11.2004).

7. In a letter dated 24.11.2004, the P filed a new main and three auxiliary requests as well as documents D98 to D100.
In a letter dated 24.11.2004, O4 submitted further observations as well as documents D101 to D107.

8. Oral proceedings were held on 24 and 25 January, 2005, during which a new auxiliary request I was submitted. Pending auxiliary requests 1 to 3 were renumbered as 2 to 4. Furthermore, during the proceedings a new auxiliary request 3 was filed which replaced pending and renumbered auxiliary request 3. The P also filed D108 (shown as Annex), which was admitted into the proceedings.

   In view of the late filing, the OD exerted its discretion under Art. 114(2) EPC not to admit Auxiliary request 1.

9. At the end of the proceedings the OD announced its interlocutory decision to maintain the patent on the basis of auxiliary request 3 and the description as amended during the proceedings.

Reasons for the decision

10. The oppositions filed by all parties are admissible. The requirements of Art. 99(1) and Art. 100 EPC, and of R. 1(1) and R. 55 EPC, are met.

11. The main request

    Claim 1 of the main request is directed to: a method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in the sequence of the BRCA1

gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof, said alteration indicating a predisposition to said cancer being 185delAG->ter39.

Independent claim 6 is directed to: a nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG->ter39.

12. Art. 123(2,3) EPC

12.1 The opponents held that the mutation referred to in claim 1 represented an arbitrary selection of a particular mutation from among many mutations listed in Tables 12, 12A and 14 of the application as originally filed, and they did not see a basis for this selection. Also, the term "SEQ ID NO: 1 or a wild-type allelic variant" was submitted to have no basis in the original disclosure, let alone a method combining all the features of claim 1. As for claim 6, it was submitted that the range of 15 to 30 nucleotides of SEQ ID NO: 1 was without basis.

12.2 The OD regards claim 17 of the application document as the most obvious basis for new claim 1. This claim is literally identical in wording except for the last half sentence specifying the mutation. Instead of referring literally to 185delAG->ter39, the originally filed claim reads: said alterations indicating a predisposition to said cancer being selected from the mutations set forth in Tables 12, 12A and 14. The reference in claim 1 to Table 14 (and to the other Tables) is a clear and unambiguous reference to the many mutations listed therein. This reference represents the most concise form of referring to the specific mutations. Thus, the claim as originally filed is directed to methods of diagnosing a predisposition for breast and ovarian cancer by essentially determining if any of the mutations individually listed in said Tables is present. Since 185delAG->ter39 is the second mutation of Table 14, claim 17 as originally filed clearly and unambiguously disclosed a method of diagnosing a predisposition to breast and ovarian cancer which comprised determining if the alteration was 185delAG->ter. The OD agrees therefore with the P that claim 1 meets the requirements of Art. 123(2) EPC. Since independent claims 1 and 2 are derived from claims 16 and 17 as granted by simply deleting all mutations but the 185delAG->ter39, there can be no extension of scope (Art. 123(3) EPC).

12.3 As for the range of 15 to 30 nucleotides of claim 6, there was agreement among

all parties that there is no explicit disclosure. The OD regards originally filed claim 4 in combination with the definition of probes (pp.14/15) as sufficient basis.
Original claim 4 is directed to a nucleic acid probe wherein the nucleotide sequence is a portion of a nucleic acid encoded by SEQ ID NO: 1 including a mutation from the list set forth i.a. in Table 14. Thus, original claim 4 covers probes, i.e. portions of SEQ ID NO: 1, including the 185delAG mutation.
According to p. 15, lines 8-9, the probes may be short, e.g. in the range of about 8-30 base pairs, and furthermore according to p. 15, lines 22-23, at least about 15 nucleotides and fewer than about 6 kb. There are furthermore indications that short probes, i.e. the lower end of the range of 15-6000 bps are of special interest. The passages are: p. 11, line 14, describing probes as oligomers of about 30 nucleotides in length; p. 14, lines 19-22, describing probes as comprising at least 15 nucleotides, more usually about 7-15 codons (21 to 45 bps) and most preferably about 35 codons (105 bps).
Following T17/85, the instant application documents disclose a minimal value of 15 nucleotides (p. 14, line 19) within the broader range of 8 to 30 nucleotides (p. 15, lines 8-9), and an upper limit of 30 nucleotides of said broader range, hence it also discloses the range from this minimal value of 15 to the upper limit of 30 nucleotides. A similar argument can be made starting from the range of 15 to 6000 bps. According to p. 11, probes can be of 30 nucleotides in length. In combination with the statement that 30 can be the upper limit (of 8 to 30), the description discloses the range of 15 to 30 bps.
A shorter explanation of the same fact is that the disclosure of two overlapping ranges, i.e. 8 to 30 and 15 to 6000, respectively, also discloses the range of overlap, i.e. 15 to 30.
The OD is therefore of the opinion that the claimed range of 15 to 30 nucleotides is directly and unambiguously derivable from the application as filed. Thus, claim 3 meets the requirements of Art. 123(2) EPC.

Claim 3 as granted was directed to nucleic acid probes where the nucleotide sequence is a portion of a sequence which is SEQ ID 1 and contains a mutation as defined in claim 1. The 185delAG->ter39 mutation is the second mutation in claim 1. Claim 3 as granted contained no limitation of the length of the probes.
Claim 6 of the main request is directed to probes of 15 to 30 nucleotides in length comprising the 185delAG->ter39 mutation. The size range of the claimed probes is thus narrower than the range of the probes in claim 3 as granted. Hence, there is no contravention of Art. 123(3) EPC.

13. Art. 84 EPC

13.1 The Opponents submitted that the expression "wild-type allelic variant" lacked clarity in the absence of a definition of the function of the disclosed BRCA1 protein.

13.2 First, the OD is of the opinion that this expression was already present in claim 16 as granted and is therefore under formal aspects (Art. 84 EPC; T301/87) not open to an objection.
Second, even if the term were open to an objection, the OD is of the opinion that it is clear in the light of the patent specification. On p. 12, line 7, it is stated that individuals with the wild-type BRCA1 gene do not have cancer resulting from the BRCA1 allele. On p. 13, line 37, it is stated that the term BRCA1 allele refers to normal alleles as well as to alleles carrying variations that predispose individuals to develop cancer. Normal alleles and wild-type alleles are in this context synonymous. In the present context, it is therefore clear that the method of claim 1 requires comparison of a patient sequence with SEQ ID NO: 1 or an allelic variant which does not contain an alteration predisposing to cancer.

14. Art. 83 EPC

14.1 The Opponents submitted in essence that the method of claim 1 left the term "wild-type allelic variant" open to interpretation to such an extent that the person of skill could not know if there was a predisposition to cancer or not. Also, at the time of filing, there were insufficient data to allow the person of skill to draw a conclusion about the importance of the mutation.

14.2 In this context, the P submitted D108 to demonstrate that the mutation 185delAG ->ter39 was routinely assayed.

14.3 The OD is of the opinion that the latter objection relating to the availability of sufficient statistical data is in essence an objection under Art. 84 EPC for lack of support by the description. But even if one were to admit the objection, the OD considered the data on file sufficient. The mutation 185delAG has been found in several families (cf. Tables 14, 15) and is regarded as relatively common (p. 60, line 52 of the application as published). The conclusion in this paragraph is cautious in view of the fact that the tested families and the mutants found may not

be representative for other sets of patients. The final statement points however out, that the 185delAG mutation is also found in probands with minimal or no family history. The OD considers these statements sufficient to support claim 1. As to the objection that the method cannot be carried out by the person of skill (Art. 83 EPC), the OD is of the opinion that the description provides sufficient structural information about the BRCA1 gene in order to perform the method of claim 1. The essential feature of the method is the detection of the deletion of an A and a G at positions 185/186 of SEQ ID No: 1 or at the corresponding position of a wild-type allelic variant. The complete structure of the BRCA1 gene as well as several ways of testing for the deletion are mentioned (SEQ ID No: 1; p. 10 of the application document). From D108 it can be taken that this deletion is routinely tested for, and none of the cited documents mentions any technical difficulties in assessing the deletion. The OD agrees with the P, that the requirements of Art. 83 EPC are met.

15. Priority

15.1 The final sequence of the BRCA1 gene as defined in SEQ ID No: 1 is for the first time disclosed in P5 (US409305). The Opponents submitted in essence that the subject matter of claim 1 was defined by reference to SEQ ID NO: 1 and was therefore entitled to a priority date of 24.03.1995 (P5).

15.2 The P considered the subject matter to be disclosed in the priority application of 29.11.1994 (P4, US348824) because the essential feature of the claim was deletion of nucleotides AG at position 185/186. This could be found in Tables 14 and 15 of P4. The few differences in SEQ ID NO: 1 were not crucial.

15.3 The OD disagrees with the P's view that SEQ ID NO: 1 is a technical feature which is not related to the function and effect of the invention. In the P's submission, the function to be tested is the deletion at positions 185/186 while the remainder of the sequence is of less importance and should therefore be allowed to vary.
According to decision G 2/98 (OJ EPO 2001, 413), the requirement for claiming priority of 'the same invention', referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject- matter of the claim directly and unambiguously, using

common general knowledge, from the previous application as a whole (cf. decision G 2/98, point 9 of the reasons).
Furthermore, according to G 2/98 the concept of the same invention must be given a narrow or strict interpretation equating it with the concept of the same subject-matter. An extensive or broad interpretation making a distinction between technical features which are related to the function and effect of the invention and technical features which are not, with the possible consequence that a claimed invention is considered to remain the same even though a feature is modified or deleted, or a further feature is added, is inappropriate and prejudicial to a proper exercise of priority rights.
The OD considers Seq ID 1 to constitute an essential feature of claim 1. The claim is directed to a method of determining whether there is a germline alteration in a BRCA1 gene compared to SEQ ID NO: 1 or a wild-type allelic variant thereof. SEQ ID NO: 1 is thus not only the reference sequence for the assessment of whether there is a deletion at positions 185/186 or not but also the reference sequence for the definition of wild-type allelic variants. Hence, it is essential. Since the exact sequence of SEQ ID NO: 1 has been disclosed in P5, the claim has basis in said priority application.

16. Art. 54 EPC

16.1 Documents D5 and D6 were both published before the filing date of P5. For the purpose of identifying the mutations, both documents refer to the BRCA1 sequence deposited at Genbank under accession number U14680 (D5, Table 3; D6, p. 398, left column) and available to the public since October 8, 1994. At least as far as the numbering is concerned, this sequence matches Seq ID No: 1 of P5. Thus, there is no doubt that both documents refer to the same 185delAG mutation as the instant application (D5, Table 3; D6, Table 3). In both documents del185AG ->ter39 is identified as one of the relatively common mutations (D5, p. 395, 1st paragraph; D6, p. 539, right hand column, "frequency of recurrent mutations"). In these documents, the method of detecting the 185delAG mutation has not been applied to the diagnosis of a predisposition to breast or ovarian cancer but rather to the assessment of the genetic status of affected patients. Thus, there is no explicit disclosure of the diagnostic method of claims 1 or 2. However, both documents conclude with a suggestion that screening for these recurrent mutations could lead to a relatively simple diagnostic test (D5, abstract, "Conclusions") or that screening for BRCA1 mutations in high risk woman could

be facilitated if common mutations are sought first (D6, p. 396, right hand column). Thus, D5 directly suggests to use a screen for the presence of the 185del->AG mutation in a diagnostic test. Taking into consideration the whole context of these documents, the OD considers the concluding remarks of both documents to anticipate the subject matter of claims 1 and 2.
Consequently, the main request lacks novelty (Art. 54(2) EPC).

17. Auxiliary Request 1

17.1 This request was submitted at the oral proceedings.
Claims 1 and 2 of this request differ from the main request in that the reference to Seq ID 1 and allelic variants thereof was replaced by a reference to GenBank accession number U-14680 of October 8, 1994.

As a basis for this element, the P referred to p. 43, line 7, of the application document and to the corresponding passage on p. 74, line 18, of P4.
As a reason for the late filing, the P mentioned that this amendment had only come to his mind after the oral proceedings of a related case, the week before, had shown that Auxiliary request 1 as filed with letter of 24.11.2004 would probably not overcome the objections of the Os. The P also submitted that the deposited sequence U-14680 had been cited as novelty destroying and that therefore the opponents were familiar with this item.

17.2 The opponents strongly objected to the admission of this new request because the amendment was completely unexpected and led to new problems under Art. 123(2,3) EPC, Art. 84 EPC, and Art. 87 EPC.

17.3 It is the ODs opinion that Auxiliary request 1 is inadmissible at this stage of the proceedings. Since the main request has been maintained, it is an additional request, which was filed at the latest possible moment (during oral proceedings) and therefore only allowable under specific circumstances (cf. e.g. T 153/85, T 648/96, T 794/94). The criteria for admissibility have been developed for proceedings before the Boards of Appeal but were also held to apply to opposition proceedings (T 648/96, pt. 2.2).
A prerequisite is clear admissibility in order to avoid undue delay or interruption of the proceedings (T 406/86, pt. 3.2; T 648/96, pt. 2.2; T 794/94, pt. 2.1).
New claims 1 and 2 define the reference sequence used for diagnosing a

predisposition to breast or ovarian cancer by reference to a sequence deposited at GenBank under accession number U-14680 at October 8, 1994. Thus, a feature from the description has been introduced into the claim. Up to this point of the proceedings, it was the P's position (cf. P's submissions in Annex III, pp. 13-15, of 10.12.2002), that the sequence deposited as U-14680 at October 8, 1994 was different from SEQ ID NO: 1 of the granted claims. Therefore, the OD agrees with the Os that this is a completely unexpected submission comprising new subject matter. They can therefore not be reasonably expected to be prepared for this case.

Moreover, the proposed amendments would only be admissible if they were clearly allowable (e.g. T 631/92, pt. 2.1). However, a preliminary analysis under Art. 123(2,3) and Art. 84 EPC reveals that the claims are not clearly allowable. The description contains a reference to U-14680 but does not mention a date of October 8, 1994. Thus, there is possibly no basis for this feature of the claims (Art. 123(2) EPC). As long as the exact history of U-14680 has not been established, it is furthermore open, if the shift from Seq ID 1 to U-14680 as a reference sequence would lead to an extension or shift of the scope of protection (Art. 123(3) EPC).

Introduction of a reference to a DNA sequence in an external database is also inadequate to define the subject matter in a claim. The sequence of U-14680 is not disclosed in any part of the patent application or the patent specification. Defining the claimed subject matter in this way does not put the person of skill into a position of establishing the scope of protection on the basis of the patent specification alone. Hence, the claims are not clear (Art. 84 EPC).

In view of these new, unresolved issues, the OD does not consider Auxiliary request 1 to be clearly allowable under Articles 123(2,3) and 84 EPC.

Furthermore, in view of the fact that priority has been an issue from the beginning of opposition proceedings, the OD does not accept P's reasons for the late submission. It therefore exercises its discretion under Art. 114(2) EPC not to admit Auxiliary Request 1.

18. Auxiliary Request 2

Basically, the first claim is directed to a method for diagnosing a predisposition for breast or ovarian cancer comprising the detection of a germline alteration defined as the deletion of AG in a position which in turn is defined by reference to a

human BRCA1 gene. This latter BRCA1 gene is defined as being obtainable by cloning it either from a genomic or from a cDNA library (as specified in the claim), and encoding a polypeptide of 1863 amino acids in length, having a molecular weight of 208 kilodaltons, and comprising SEQ ID No: 82.

19. Art. 123(2) EPC, Art. 84 EPC

19.1 The P provided detailed information on the basis of the disclosure of the claimed subject matter in the application document as filed.

19.2 The Opponents regarded the claim as a combination of features which was not directly and unambiguously derivable from the application as filed (mosaicing). Furthermore, it was questioned if a product by process definition should be allowed in a method (process) claim at all. A clarity objection was raised against the feature "208 kilodaltons" because the way of assessing it was unspecified and different results would be obtained depending on the method used.

19.3 The OD takes the view that there is no fundamental problem with using a product by process definition for a reference product in a method claim. This holds true as long as the reference product is unambiguously defined by the specified process(es). The prerequisite is a clear and unambiguous basis in the application documents as filed.

The OD recognizes an unambiguous basis for the subject matter of the first eight lines of claim 1 (cf. above, point 12.2). However, the subsequent specification of the BRCA1 gene lacks basis.

The processes of screening for and isolating the BRCA1 gene from a genomic or a cDNA library produce a family of genes that may differ structurally at various positions. From this family of genes, the definition of claim 1 requires the selection of a subgroup of molecules defined as encoding a BRCA1 protein having 1863 amino acids in length, a molecular weight of 208 kilodaltons and comprising SEQ ID NO: 82 (the zinc finger domain). These latter three elements are all disclosed in Example 8 (p. 42/43 of the application as published), SEQ ID NO: 82 being identical to the sequence of Fig. 5 discussed therein. These features are derived from the specific sequence of SEQ ID NO: 1. But Example 8 does not disclose a family of BRCA1 genes defined by sharing the afore mentioned three features. Example 8 discloses a BRCA1 protein in which not only the segment of SEQ ID NO: 82 is completely specified but also the remainder of the sequence (SEQ ID

NO: 2). Based on this specific sequence of 1863 amino acids, a molecular mass for the protein of SEQ ID NO: 2 of 208 kilodaltons is estimated. The present claim 1 now presents a definition of a BRCA1 gene combining three select features from Example 8 with a generic definition of the BRCA1 gene. The OD considers already this combination of a generic definition with the three specific elements from Example 8 as not directly and unambiguously derivable from the application document.

Moreover, the OD can also not recognize a basis for the definition of the BRCA1 gene as being obtainable by using the probes listed in claim 1. For instance the zinc finger element was nowhere suggested to be useful as a probe, nor is it a likely candidate for a probe. In view of the cited considerable homology (p. 43, line 13) with known domains, it seems more likely that the person of skill would not use probes comprising the zinc finger element. This notion finds support on. p. 45 (line 51) of the application document, where probes were used to detect BRCA1 like sequences in different species under low stringency conditions. These probes specifically lacked the zinc finger domain. The second probe has been used for Northern blots but has also not been suggested to be useful for genomic cloning.
For all these reasons, the OD considers claims 1 and 2 to contravene the requirements of Art. 123(2) EPC.

19.4 The OD agrees with the Os that the feature of "a molecular weight of 208 kilodaltons" is open to interpretation in the absence of an indication how it is determined. The claim is therefore unclear (Art. 84 EPC).

19.5 Auxiliary Request 2 does therefore not meet the requirements of articles 123(2) and 84 EPC.

20. Auxiliary Request 3

Claim 1 is directed to: a nucleic acid probe consisting of 15 to 30 nucleotides of SEQ ID No: 1 and containing the mutation 185delAG->ter39.
Claim 2 is directed to a replicative cloning vector which comprises an isolated nucleic acid according to claim 1 and a replicon operative in a host cell for said vector.
Claim 3 is directed to host cells in vitro transformed with the vector of claim 2.

21. Art. 123(2,3) EPC, Art. 83 EPC, Art. 84 EPC

In view of the OD's opinion about claim 6 of the main request (cf. pt. 12.3 above), the Opponents didn't have any further objections under the cited articles.
The OD cannot recognize any problems under these articles and is therefore satisfied that the respective requirements are met.

22. Priority

The Opponents submitted in essence that claim 1 still contained a reference to SEQ ID NO: 1 which constituted a technical feature of the claim and was therefore only entitled to the priority date of 24.03.1995 (P5).

The OD disagrees with this view. The subject matter of claim 1 is a probe consisting of 15 to 30 nucleotides of SEQ ID NO: 1 and containing the mutation 185delAG->ter39. The subject matter is therefore not the whole of SEQ ID NO: 1 but nucleotide fragments of defined length derived from the segment spanning nucleotides 157 to 214 of SEQ ID NO: 1.
P4 discloses probes, nucleic acid oligomers, each of which contains a region of the BRCA1 gene sequence harboring a known mutation (p. 20, lines 2-3). The 185delAG mutation is disclosed in Table 14 (further support for this can be found in claim 2 of P4). The same passages as in the application document can be found in P4, discussing the length of suitable probes (p. 26, lines 25-26; p. 28, line 17; p. 29, lines 5-7). If one accepts these passages as a basis for a claim to probes of 15 to 30 nucleotides in length (cf. above, point 12.3), then P4 must be seen as disclosing probes of 15 to 30 nucleotides in length covering the 185delAG deletion. This deletion in Table 14 is numbered by reference to sequence U14680, i.e. the deletion is in codons 22 and 23, corresponding to nucleotides 129 and 130 of SEQ ID NO: 1 of P4 (the coding sequence of SEQ ID NO: 1 (P4) begins at nucleotide 64 (p. 106)). Probes of at most 30 nucleotides in length and containing the mutation 185delAG must thus be derived from the nucleotide segment spanning nucleotides 100 to 158 of said SEQ ID NO: 1. Close inspection of this stretch and comparison with the respective stretch of nucleotides of SEQ ID NO: 1 of the application document as filed reveals a complete match. Thus, the subject matter of claim 1 is structurally identical to what was disclosed in P4. Consequently, the OD takes the view that P4 discloses the claimed subject matter in an enabling manner, taking into account the whole

disclosure (G 2/98) and claim 1 enjoys priority from P4.

23. Art. 54(2) EPC

The Opponents had no objections under Art. 54(2) EPC.
None of the documents on file discloses probes as defined in claim 1 or vectors comprising such probes according to claim 2. The requirements of this article are therefore met.

24. Art. 56 EPC

24.1 The Opponents submitted in essence that the technical problem to be solved was the finding of further mutations of diagnostic value in BRCA1. Its solution was obvious after the publication of D1 and U14680, i.e. after localisation and sequencing of the BRCA1 gene. This reasoning was supported by D91 (a submission by the P in a parallel case) stating that within a matter of weeks after the publication at least two other groups had identified various predisposing mutations. The selection of the 185delAG mutation was arbitrary because there was neither a prejudice nor a particular problem to be overcome nor an unexpected result. The 185delAG mutation was the most common and would thus inevitably have been found in the ongoing screens. Families BOV3 (D9) and 2979 (D42) were both later found to contain this particular mutation (D47).

24.2 Claim 1 is now directed to a nucleic acid probe of specified length and sequence which is suitable to detect a particular mutation in the BRCA1 gene. According to Table 15 and the paragraph bridging pp. 60/61 of the application as filed, the 185delAG mutation is relatively frequent. It was also found multiple times in targeted screening of probands from families with minimal or no family history.

All parties and the OD consider D1 to represent the closest prior art. D1 discloses the gene sequence of BRCA1, lists some predisposing mutations (Table 2) and concludes by stating: Nevertheless, the percentage of total breast and ovarian cancer caused by mutant BRCA1 alleles will soon be estimated, and individual mutations and penetration frequencies may be established. This in turn may predict accurate genetic screening for predisposition to a common deadly disease.

Vis-à-vis D1, the technical problem to be solved is thus the provision of a means to detect a frequently occurring predisposing mutation in BRCA1.

This problem is solved by the probes of claim 1.

The OD agrees with the Os that the mere identification of further predisposing mutations did not pose particular technical problems to the person of skill after the publication of D1. Also, the person of skill certainly had an interest in finding further predisposing mutations (cf. e.g. D9, D12, D42). The Os argued that finding the mutation was a matter of time and since it was a frequent mutation, it would have been found inevitably.
This does however not imply that the person of skill had a reasonable expectation of success of finding a particularly frequent mutation. D1 itself does not provide any information to lead the person of skill to the claimed probes. Also, D1 provides no information about the frequency of individual mutations. Although some publications on file such as D9 or D42 disclose pedigrees of affected families they do not disclose any of the specific mutations because at that time no sequence information was available. For the same reason they cannot provide any information about the frequency of occurrence of particular mutations. Even if one assumes that samples of the affected different families were available to the person of skill, e.g. from D9, D20, or D42 he would not have known which sample to choose from. Therefore, when using D1 alone or in combination with any of the documents D9, D20 or D42, he would not have identified with a reasonable expectation of success the 185delAG mutation as a frequent mutation.
The OD agrees with P's view that the screening for frequently occurring mutations provides an advantage in screening because by screening for the more frequent mutations first, the number of tests and hence the costs may be reduced. This advantage is seen in the application as filed where it is stated that the 185delAG mutation was found multiple times in patients not selected for family history (p.60, line 58 to p. 61, line 2). Therefore, the OD considers the claims of Auxiliary request 3 to involve an inventive step.

25. Art. 52(2) EPC

25.1 O6 cited D89 and submitted in essence that the isolation of the BRCA1 gene or of any human gene for that matter was a mere discovery which constituted no patentable invention.

25.2 European Directive 98/44 EU and the corresponding implementing Regulations of the EPC clearly state that "an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element" (Rule 23e(2) EPC, Art. 5(2) EU Directive).
The very wording of this implementing Rule contradicts O6's submission. There is no fundamental bar to the patenting of complete or partial human gene sequences (cf. also T272/95, Reasons 4-9).

Claims 1 to 3 directly or indirectly relate to DNAs encoding parts of the human BRCA1 protein, which is described throughout the patent in suit as having been obtained by technical processes (e.g. Example 8). They, thus, meet the definition of patentable elements of the human body given in Rule 23(e)(2) EPC.
Accordingly, they do not fall within the category of inventions which may not be patented for being discoveries (Article 52(2)(a) EPC).

26. Art. 57 EPC

26.1 No objections have been raised against the granted claims to probes or vectors and host cells comprising these probes (granted claims 3 to 6).
The OD notes that the patent application taught the use of probes in diagnosing a predisposition to breast or ovarian cancer (p. 19) and therefore meets the requirement of Rule 23e(3) EPC and Art. 57 EPC.

27. Art. 53(a) EPC

27.1 O6 submitted that the patent should be revoked under Art. 53(a) EPC in view of the socio economic consequences which in this case were well documented (D55-D58, D63, D67). He requested that in analogy with R. 23d(d) EPC there should be found a balance between the benefits and the drawbacks to society due to the grant of a monopoly.

27.2 First, the OD notes that the present set of claims relates to specific probes, vectors and cells, and not to genes. The OD cannot recognize in what respect the publication or exploitation of the now claimed invention, i.e. the defined probes and vectors which are widely considered to be useful in the field of

diagnostics (D108), could be contrary to order public or morality.

Even if the claims were directed to genes, the OD could not follow O6' arguments. As can be taken from the clear wording of Art. 53(a) EPC and from the relevant case law of the EPO boards of appeal (T 19/90, OJ 1990, 476 and T 356/93, OJ 1995, 545; T 272/95 of 23 October 2002), Art. 53(a) EPC can only apply in rather exceptional cases, namely where the publication or exploitation of the invention as claimed is in conflict with basic legal or ethical values. None of the objections raised by O6 is of such nature. O6 focused on possible negative effects of the patenting of the invention in suit and pointed to financial and economic drawbacks or dependencies and negative consequences for the health system. The EPO has however not been vested with the task of taking into account the socio-economic effects of the grant of patents in specific areas and of restricting the field of patentable subject-matter accordingly (G1/98, OJ EPO 2000, 111, Reasons, point 3.9; Guidelines for examination in the EPO, C-IV, 3.3a). The standard to apply for an exclusion under Art. 53(a) EPC is whether the publication or the exploitation of the invention is contrary to ordre public or morality. Art. 53(a) EPC does thus not provide the EPO with the competence to refuse or revoke a patent by assessing certain alleged negative consequences which may result from the grant of an exclusive right in an individual case.

Finally, Rule 23(e)(2) EPC, which corresponds to Art. 5(2) of Directive 98/44 of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions clearly defines which biological material originating from the human body may be patented (cf. pt. 25.2 above). It follows from the text of the Rule itself that the matter of the patent in suit is not to be considered as an exception to patentability under Article 53(a) EPC (see T 272/95 of 23 October 2002, Reasons, 6-9). This is in conformity with the established practice of the EPO (cf. Guidelines, C-IV, 2a.2; see also Relaxin decision, OJ EPO 1995, 388)

28. The OD is therefore of the opinion that the claims of the Auxiliary Request meet the requirements of the EPC.

ANNEX 1: Cited Documents

	D no.	OI-III	OIV	OV	OVI
Miki et al., Science (7 October 1994) 266, 66-71	D1	*	D102	D5	
Castilla et al., Nature Genetics (December 1994) 8, 387-391	D2	*	D104	D6	
Friedman et al., Nature Genetics (December 1994) 8, 399-404	D3	*	D101	D2	
Futreal et al., Science (7 October 1994) 266, 120-122	D4	*	D103	D1	
Shattuck-Eidens et al., JAMA (February 1995) 273, 535-541	D5	*	D307	D4	
Simard et al., Nature Genetics (December 1994) 8, 392-398	D6	*	D106	D3	
Abstract, Hall et al., Science (1990) 250, 1684-1689	D7	*			
Bishop & Eaton, Am. J. Hum. Genet. (1993) 52, 677	D8	*			
Kelsell et al., Hum. Mol. Genet. (1993) 2, 1823-1828	D9	*	D143		
Jones et al., Hum. Mol. Genet. (1994) 3, 1927-1934	D10	*			
Albertsen et al., Nature Genetics (1994) 7, 472-479	D11	*			
Weber et al., Cancer (August 1994) 74 (3 suppl.) 1013-1020	D12	*			
Brown et al., Proc. Natl. Acad. Sci. USA(1995) 92, 4362-4366	D13	*			
Rowell et al., Am. J. Hum. Genet. (November 1994) 55, 861-865	D14	*			
Black & Solomon, Tends Genet (January 1993) 9, 22-26	D15	*			
Weber et al., Cold Spring Harb. Symp. Quant. Biol. (1994) 59, 531-536	D16	*			
Information re Genbank sequence U14680	D17	*			
Program from the congress relating to BRCA1 at Lillehammer, 27 February – 1 March 1995 + list of participants	D18	*			
Ford et al., Lancet (1994) 343, 692-695	D19		D134		
Easton et al., Am. J. Hum. Genet. (1993) 52, 678-701	D20		D139		D33
Hall J M et al., Science (1990) 250, 1684-1689	D21	See D10	D147		D28
Anderson et al., Genomics (1993) 17, 618-623	D22		D170		
Szabo et al., Breast Cancer information core database (2000) 16, 123-131	D23		D185		
Bakker at al., Lancet (1985) 1, 655-658	D24		D190		
Hogervorst et al., Nature Genetics (June 1995) 10, 208-212	D25		D191	D12	
USSN 08/246,602	D26		D198	D20	
Struewing et al., Am. J. Hum. Genet. (1995) 57, 1-7	D27		D305	D8	

Durocher et al., Hum. Mol. Genet. (1996) 5, 835-842	D28		D308	D15/ 18	
Tonin et al., Am. J. Hum. Genet. (1995) 57, 189	D29		D318	D13	
Inoue et al., Cancer Res. (1995) 55, 3521-3524	D30		D319		
Grompe, Nature Genetics (1993) 5, 111-117	D31		D322		
Smith et al., Am. J. Hum. Genet. (1993) 52, 767-776	D32		D 332		
Steichen-Gerdorf et al., Am. J. Hum. Genet. (1994) 55, 870-875	D33		D333		
Biesecker et al., JAMA (1993) 269, 1970-1974	D34		D335		
Merajver et al., Nature Genetics (April 1995) 9, 439-443	D35		D336	D7	
Hosking et al., Nature Genetics (April 1995) 9, 343-344	D36		D337	D9	
Szabo & King, Hum. Mol. Genet. (1995) 4,1811-1817	D37		D338		
Spurr et al., Am. J. Hum. Genet. (1993) Am. J. Hum. Genet.	D38		D339		
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Boyd et al., Nature (1995) 375, 541-542	D43		D345	D10	
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Watson et al., Recombinant DNA, Scientific American Books,esp. Ch 27	D46		D350		
Extracts from the BIC database	D47		D401-407	D17	
E-mail from Dr Mary-Claire King	D48		D411		
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Ford, et al . The Lancet, 343, March 19, 1994, 692-695	D52				D4
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Ethics Commission of The French Governement, Opinion 8. 6. 2000	D71				D23
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EPO Enlarged Board of Appeal Decision G 1/91 (headnote provided)
EPO Appeal Board Decision T 939/92 (copy provided)
Decision of the Opposition Division re European Patent no. 0322240 as published in EPOR (2002) 2 (copy provided).

Opposition against EP-Patent 0 705 903
(95 30 5605.8)
University of Utah Research Foundation
~~Our Ref.: K2709 OPP(EP) S3~~

CONTINUATION OF THE CONSOLIDATED LIST OF DOCUMENTS

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Bakker Declaration	D104			D101		
Mazoyer Declaration	D105			D102		
WO 95/19369 (Holt et al.)	D106			D103		
U14680 BlastN Sequence Comparison	D107			D104		

EXHIBIT E

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

MAIN REQUEST

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in the sequence of the BRCA1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said alteration indicating a predisposition to said cancer being 185delAG→ter39.

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is a mutation in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.

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AUXILIARY REQUEST I

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is ~~a~~ germline alteration **185delAG→ter39** in the sequence of the BRCA1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in ~~SEQ ID NO: 1 or a wild-type allelic variant thereof, said alteration indicating a predisposition to said cancer being 185delAG→ter39.~~ **GenBank, accession number U-14680 of October 8, 1994**

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is ~~a~~ mutation **185delAG→ter39** in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in ~~SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.~~ **GenBank, accession number U-14680 of October 8, 1994.**

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for

hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.

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Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

AUXILIARY REQUEST 2

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in a tissue sample of said subject, said germline alteration indicating a predisposition to said cancer being that, compared to a human BRCA1 gene that has the coding sequence for a full-length human BRCA1 polypeptide, the third nucleotide of codon 22, A, and the first nucleotide of codon 23, G, are deleted resulting in a nucleotide sequence encoding 38 amino acids,

wherein said full-length human BRCA1 polypeptide

- has 1863 amino acids,
- has a molecular weight of 208 kilodaltons, and
- comprises the amino acid sequence of SEQ ID NO: 82,

said coding sequence being comprised in a genomic DNA which is obtainable by:

(a) providing a human genomic library;

(b) screening the genomic library using a probe selected from the group consisting of:

(i) the following DNA sequence:

TGT CCC ATC TGT CTG GAG TTG ATC AAG GAA CCT GTC
TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC
ATG CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA
CAG TGT CCT TTA TGT AAG

(ii) the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC

CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

(iii) the DNA sequence of any one of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 67, 72 and 81

and

(c) producing a genomic DNA comprising said coding sequence;

wherein said genomic DNA comprising said coding sequence is more than 100 kb in length; and

wherein the first exon within said genomic DNA immediately follows the nucleotide sequence corresponding to SEQ ID NO: 35; or

said coding sequence being comprised in a cDNA which is obtainable by:

(aa) providing a cDNA library using human mRNA from breast, thymus, testis or ovary;

(bb) screening the cDNA library using a probe selected from the group consisting of:

(i) the following DNA sequence:

TGT CCC ATC TGT CTG GAG TTG ATC AAG GAA CCT GTC
TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC
ATG CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA
CAG TGT CCT TTA TGT AAG

and

(ii) the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG

AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

(cc) producing a cDNA comprising said coding sequence;

wherein said coding sequence comprises the following nucleotide sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

wherein upon hybridization of a Northern blot with a fragment of said cDNA a single transcript of 7.8 kb is identified in breast, thymus, testis and ovary tissue.

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is a mutation in a sample from said lesion, said mutation being that, compared to a human BRCA1 gene that has the coding sequence for a full-length human BRCA1 polypeptide, the third nucleotide of codon 22, A, and the first nucleotide of codon 23, G, are deleted resulting in a

nucleotide sequence encoding 38 amino acids, wherein said full-length human BRCA1 polypeptide and said coding sequence are as defined in claim 1.

3. A method as claimed in claim 1 or claim 2 which comprises analyzing mRNA or protein of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele.

4. A method as claimed in claim 3 wherein the mRNA encoded by the BRCA1 gene in said sample is investigated.

5. A method as claimed in claim 4 wherein mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

6. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

7. A method as claimed in claim 5 or 6 wherein said probe is an allele-specific probe for a mutant BRCA1 allele as defined in claim 1.

8. A method as claimed in claim 1 or claim 2 which comprises determining whether there is a mutation in the BRCA1 gene in said sample by observing shifts in electrophoretic mobility of single-stranded DNA from said sample on non-denaturing polyacrylamide gels.

9. A method as claimed in claim 1 or claim 2 wherein all or part of the BRCA1 gene in said sample is amplified and the sequence of said amplified sequence is determined.

10. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are

employed which are specific for a mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

11. A method as claimed in claim 1 or claim 2 wherein all or part of the BRCA1 gene in said sample is cloned to produce a cloned sequence and the sequence of said cloned sequence is determined.

12. A method as claimed in any one of claims 1 to 4 which comprises determining whether there is a mismatch between molecules (1) BRCA1 gene genomic DNA or BRCA1 mRNA isolated from said sample, and (2) a nucleic acid probe complementary to human wild-type BRCA1 gene DNA, when molecules (1) and (2) are hybridized to each other to form a duplex.

13. A method as claimed in any one of claims 1 to 4 wherein amplification of BRCA1 gene sequences in said sample is carried out and hybridization of the amplified sequences to one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1 is determined.

14. A method as claimed in claim 1 or claim 2 which comprises determining in situ hybridization of the BRCA1 gene in said sample with one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1.

15. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

16. A replicative cloning vector which comprises an isolated nucleic acid according to claims 15 and a replicon operative in a host cell for said vector.

17. Host cells in vitro transformed with a vector as claimed in claim 16.

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

AUXILIARY REQUEST III

1. A nucleic acid probe ~~having~~ consisting of 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

2. A replicative cloning vector which comprises an isolated nucleic acid according to claim 1 and a replicon operative in a host cell for said vector.

3. Host cells in vitro transformed with a vector as claimed in claim 2.

An External Quality Assessment scheme for genetic testing of familial Breast / Ovarian Cancer

Clemens R. Mueller[1], Dominique Stoppa-Lyonnet[2], Ulf Kristoffersson[3]

[1] University of Wuerzburg, Wuerzburg, Germany, [2] Institut Curie, Paris, France, [3] Lund University Hospital, Lund, Sweden

INTRODUCTION

Breast and ovarian cancers (Br/Ov) are the most frequent cancers in women with a life-time risk of about 10 % in Western countries. About 5 % of all cases are thought to be familial due to mutations in the BRCA1 and BRCA2 genes. Given the prevalence of Br/Ov cancers, mutation screening of the BRCA genes is now being offered to at risk women. The main benefit of mutation detection is the predictive testing of relatives of identified mutation carriers. In 1999 a pilot External Quality Assessment (EQA) scheme was offered by the **European Molecular Genetics Quality Network (EMQN)** for the genetic testing of the BRCA1 gene. Following the successful trial, the scope of the scheme was widened in 2000 to include a case of a predictive test for a known family mutation and testing for the BRCA2 gene. The scheme was also offered to a wider audience of laboratories. The breakdown of participants by country is given in **Table 1.**

Table 1: EQA scheme participants

Country	1999	2000
Australia	-	1
Belgium	3	5
Czech Republic	1	1
Cyprus	-	1
Denmark	1	1
France	9	5
Germany	2	1
Israel	1	-
Italy	-	3
Latvia	-	1
Sweden	2	1
The Netherlands	1	4
United Kingdom	1	3
Total	21	28
No results returned	7	3

CASES AND QUESTIONS

In 1999, three genomic DNA samples were distributed and the analysis of exons 2, 13 and 17 of the BRCA1 gene was requested (**Table 2**). In 2000 the scheme included two samples for the BRCA1 gene (exons 2 and 11) plus one sample for BRCA2, exon 27 (**Table 3**). In both years, missense ("unclassified variants") and truncating mutations had to be detected, the 2000 scheme included a predictive diagnosis for the prevalent Ashkenazi mutation in the BRCA1 gene, 185delAG. This way, the most common situations for interpretation were covered. Various mutation (pre-)screening methods were used but results were based on sequence data in all but one cases.

Table 2: 1999 cases

Gene	Exon	Nt change	AA change	Conclusions
BRCA1	2	C140T	Arg7 > Arg	UV, splice site activation? Risk unchanged
BRCA1	17	A5176G	His1686 > Arg	UV, causal role possible but not proven, risk unchanged
BRCA1	13	C4446T	Arg1443 > Stop	Truncating mutation, highly probable to be causal, life-time risk increased

Table 3: 2000 cases

Gene	Exon	Nt change	AA change	Conclusions
BRCA1	2	185delAG	frameshift	carrier, high life-time risk
BRCA1	11	1259delG	frameshift	truncating, highly probable to be causal, life-time risk increased
BRCA2	27	A10462G	Ile3412 > Val	UV, polymorphism, risk unchanged

MATERIALS

Thanks to generous gifts of the Curie Institute in Paris, all samples could be prepared from cell lines. No problems with the quality of the samples were reported, a few labs asked for a second sample for confirmation which was provided

RESULTS

The overall results are listed in **Table 4** based on the total number of reports returned and the total number of cases analysed.

Table 4: EQA scheme results

Year	1999	2000
Samples sent out	21	28
Reports returned	14	25
Cases analysed	40	68
Diagnostic errors (mistakes leading to wrong diagnosis)	1	4
Error rate (diagnostic error/cases analysed)	2.5%	5.8%
Genotyping marks (Mean: max. of 2.00 points)	1.83	1.76
Interpretation marks (Mean: max of 2.00 points)	1.61	1.46

As was observed in other schemes, the error rate went up and the average marks decreased with the opening of the scheme to a broader participation. Most likely, this reflects the real situation better than the initial pilot scheme for which "the" national experts are likely to be nominated.

In the 1999 scheme, the sequence change C140T in exon 2 of BRCA1 (case 1) was not detected in 1 laboratory. One lab refused to analyse a sample because it was from a non-affected woman. Another lab found an extra sequence change in one sample. Both cases caused subsequent discussions (see below).

In the 2000 scheme, the sequence change 1259delG in exon 11 of BRCA1 (case 2) was not detected by 2 laboratories. The sequence change A10462G in exon 27 of BRCA2 (case 3) was not detected by 2 other labs.

ADMINISTRATION AND ASSESSMENT

Some participants were hard to contact by e-mail because of hand-written addresses. Online subscription may be a better option in the future. Reports were accepted either as hard copies or e-mail attachments. One e-mail did not at all reach the scheme provider. A brief confirmation of receipt of the scheme materials (by the participants) and of the reports (by the scheme provider) may help to identify mailing problems early on.

Dominique Stoppa-Lyonnet (Paris) and Ulf Kristofferson (Lund) served as assessors. During the evaluation of the reports it was very helpful to have the expertise of a molecular biologist (DSL) and a clinical geneticists (UK).

PARTICIPANTS FEEDBACK

There were only a few comments by the participants, mainly dealing with problems of marking or nomenclature. The refusal by one lab to test an unaffected woman was based on a misunderstanding of the scheme's intentions. Schemes are not designed to catch out participants or to test laboratory policies. A difficult case arose when one lab found two mutations in one sample, including the "true" one. Their report was not clear on the interpretation of this unusual result and initially scored as a diagnostic error. Upon the participant's complaint, the assessors' scoring was revised after consultation with the EMQN office.

CONCLUSIONS

The experiences from this scheme illustrate the well known problems associated with the use of DNA sequencing to identify unknown heterozygous mutations. Although sequencing is regarded as the "gold standard" of mutation detection by many, it requires careful internal and external quality assessment to arrive at the desired high sensitivity and specificity.

ADDITIONAL INFORMATION

REFERENCES

European Best Practice Guidelines for familial Breast/Ovarian Cancer
www.emqn.org/bpguidelines

THE SCHEME

THE FAMILIAL BREAST/OVARIAN CANCER SCHEME IS ORGANISED AND RUN BY THE EUROPEAN MOLECULAR GENETICS QUALITY NETWORK (EMQN)

Contact Dr Simon Patton or Dr Rob Elles, Regional Molecular Genetics laboratory, St Mary's Hospital, Hathersage Road, Manchester M13 0JH, UK. Tel: +44.161.276.6741/6129. Email: office@emqn.org

EMQN is funded by the European Commission (Contract No. SMT4-CT98-7515)

RELATED POSTERS

P1077- The European Molecular Genetics Quality Network
P1079 - EQA scheme for Huntington Disease
P1080 - EQA scheme for Duchenne Muscular Dystrophy
P1081 - EQA scheme for Friedreich Ataxia
P1082 - EQA scheme for Charcot Marie Tooth Disease
P1083 - EQA scheme for Y-Chromosome Microdeletions

Europäisches Patentamt
GD2-Einspruch

European Patent Office
DG2 - Opposition

Office européen des brevets
DG2 - Opposition

Application No.: 95 305 605.8

Patent No.: EP-B-0705903

Minutes of the oral proceedings before the OPPOSITION DIVISION

The proceedings were public.

Proceedings opened on 24.01.2005 at 0905 hours

Present as members of the opposition division:

Chairman:	Isert, B
1st member:	Stolz, B
2nd member:	Sprinks, M
Legal member:	Treichel, P
Minute writer:	Sprinks, M

Present as or for the party or parties:

- For the Proprietor(s): THE UNIVERSITY OF UTAH RESEARCH FOUNDATION

  H.R. Jaenichen (Representative)
  O. Malek (European Patent Attorney)
  D. Shattuck (Inventor)

- For the Opponent 1: INSTITUT CURIE

  J. Warcoin (Representative)
  F. Faivre Petit (European Patent Attorney)
  D. Stoppa-Lyonnet (Technical Expert)
  F. Lazard
  D. Delaplace

- For the Opponent 2: ASSISTANCE PUBLIQUE-HOPITAUX DE PARIS

  c.f. O1

- For the Opponent 3: INSTITUT GUSTAVE ROUSSY-IGR

  c.f. O1

- For the Opponent 4: Vereniging van Stichtingen Klinische Genetica

  W. Bird (Representative)
  I. De Baere (Candidate)
  L. Paemen
  G. Matthijs (Technical Expert)

- For the Opponent 5: De Staat der Nederlanden
  Minister van Volksgezondheid, Welzijn en Sport

  B. Swinkels (Representative)

Documents for the maintenance of the patent as amended

Auxiliary Request 3

In the text for the Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

Description, Pages

25-59, 61-138	of the patent specification
3-24, 60	filed during Oral proceedings on 25.01.2005

Claims, Numbers

1-3	filed during Oral proceedings on 24.01.2005

Drawings, Figures

1-10	of the patent specification

- For the Opponent 6: Greenpeace e.V.

  C. Then (Representative)

The identity of the person/s (as well as, if applicable, that of the witness or witnesses) and, where necessary, the authorisation to represent/authority to act were checked.

Essentials of the discussion and possible relevant statements of the parties:

After deliberation of the opposition division,

- the chairman announced the following **decision**:

"Account being taken of the amendments made by the patent proprietor during the opposition proceedings, the patent and the invention to which it relates are found to meet the requirements of the European Patent Convention. The currently valid documents are those according to the claims of Auxiliary Request III filed on 24.01.05; amended pages 3-24 and 60 of the description filed on 25.01.05; pages 1-2, 25-59 and 61-138 of the description and figures 1-10H of the patent as granted.."

Regarding the reasons for the decision, the chairman referred to:

Article 102(3) EPC.

The party/parties was/were informed that the minutes of the oral proceedings and a written reasoned decision (including an indication of the possibility of appeal) will be notified to him/them as soon as possible.

The chairman **closed the oral proceedings** on 25.01.2005 at 1405 hours.

Isert, B
Chairman

Sprinks, M
Minute Writer

Annex(es):
Main and Aux. Requests I-III, description p.3-24 and 60, D108

Form 2339.4

1. The chairman of the Opposition Division (OD) opened the proceedings at 0905 on 24.01.05 and briefly reviewed the file. He informed the parties that the proceedings would be sound recorded in accordance with the **Guidelines E-III, 10.1**.

2. The Proprietor (P) stated that he maintained his main request (MR) and auxiliary requests (AR) filed on 23.11.04 and asked for the opportunity to draft new ARs.

3. All six opponents (O) requested complete revocation. In addition O5 requested either that no further amendments to the requests be allowed, giving procedural abuse as the reason, or if further requests were allowed, that proceedings be suspended and costs be apportioned.

4. The chairman opened discussion on the MR w.r.t. **Article 123(2)(3) and 84 EPC**. O1-3 objected to claim 1 under **Art. 123(2) EPC**, reasoning that there was no original disclosure of a wild type allelic variant as a reference sequence. O1-3 added that there was only one mutation selected and this specific selection was not supported and that for claims 6-8, the range of 15-30 was not supported and that no specific length of probe was disclosed. Under **Art. 84 EPC** O1-3 stated that the expression wild type variant was unclear, particularly in a screening method. O4 agreed with O1-3 and added that claim 1 added matter by mosaicing features. O5 added that the arbitrary selection of a particular mutation in claim 1 added matter as it was targeted at Ashkenazi Jews and that this connection was only disclosed after filing. Furthermore, the size of 30 in claim 6 was only originally disclosed for a specific method and mutations. O6 added nothing.

5. P stated that the expression "wild type allelic variant" could not be objected to now as it was in the granted claims and the application as filed and had not changed. P added that the particular mutation in claim 1 was already in the list of mutations in granted claim 16 and could not legally be considered unclear. All that had been done was to delete all unpatentable mutations. P gave Example 15, Tables 14-17 and the paragraph bridging page 60 and 61 of the published application as basis for the mutation, and cited T10/97 to support the allow ability of deleting individual members from a list. W.r.t. the basis for the range of 15-30 nucleotides in claim 6, P indicated granted claim 3 as basis together with page 10 lines 29-34, page 11 line 12 and the section entitled "probes" starting on page 14 line 55. P also cited

T201/83 and T925/98, adding that there could be no **Art. 123(3)** objection as this was a restriction.

6. O1-3 reiterated that there was no original disclosure of using a wild type sequence as a reference for comparison and O4 repeated that this was unclear. OD asked P why he had chosen the range 15-30. P replied that it was so that the claim didn't include anything that had changed in the priority. After a short break, P indicated that page 15 line 8 was additional basis for this range selection.

7. After deliberation, the chairman gave the OD's opinion that the MR fulfilled the requirements of **Art. 123(2)(3) and 84 EPC** and opened the discussion on **Art. 83 EPC**.

8. O1-3 stated that the term wild type was not defined and therefore could not be used to make a comparison for pathology. O4 agreed and O5 added that one couldn't differentiate between non-predisposing alterations and mutants. P replied that those in the art could carry out the claim and that the opponents had done it. P requested that D108 be admitted in support of this and added that it should be attempted to make technical sense of the claim, citing T552/00 and T190/99, and that with only one mutation this was easy.

9. OD requested a copy of D108. After taking time to study the document, the chairman asked the parties for their comments. O1-3 requested that this document not be admitted as it was filed too late. O4 and O5 stated that it was not relevant to the use of wild type alleles and O4 added that it showed that in 5.8% of cases there were problems with errors. P referred to D104 in support that the method could be carried out, adding that there are false positives and negatives in any screening method. O4 submitted that Dr. Becker (D104) took risks with the analysis.

10. OD decided to admit D108 as relevant and after deliberation, the chairman gave the OD's opinion that the MR fulfilled the requirements of **Art. 83 EPC**. The chairman then opened the discussion on **Art. 87 EPC**.

11. O1-3 maintained that only the fifth priority (P5) was valid as claim 1 referred to SEQ ID NO:1 and that this was different in the fourth priority (P4). O1-3 added

that the mutation 185delAG-ter39 indicated the position of an AG in the sequence and that in P4 position 185 corresponded to AC instead - therefore the P4 sequence could not be used as a reference. O4-6 agreed.

P replied that the mutation name indicated a termination codon and that if one tried to make technical sense of the claim it would be clear where the mutation should be. P referred to Exhibit 1A, and Example 15 and page 95 line 7 of P4.

O4 referred to G2/98 and stated that the Enlarged Board of Appeal interpreted the principal of same invention narrowly. Subject-matter had to be the same for priority to be valid. This was extremely important for **Art. 54(3)**. O4 referred to T0351/01 in which differences outside the coding region were still considered to result in different subject-matter. O4 stated that SEQ ID NO:1 was an essential feature of claim 1, also because, absent any functional assay, it was needed to define the wild type allelic variants referred to therein. O5 agreed and added that priority was not the same as inventive step - no experiments to correct mistakes were allowed.

P again referred to Example 15 and stated that the technical contribution should be considered. One would only look at the relevant place in the gene to find the mutation and this had not been changed.

O4 stated that the sequence information was essential for the method of diagnosis as one had to be certain that any mutation was linked to disease. O5 quoted P as saying that formal requirements should be balanced with the technical contribution. O5 said that P4 was after the Science publication (D4) and that P chose to have SEQ ID NO:1 in the claims. P replied that 15 irrelevant changes wouldn't change the diagnosis. After breaking for lunch, P added that on page 95, P4 showed that 68 people were tested and diagnosed showing that the sequence changes didn't make a difference.

12. After deliberation, the chairman gave the OD's opinion that the first valid priority for the MR was P5. He then opened the discussion on novelty.

13. O1-3 referred to D5 and D6, particularly Table 3, stating that both described the mutation in claim 1 in the context of the claimed screening method. O4-6 and PR had nothing to add.

14. After a break, the chairman gave the OD's opinion that claims 1 and 2 of the MR were not novel over at least D5.

15. P asked to submit a new AR I (see Annex). He stated that P4 referred to Genbank entry U14680 and that D107 showed its history. He indicated the reference to U14680 in the application as filed on page 43 line 6, and on page 43 of the granted patent, stating that the screening method using U14680 hadn't changed since P4.

16. OD asked P why this request was filed so late. P replied that it had only come to mind after the oral proceedings on a related case the week before, during which an AR with product-by-process claims had not been allowed.

17. O5 strongly objected to the admission of the new request, stating that it had caught the opponents off guard. It raised so many issues with **Art. 123(2)(3), 84 and 87 EPC** that he requested suspension of the proceedings if it was admitted. PR replied that the opponents had already known of U14680 as prior art and that the claim was simple to understand. O1-3 said that to go from the product-by-process claims of original AR I to new claims referring to U14680 was a complete change of claim form and raised issues with **Art. 123(2)(3) EPC**. O4 asked OD to consider **Rule 71a(2) EPC** as P had been aware of the problems with SEQ ID NO:1 and consequently the new claims were filed too late.

18. After a break for cogitation, the chairman informed the parties that in the interests of procedural fairness, the new AR could not be accepted by OD as the problems with SEQ ID NO:1 had been known for some time. The request was therefore denied in accordance with **Rule 71a(2) and Article 114(2) EPC**. Pr then requested renumbering of the ARs such that the new AR became AR I, AR I became AR II etc.

19. The chairman opened discussion on AR II w.r.t. **Art. 123(2)(3) and 84 EPC**.

20. O1-3 stated that the product-by-process claims were not acceptable under **Art. 123(2) EPC** as there was no basis in the original application for combining a process of isolating coding sequences and then restricting the results using the parameters of length and molecular weight. Furthermore, the claim required a combination of elements from 13 different passages in the application and that parts b(i) and bb(i) required the use of a sequence as a probe, which use was not in P4 or the application as filed. W.r.t. **Art. 123(3) EPC**, O1-3 said that the claims also encompassed the use of pathological genes in the method, broadening the scope of protection. W.r.t. **Art 84 EPC**, O1-3 stated that the expression "being comprised" in claim 1 was of indefinite scope, that there was no indication of how the molecular weight was to be measured, that the term "wherein" suggested only a result to be achieved, and that claim 1 was not concise as it covered 3 pages, such that its scope was impossible to determine without undue burden.

21. O4 stated that the human BRCA1 sequence now referred to was different to that of the granted claim and that it was P's responsibility to prove that there was no extension of scope under **Art 123(3) EPC**. W.r.t. **Art 123(2) EPC**, O4 said that claim 1 was a mosaic of features not linked in the application as originally filed and that there was no basis for "producing a genomic DNA". O4 also objected to the claim for lack of clarity as the form was so complex, and for lack of support as no genomic DNA was produced in the description. Under **Art 123(3) EPC**, O5 added that the parameters of 1863 amino acids and the molecular weight of 208 kilodaltons were only originally disclosed in the context of SEQ ID NO:2. O5 added that in the sense of T0552/91, product-by-process claims should only be used in exceptional circumstances and the result should be specific, and that this was not the case here.

22. P cited T552/91 and T923/92 adding nothing more.

23. After a break for consideration, the chairman gave the OD's decision that AR II was not acceptable under **Art. 123(2)(3) or 84 EPC**. Discussion began on AR III w.r.t **Art. 123(2)(3), 84 and 87 EPC**

24. O1-3 stated that SEQ ID NO:1 was still in claim 1 and therefore P5 was still to be considered the first valid priority. O4 considered "having" to mean "comprising" such that the claim encompassed the whole of SEQ ID NO:1. P replied that the

structural formula had never change since P4 and that therefore P4 was valid.

25. In order to clarify the situation, OD asked P directly if the wording "having" encompassed nucleic acids longer than 30 nucleotides. P replied that the probe could not be "extraordinarily long". After O1-3 and O4 reiterated their arguments, P clearly stated that the claims covered probes longer than 30 nucleotides but added that it would make no technical sense to make them longer than 1308 nucleotides. O4 replied that the application described probes from 15 to 6000 nucleotides and that since no use was specified in the claim, the whole of SEQ ID NO:1 was covered.

26. After deliberation, OD announced that it still considered P5 not P4 as the first valid priority since "having" was clearly intended to be interpreted in an open-ended manner in the claim and therefore covered sequence that had changed between them.

27. P then submitted a new AR and abandoned previous AR III. The new AR became AR III (see Annex), in which the expression "having" was replaced with "consisting of". The chairman then announced a break until the following day.

28. The chairman summarised the proceedings of the previous day and opened discussion on the new AR III.

29. P stated that the request had been made to overcome the priority problem. None of the opponents had any objections w.r.t. admissibility, **Art. 123(2)(3), 83 or 84 EPC**.

30. O1-5 maintained that P5 was still the first valid priority. O6 agreed. P stated that the opponents had not indicated why they thought it was not the same invention as P4, since the part of SEQ ID NO:1 referred to in the claim had not changed.

31. After a brief pause for OD to confer, the chairman gave the OD's opinion that P4 was valid for AR III and opened discussion on **Art. 54 EPC**. None of the opponents had objections under novelty. Consequently, the chairman announced that the subject-matter of the claims was novel and opened discussion on **Art 56 EPC**.

32. O1-3 stated that if P4 was considered valid then D1 and D4 were the most relevant documents and the problem to be solved was to find new mutations in BRCA1. He added that P had created a new problem by limiting the invention to the specific population of Ashkenazi Jews and that this was not in the patent application. O1-3 said that access to a particular population did not make an inventive step and that the problem was not relevant, citing D29 and D45 as the first time it was mentioned. He also said that this was an ex post facto analysis, cited T268/89, adding that in D41 two populations were checked and that just because the mutation was found more in one than the other it didn't justify an inventive step.

O4 wanted it on record that he was not motivated by any political party. He agreed with O1-3's formulation of the technical problem and expressed concerns about the claims in connection with **Art. 52(4) EPC**. He cited T0024/91 and G5/85 and defined the skilled person as a team of scientists comprising a doctor who had a civic duty and access to normal patient information and DNA samples. O4 cited D6 page 397 to show that the methodology was standard and that screening could be done on "whichever patient comes through the door". He also cited D1 Table 2 on page 69, pointing to the kindred 1901 mutation 188del11 as an indication that a skilled person would look in exon 2 for further mutations and find that of the invention. O4 added that D9 disclosed family BOV3 which in D47 was later found to contain the mutation in the claims and added D42 and D20 as further support that samples were freely available which would have made it extremely easy to find the mutation.

O5 added that the kindred 1901 mutation was "right next door" to the mutation in the claims and that post-published D3 showed that certain primers would have provided the appropriate fragment.

O6 stated that finding a new structure alone did not make an invention but that a new function was required.

P replied that a surprising technical effect could be used to support inventive step and that the claimed mutation was surprisingly common, as disclosed in the patent. He stressed that one could always use an effect found later in for inventive step. P pointed out that the connection to Ashkenazi Jews was not important for

inventive step, but simply that the mutation was highly relevant. He pointed out that no diagnostic process was claimed. P said that this mutation was not an arbitrary selection because it was particularly relevant similar to particularly useful mutants. P cited T737/96 and stated that a hope to succeed was not enough. He added that the high mutation rate at this particular position made the claimed mutation particularly useful for a screening process and that its unexpected existence and properties made it inventive in a similar way to inventive splice variants, citing T182/03.

O1-3 insisted that high frequency of a mutation was not an inventive effect but simply made it easy to find. O4 added that it was not like the case with a new chemical compound with unexpected properties, but rather the result of obvious analysis, continuing that the mutation in D5 Table 3 (188del) had the same technical effect. O5 stated that the analogy to T737/96 was not relevant and O6 stated that to do business was not a technical problem.

P said that a skilled person needed a reason to try and a reasonable expectation of success, and that as far as obviousness was concerned, an organised search was irrelevant if the result was surprising. OD asked P if he considered the fact that the mutation was common to be the technical effect. P replied that it was hindsight that it was common. OD asked P about the availability of familial DNA in D9 (BOV3)and D42 (2979). P replied that the families were not identified so one could not get probes. O1-5 reiterated their previous arguments. P replied that the fact that D1 looked at lots of families and did not show the mutation meant that it was not inevitable.

33. After a break for cogitation, the chairman announced that the OD found the subject-matter of AR III to be inventive. He then opened discussion on **Art. 52, 53 and 57 EPC**.

34. O1-5 did not speak. O6 said that it was impossible to examine the ethical relevance and external effects of patent monopolisation, citing G1/98. He added that patents shouldn't damage society and that monopoly of patient DNA was unethical, especially when some patients did not agree, when the disease had a life-threatening character and when one patient group was affected.

P replied that no-one expected the EPO to grant unethical patents. He added that any doctor could visit Myriad's homepage and order a test, and that without monopoly there would be fewer diagnostics.

O6 said that the patent was concerned with getting money back for time and that this was not to do with patent law. He also expressed concerns about the separation of testing and counselling. OD asked O6 which of his submissions were relevant to the claims of AR III. O6 cited D67.

P pointed out that the EPO had developed principals for biotechnology according to the EU Biotechnology Directive, adding that just because one person had said that certain genes shouldn't be patented it didn't correspond to patent law. O6 pointed out that the list of exceptions to patentability in **Rule 23d EPC** was not exhaustive.

35. After a further break for discussion, the chairman announced that the OD found the subject-matter of AR III to comply with **Art. 52, 53 and 57 EPC**. He asked the parties if they had any further requests. O5 mentioned his earlier request that no further requests of P be admitted. The chairman indicated that OD had already rendered this moot by refusing to admit AR I with its Genbank reference. No party had any further requests.

36. P was asked to file an amended description which he did. After O1-6 made requests for and agreed further amendments, the chairman announced OD's decision to maintain the patent in amended form based on AR III filed during the proceedings on 24.01.05 and pages of the description filed on 25.01.05.

37. Oral proceedings were closed at 1405 on 25.01.05.

Annex

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

MAIN REQUEST

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in the sequence of the BRCA1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said alteration indicating a predisposition to said cancer being 185delAG→ter39.

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is a mutation in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.

24/1/05

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

AUXILIARY REQUEST I

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is ~~a~~ germline alteration **185delAG→ter39** in the sequence of the BRCA1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in ~~SEQ ID NO: 1 or a wild-type allelic variant thereof, said alteration indicating a predisposition to said cancer being 185delAG→ter39.~~ **GenBank, accession number U-14680 of October 8, 1994.**

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is ~~a~~ mutation **185delAG→ter39** in the sequence of the BRCA1 gene in a sample from said lesion compared to the nucleotide sequence set forth in ~~SEQ ID NO: 1 or a wild-type allelic variant thereof, said mutation being 185delAG→ter39.~~ **GenBank, accession number U-14680 of October 8, 1994.**

3. A method as claimed in claim 1 or 2, which comprises analyzing mRNA of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele, wherein said mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

4. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe, being allele-specific for said alteration/mutation, is contacted with genomic DNA isolated from said sample under conditions suitable for

hybridization of said probe to said gene and hybridization of said probe is determined.

5. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are employed which are specific for the mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

6. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

7. A replicative cloning vector which comprises an isolated nucleic acid according to claim 6 and a replicon operative in a host cell for said vector.

8. Host cells in vitro transformed with a vector as claimed in claim 7.

EXHIBIT E

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

AUXILIARY REQUEST II

1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germline alteration in a tissue sample of said subject, said germline alteration indicating a predisposition to said cancer being that, compared to a human BRCA1 gene that has the coding sequence for a full-length human BRCA1 polypeptide, the third nucleotide of codon 22, A, and the first nucleotide of codon 23, G, are deleted resulting in a nucleotide sequence encoding 38 amino acids,

wherein said full-length human BRCA1 polypeptide

- has 1863 amino acids,
- has a molecular weight of 208 kilodaltons, and
- comprises the amino acid sequence of SEQ ID NO: 82,

said coding sequence being comprised in a genomic DNA which is obtainable by:

(a) providing a human genomic library;

(b) screening the genomic library using a probe selected from the group consisting of:

(i) the following DNA sequence:

TGT CCC ATC TGT CTG GAG TTG ATC AAG GAA CCT GTC
TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC
ATG CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA
CAG TGT CCT TTA TGT AAG

(ii) the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC

CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

(iii) the DNA sequence of any one of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 67, 72 and 81

and

(c) producing a genomic DNA comprising said coding sequence;

wherein said genomic DNA comprising said coding sequence is more than 100 kb in length; and

wherein the first exon within said genomic DNA immediately follows the nucleotide sequence corresponding to SEQ ID NO: 35; or

said coding sequence being comprised in a cDNA which is obtainable by:

(aa) providing a cDNA library using human mRNA from breast, thymus, testis or ovary;

(bb) screening the cDNA library using a probe selected from the group consisting of:

(i) the following DNA sequence:

TGT CCC ATC TGT CTG GAG TTG ATC AAG GAA CCT GTC
TCC ACA AAG TGT GAC CAC ATA TTT TGC AAA TTT TGC
ATG CTG AAA CTT CTC AAC CAG AAG AAA GGG CCT TCA
CAG TGT CCT TTA TGT AAG

and

(ii) the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG

AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

(cc) producing a cDNA comprising said coding sequence;

wherein said coding sequence comprises the following nucleotide sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TGC A

and

wherein upon hybridization of a Northern blot with a fragment of said cDNA a single transcript of 7.8 kb is identified in breast, thymus, testis and ovary tissue.

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is a mutation in a sample from said lesion, said mutation being that, compared to a human BRCA1 gene that has the coding sequence for a full-length human BRCA1 polypeptide, the third nucleotide of codon 22, A, and the first nucleotide of codon 23, G, are deleted resulting in a

nucleotide sequence encoding 38 amino acids, wherein said full-length human BRCA1 polypeptide and said coding sequence are as defined in claim 1.

3. A method as claimed in claim 1 or claim 2 which comprises analyzing mRNA or protein of said sample to determine whether an expression product is present indicative of expression of a mutant BRCA1 allele.

4. A method as claimed in claim 3 wherein the mRNA encoded by the BRCA1 gene in said sample is investigated.

5. A method as claimed in claim 4 wherein mRNA from said sample is contacted with an oligonucleotide BRCA1 gene probe under conditions suitable for hybridization of said probe to an RNA corresponding to said BRCA1 gene and hybridization of said probe is determined.

6. A method as claimed in claim 1 or claim 2 wherein an oligonucleotide BRCA1 gene probe is contacted with genomic DNA isolated from said sample under conditions suitable for hybridization of said probe to said gene and hybridization of said probe is determined.

7. A method as claimed in claim 5 or 6 wherein said probe is an allele-specific probe for a mutant BRCA1 allele as defined in claim 1.

8. A method as claimed in claim 1 or claim 2 which comprises determining whether there is a mutation in the BRCA1 gene in said sample by observing shifts in electrophoretic mobility of single-stranded DNA from said sample on non-denaturing polyacrylamide gels.

9. A method as claimed in claim 1 or claim 2 wherein all or part of the BRCA1 gene in said sample is amplified and the sequence of said amplified sequence is determined.

10. A method as claimed in claim 1 or claim 2 wherein oligonucleotide primers are

employed which are specific for a mutant BRCA1 allele as defined in claim 1 to determine whether said allele is present in said sample by nucleic acid amplification.

11. A method as claimed in claim 1 or claim 2 wherein all or part of the BRCA1 gene in said sample is cloned to produce a cloned sequence and the sequence of said cloned sequence is determined.

12. A method as claimed in any one of claims 1 to 4 which comprises determining whether there is a mismatch between molecules (1) BRCA1 gene genomic DNA or BRCA1 mRNA isolated from said sample, and (2) a nucleic acid probe complementary to human wild-type BRCA1 gene DNA, when molecules (1) and (2) are hybridized to each other to form a duplex.

13. A method as claimed in any one of claims 1 to 4 wherein amplification of BRCA1 gene sequences in said sample is carried out and hybridization of the amplified sequences to one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1 is determined.

14. A method as claimed in claim 1 or claim 2 which comprises determining in situ hybridization of the BRCA1 gene in said sample with one or more nucleic acid probes which comprise a wild-type BRCA1 gene sequence or a mutant BRCA1 gene sequence as defined in claim 1.

15. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

16. A replicative cloning vector which comprises an isolated nucleic acid according to claims 15 and a replicon operative in a host cell for said vector.

17. Host cells in vitro transformed with a vector as claimed in claim 16.

24/1/05

EP 95 30 5605.8
Myriad Genetics, Inc.
Our Ref.: K2709 OPP(EP) S3

AUXILIARY REQUEST III

1. A nucleic acid probe ~~having~~ consisting of 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG→ter39.

2. A replicative cloning vector which comprises an isolated nucleic acid according to claim 1 and a replicon operative in a host cell for said vector.

3. Host cells in vitro transformed with a vector as claimed in claim 2.

a nucleic acid probe consisting of 15 to 30 nucleotides of SEQ ID NO:1 and containing mutation 185 delAG - 0 to 39. Such probe can be used 25/1/05

Description

[0001] The present invention relates generally to the field of human genetics. Specifically, the present invention relates to ~~[method and materials used]~~ to isolate and detect a human breast and ovarian cancer predisposing gene (BRCA1), some mutant alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. ~~More specifically, the invention relates to~~ germline mutations in the BRCA1 gene and ~~their use~~ in the diagnosis of predisposition to breast and ovarian cancer. can be used / to detect / nucleic acid probe

[0002] The publications and other materials used herein to illuminate the background of the invention, and in particular, cases to provide additional details respecting the practice, are incorporated herein by reference, and for convenience, are referenced by author and date in the following text and respectively grouped in the appended List of References.

BACKGROUND OF THE INVENTION

[0003] The genetics of cancer is complicated, involving multiple dominant, positive regulators of the transformed state (oncogenes) as well as multiple recessive, negative regulators (tumor suppressor genes). Over one hundred oncogenes have been characterized. Fewer than a dozen tumor suppressor genes have been identified, but the number is expected to increase beyond fifty (Knudson, 1993).

[0004] The involvement of so many genes underscores the complexity of the growth control mechanisms that operate in cells to maintain the integrity of normal tissue. This complexity is manifest in another way. So far, no single gene has been shown to participate in the development of all, or even the majority of human cancers. The most common oncogenic mutations are in the H-ras gene, found in 10-15% of all solid tumors (Anderson *et al.*, 1992). The most frequently mutated tumor suppressor genes are the TP53 gene, homozygously deleted in roughly 50% of all tumors, and CDKN2, which was homozygously deleted in 46% of tumor cell lines examined (Kamb *et al.*, 1994). Without a target that is common to all transformed cells, the dream of a "magic bullet" that can destroy or revert cancer cells while leaving normal tissue unharmed is improbable. The hope for a new generation of specifically targeted antitumor drugs may rest on the ability to identify tumor suppressor genes or oncogenes that play general roles in control of cell division.

[0005] The tumor suppressor genes which have been cloned and characterized influence susceptibility to: 1) Retinoblastoma (RB1); 2) Wilms' tumor (WT1); 3) Li-Fraumeni (TP53); 4) Familial adenomatous polyposis (APC); 5) Neurofibromatosis type 1 (NF1); 6) Neurofibromatosis type 2 (NF2); 7) von Hippel-Lindau syndrome (VHL); 8) Multiple endocrine neoplasia type 2A (MEN2A); and 9) Melanoma (CDKN2).

[0006] Tumor suppressor loci that have been mapped genetically but not yet isolated include genes for: Multiple endocrine neoplasia type 1 (MEN1); Lynch cancer family syndrome 2 (LCFS2); Neuroblastoma (NB); Basal cell nevus syndrome (BCNS); Beckwith-Wiedemann syndrome (BWS); Renal cell carcinoma (RCC); Tuberous sclerosis 1 (TSC1); and Tuberous sclerosis 2 (TSC2). The tumor suppressor genes that have been characterized to date encode products with similarities to a variety of protein types, including DNA binding proteins (WT1), ancillary transcription regulators (RB1), GTPase activating proteins or GAPs (NF1), cytoskeletal components (NF2), membrane bound receptor kinases (MEN2A), cell cycle regulators (CDKN2) and others with no obvious similarity to known proteins (APC and VHL).

[0007] In many cases, the tumor suppressor gene originally identified through genetic studies has been shown to be lost or mutated in some sporadic tumors. This result suggests that regions of chromosomal aberration may signify the position of important tumor suppressor genes involved both in genetic predisposition to cancer and in sporadic cancer.

[0008] One of the hallmarks of several tumor suppressor genes characterized to date is that they are deleted at high frequency in certain tumor types. The deletions often involve loss of a single allele, a so-called loss of heterozygosity (LOH), but may also involve homozygous deletion of both alleles. For LOH, the remaining allele is presumed to be nonfunctional, either because of a preexisting inherited mutation, or because of a secondary sporadic mutation.

[0009] Breast cancer is one of the most significant diseases that affects women. At the current rate, American women have a 1 in 8 risk of developing breast cancer by age 95 (American Cancer Society, 1992). Treatment of breast cancer at later stages is often futile and disfiguring, making early detection a high priority in medical management of the disease. Ovarian cancer, although less frequent than breast cancer is often rapidly fatal and is the fourth most common cause of cancer mortality in American women. Genetic factors contribute to an ill-defined proportion of breast cancer incidence, estimated to be about 5% of all cases but approximately 25% of cases diagnosed before age 40 (Claus *et al.*, 1991). Breast cancer has been subdivided into two types, early-age onset and late-age onset, based on an inflection in the age-specific incidence curve around age 50. Mutation of one gene, BRCA1, is thought to account for approximately 45% of familial breast cancer, but at least 80% of families with both breast and ovarian cancer (Easton *et al.*, 1993).

[0010] Intense efforts to isolate the BRCA1 gene have proceeded since it was first mapped in 1990 (Hall *et al.*, 1990;

Narod *et al.*, 1991). A second locus, BRCA2, has recently been mapped to chromosome 13q (Wooster *et al.*, 1994) and appears to account for a proportion of early-onset breast cancer roughly equal to BRCA1, but confers a lower risk of ovarian cancer. The remaining susceptibility to early-onset breast cancer is divided between as yet unmapped genes for familial cancer, and rarer germline mutations in genes such as TP53 (Malkin *et al.*, 1990). It has also been suggested that heterozygote carriers for defective forms of the Ataxia-Telangectasia gene are at higher risk for breast cancer (Swift *et al.*, 1976; Swift *et al.*, 1991). Late-age onset breast cancer is also often familial although the risks in relatives are not as high as those for early-onset breast cancer (Cannon-Albright *et al.*, 1994; Mettlin *et al.*, 1990). However, the percentage of such cases due to genetic susceptibility is unknown.

[0011] Breast cancer has long been recognized to be, in part, a familial disease (Anderson, 1972). Numerous investigators have examined the evidence for genetic inheritance and concluded that the data are most consistent with dominant inheritance for a major susceptibility locus or loci (Bishop and Gardner, 1980; Go *et al.*, 1983; Williams and Anderson, 1984; Bishop *et al.*, 1988; Newman *et al.*, 1988; Claus *et al.*, 1991). Recent results demonstrate that at least three loci exist which convey susceptibility to breast cancer as well as other cancers. These loci are the TP53 locus on chromosome 17p (Malkin *et al.*, 1990), a 17q-linked susceptibility locus known as BRCA1 (Hall *et al.*, 1990), and one or more loci responsible for the unmapped residual. Hall *et al.* (1990) indicated that the inherited breast cancer susceptibility in kindreds with early age onset is linked to chromosome 17q21; although subsequent studies by this group using a more appropriate genetic model partially refuted the limitation to early onset breast cancer (Margaritte *et al.*, 1992).

[0012] Most strategies for cloning the 17q-linked breast cancer predisposing gene (BRCA1) require precise genetic localization studies. The simplest model for the functional role of BRCA1 holds that alleles of BRCA1 that predispose to cancer are recessive to wild type alleles; that is, cells that contain at least one wild type BRCA1 allele are not cancerous. However, cells that contain one wild type BRCA1 allele and one predisposing allele may occasionally suffer loss of the wild type allele either by random mutation or by chromosome loss during cell division (nondisjunction). All the progeny of such a mutant cell lack the wild type function of BRCA1 and may develop into tumors. According to this model, predisposing alleles of BRCA1 are recessive, yet susceptibility to cancer is inherited in a dominant fashion: women who possess one predisposing allele (and one wild type allele) risk developing cancer, because their mammary epithelial cells may spontaneously lose the wild type BRCA1 allele. This model applies to a group of cancer susceptibility loci known as tumor suppressors or antioncogenes, a class of genes that includes the retinoblastoma gene and neurofibromatosis gene.

[0013] By inference this model may also explain the BRCA1 function, as has recently been suggested (Smith *et al.*, 1992).

[0014] A second possibility is that BRCA1 predisposing alleles are truly dominant; that is, a wild type allele of BRCA1 cannot overcome the tumor forming role of the predisposing allele. Thus, a cell that carries both wild type and mutant alleles would not necessarily lose the wild type copy of BRCA1 before giving rise to malignant cells. Instead, mammary cells in predisposed individuals would undergo some other stochastic change(s) leading to cancer.

[0015] If BRCA1 predisposing alleles are recessive, the BRCA1 gene is expected to be expressed in normal mammary tissue but not functionally expressing in mammary tumours. In contrast, if BRCA1 predisposing alleles are dominant, the wild type BRCA1 gene may or may not be expressed in normal mammary tissue. However, the predisposing allele will likely be expressed in breast tumour cells.

[0016] The 17q linkage of BRCA1 was independently confirmed in three of five kindred with both breast cancer and ovarian cancer (Narod *et al.*, 1991). These studies claimed to localize the gene within a very large region, 15 centi-Morgans (cM), or approximately 15 million base pairs, to either side of the linked marker pCMM86 (D17S74). However, attempts to define the region further by genetic studies, using markers surrounding pCMMS6, proved unsuccessful. Subsequent studies indicted that the gene was considerably more proximal (Easton *et al.*, 1993) and that the original analysis was flawed (Margaritte *et al.*, 1992). Hall *et al.*, (1992) recently localized the BRCA1 gene to an approximately 8 cM interval (approximately 8 million base pairs) bounded by Mfd15 (D17S250) on the proximal side and the human GIP gene on the distal side. A slightly narrower interval for the BRCA1 locus, based on publicly available data, was agreed upon at the Chromosome 17 workshop in March of 1992 (Faln, 1992). The size of these regions and the uncertainty associated with them has made it exceedingly difficult to design and implement physical mapping and/or cloning strategies for isolating the BRCA1 gene.

[0017] Identification of a breast cancer susceptibility locus would permit the early detection of susceptible individuals and greatly increase our ability to understand the initial steps which lead to cancer. As susceptibility loci are often altered during tumour progression, cloning these genes could also be important in the development of better diagnostic and prognostic products, as well as better cancer therapies.

SUMMARY OF INVENTION

[0018] In one aspect, the present invention provides an isolated nucleic acid comprising nucleotides 120-5708 of

SEQ. ID No: 1 having one or more of the following mutations, which are also listed in Table 14 in the examples' section of the specification:

185 ins A → ter 40
185 del AG → ter 39
Cys 64 Arg
926 ins 10 → ter 289
Val 271 Met
1128 ins A → ter 345
1294 del 40 → ter 396
1499 ins A → ter 479
codon 482 del 4 → ter
2080 ins A → ter 672
Gln 667 His
2293 del G → ter 735
2509 del AA → ter 799
Thr 826 Lys
2596 del C → ter 845
codon 852 del 1 → ter 891
Tyr 856 His
3121 del A → ter 1023
Met 1008 Ile
3166 ins 5 → ter 1025
3447 del 4 → ter 1115
3449 del 4 → ter 1115
3450 del 4 → ter 1115
Pro 1150 Ser
3745 del T → ter 1209
Glu 1214 ter
Glu 1219 Asp
Arg 1347 Gly
4184 del 4 → ter 1364
Arg 1443 ter
4873 del CA → ter 1620
Met 1628 Val
5085 del 19 → ter 1670
Thr 1852 Ser

185 del AG → ter 39

Consisting of 15 to 30 nucleotides of SEQ ID NO:1

or a complement thereof.

~~[0019] The present invention additionally provides an isolated nucleic acid comprising the nucleotide sequence set forth in Figure 10 and having base 4223A deleted or a complement thereof.~~

[0020] The invention ~~also~~ provides nucleic acid probes ~~derived from a nucleic acid of the invention as referred to above~~ which retain a mutation from amongst those listed above. Such probes may find use in diagnosing a predisposition to breast and ovarian cancer or in diagnosing a breast or ovarian lesion of a human subject for neoplasia.

[0021] Other aspects of the invention will be evident from the detailed description below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] Figure 1 is a diagram showing the order of loci neighbouring BRCA1 as determined by the chromosome 17 workshop. Figure 1 is reproduced from Fain, 1992.

[0023] Figure 2 is a schematic map of YACs which define part of Mfd15-Mfd188 region.

~~[0024] Figure 3 is a schematic map of STSs, P1, and BACs in the BRCA1 region.~~

[0025] Figure 4 is a schematic map of human chromosome 17. The pertinent region containing BRCA1 is expanded to indicate the relative positions of two previously identified genes, CA125 and RNU2, BRCA1 spans the marker D17S855.

[0026] Figure 5 shows alignment of the BRCA1 zinc-finger domain with 3 other zinc-finger domains that scored highest in a Smith-Waterman alignment. RPT1 encodes a protein that appears to be a negative regulator of the IL-2 receptor in mouse. RIN1 encodes a DNA-binding protein that includes a RING-finger motif related to the zinc-finger.

RFP1 encodes a putative transcription factor that is the N-terminal domain of the RET oncogene product. The bottom line contains the C3HC4 consensus zinc-finger sequence showing the positions of cysteines and one histidine that form the zinc ion binding pocket.

[0027] Figure 6 is a diagram of BRCA1 mRNA showing the locations of introns and the variants of BRCA1 mRNA produced by alternative splicing. Intron locations are shown by dark triangles and the exons are numbered below the line representing the cDNA. The top cDNA is the composite used to generate the peptide sequence of BRCA1. Alternative forms identified as cDNA clones or hybrid selection clones are shown below.

[0028] Figure 7 shows the tissue expression pattern of BRCA1. The blot was obtained from Clontech and contains RNA from the indicated tissues. Hybridization conditions were as recommended by the manufacturer using a probe consisting of nucleotide positions 3631 to 3930 of BRCA1. Note that both breast and ovary are heterogeneous tissues and the percentage of relevant epithelial cells can be variable. Molecular weight standards are in kilobases.

[0029] Figure 8 is a diagram of the 5' untranslated region plus the beginning of the translated region of BRCA1 showing the locations of introns and the variants of BRCA1 mRNA produced by alternative splicing. Intron locations are shown by broken dashed lines. Six alternate splice forms are shown.

[0030] Figure 9A shows a nonsense mutation in Kindred 2082. P indicates the person originally screened, b and c are haplotype carriers, a, d, e, f, and g do not carry the BRCA1 haplotype. The C to T mutation results in a stop codon and creates a site for the restriction enzyme AvrII. PCR amplification products are cut with this enzyme. The carriers are heterozygous for the site and therefore show three bands. Non-carriers remain uncut.

[0031] Figure 9B shows a mutation and cosegregation analysis in BRCA1 kindreds. Carrier individuals are represented as filled circles and squares in the pedigree diagrams. Frameshift mutation in Kindred 1910. The first three lanes are control, noncarrier samples. Lanes labeled 1-3 contain sequences from carrier individuals. Lane 4 contains DNA from a kindred member who does not carry the BRCA1 mutation. The diamond is used to prevent identification of the kindred. The frameshift resulting from the additional C is apparent in lanes labeled 1, 2, and 3.

[0032] Figure 9C shows a mutation and cosegregation analysis in BRCA1 kindreds. Carrier individuals are represented as filled circles and squares in the pedigree diagrams. Inferred regulatory mutation in Kindred 2035. ASO analysis of carriers and noncarriers of 2 different polymorphisms (PM1 and PM7) which were examined for heterozygosity in the germline and compared to the heterozygosity of lymphocyte mRNA. The top 2 rows of each panel contain PCR products amplified from genomic DNA and the bottom 2 rows contain PCR products amplified from cDNA. "A" and "G" are the two alleles detected by the ASO. The dark spots indicate that a particular allele is present in the sample. The first three lanes of PM7 represent the three genotypes in the general population.

[0033] Figures 10A-10H show genomic sequence of BRCA1. The lower case letters denote intron sequence while the upper case letters denote exon sequence. Indefinite intervals within introns are designated with vvvvvvvvvvvv. Known polymorphic sites are shown as underlined and boldface type.

DETAILED DESCRIPTION OF THE INVENTION

[0034] The present invention relates generally to the field of human genetics. Specifically, the present invention relates to methods and materials used to isolate and detect a human breast cancer predisposing gene (BRCA1), some alleles of which cause susceptibility to cancer, in particular breast and ovarian cancer. More specifically, the present invention relates to germline mutations in the BRCA1 gene and their use in the diagnosis of predisposition to breast and ovarian cancer. The invention further relates to somatic mutations in the BRCA1 gene in human breast cancer and their use in the diagnosis and prognosis of human breast and ovarian cancer.

[0035] The present invention provides an isolated polynucleotide comprising all, or a portion of the BRCA1 locus or of a mutated BRCA1 locus, preferably at least eight bases and not more than about 100 kb in length. Such polynucleotides may be antisense polynucleotides. The present invention also provides a recombinant construct comprising such an isolated polynucleotide, for example, a recombinant construct suitable for expression in a transformed host cell.

[0036] Also provided by the present invention are methods of detecting a polynucleotide comprising a portion of the BRCA1 locus or its expression product in an analyte. Such methods may further comprise the step of amplifying the portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer.

~~**[0037]** The present invention also provides variant BRCA1 polypeptides substantially free of other proteins which are encoded by a mutant BRCA1 locus as defined above and use of such polynucleotides as an immunogen for antibody production, preferably monoclonal antibody production. Also encompassed by the present invention are antigenic fragments of such polypeptides having a mutation from amongst those listed above.~~

~~**[0038]** The present invention also provides kits for detecting in an analyte a polynucleotide comprising a portion of the BRCA1 locus, the kits comprising a polynucleotide complementary to the portion of the BRCA1 locus packaged in a suitable container, and instructions for its use.~~

[0039] The present invention further provides methods of preparing a polynucleotide comprising polymerizing nucleotides to yield a sequence comprised of at least eight consecutive nucleotides of the BRCA1 locus; and methods of preparing a polypeptide comprising polymerizing amino acids to yield a sequence comprising at least five amino acids encoded within the BRCA1 locus.

[0040] The present invention further provides methods of screening the BRCA1 gene to identify mutations. Such methods may further comprise the step of amplifying a portion of the BRCA1 locus, and may further include a step of providing a set of polynucleotides which are primers for amplification of said portion of the BRCA1 locus. The method is useful for identifying said mutations for use in either diagnosis of the predisposition to cancer or the diagnosis or prognosis of cancer.

[0041] The present invention further provides methods of screening suspected BRCA1 mutant alleles to identify mutations in the BRCA1 gene.

[0042] It is a discovery of the present invention that the BRCA1 locus which predisposes individuals to breast cancer and ovarian cancer, is a gene encoding a BRCA1 protein, which has been found to have no significant homology with known protein or DNA sequences. This gene is termed BRCA1 herein. It is a discovery of the present invention that mutations in the BRCA1 locus in the germline are indicative of a predisposition to breast cancer and ovarian cancer. Finally, it is a discovery of the present invention that somatic mutations in the BRCA1 locus are also associated with breast cancer, ovarian cancer and other cancers, which represents an indicator of these cancers or of the prognosis of these cancers. The mutational events of the BRCA1 locus can involve deletions, insertions and point mutations within the coding sequence and the non-coding sequence.

[0043] Starting from a region on the long arm of human chromosome 17 of the human genome, 17q, which has a size estimated at about 8 million base pairs, a region which contains a genetic locus, BRCA1, which causes susceptibility to cancer, including breast and ovarian cancer, has been identified.

[0044] The region containing the BRCA1 locus was identified using a variety of genetic techniques. Genetic mapping techniques initially defined the BRCA1 region in terms of recombination with genetic markers. Based upon studies of large extended families ("kindreds") with multiple cases of breast cancer (and ovarian cancer crises in some kindreds), a chromosomal region has been pinpointed that contains the BRCA1 gene as well as other putative susceptibility alleles in the BRCA1 locus. Two meiotic breakpoints have been discovered on the distal side of the BRCA1 locus which are expressed as recombinants between genetic markers and the disease, and one recombinant on the proximal side of the BRCA1 locus. Thus, a region which contains the BRCA1 locus is physically bounded by these markers.

[0045] The use of the genetic markers provided by this invention allowed the identification of clones which cover the region from a human yeast artificial chromosome (YAC) or a human bacterial artificial chromosome (BAC) library. It also allowed for the identification and preparation of more easily manipulated cosmid, P1 and BAC clones from this region and the construction of a contig from a subset of the clones. These cosmids, P1s, YACs and BACs provide the basis for cloning the BRCA1 locus and provide the basis for developing reagents effective, for example, in the diagnosis and treatment of breast and/or ovarian cancer. The BRCA1 gene and other potential susceptibility genes have been isolated from this region. The isolation was done using software trapping (a computational method for identifying sequences likely to contain coding exons, from contiguous or discontinuous genomic DNA sequences), hybrid selection techniques and direct screening, with whole or partial cDNA inserts from cosmids, P1s and BACs, in the region to screen cDNA libraries. These methods were used to obtain sequences of loci expressed in breast and other tissue. These candidate loci were analyzed to identify sequences which confer cancer susceptibility. We have discovered that there are mutations in the coding sequence of the BRCA1 locus in kindreds which are responsible for the 17q-linked cancer susceptibility known as BRCA1. This gene was not known to be in this region. The present invention not only facilitates the early detection of certain cancers, so vital to patient survival, but also permits the detection of susceptible individuals before they develop cancer.

Population Resources

[0046] Large, well-documented Utah kindreds are especially important in providing good resources for human genetic studies. Each large kindred independently provides the power to detect whether a BRCA1 susceptibility allele is segregating in that family. Recombinants informative for localization and isolation of the BRCA1 locus could be obtained only from kindreds large enough to confirm the presence of a susceptibility allele. Large sibships are especially important for studying breast cancer, since penetrance of the BRCA1 susceptibility allele is reduced both by age and sex, making informative sibships difficult to find. Furthermore, large sibships are essential for constructing haplotypes of deceased individuals by inference from the haplotypes of their close relatives.

[0047] While other populations may also provide beneficial information, such studies generally require much greater effort, and the families are usually much smaller and thus less informative. Utah's age-adjusted breast cancer incidence is 20% lower than the average U.S. rate. The lower incidence in Utah is probably due largely to an early age at first pregnancy, increasing the probability that cases found in Utah kindreds carry a genetic predisposition.

Genetic Mapping

[0048] Given a set of informative families, genetic markers are essential for linking a disease to a region of a chromosome. Such markers include restriction fragment length polymorphisms (RFLPs) (Botstein *et al.*, 1980), markers with a variable number of tandem repeats (VNTRs) (Jeffreys *et al.*, 1985; Nakamura *et al.*, 1987), and an abundant class of DNA polymorphisms based on short tandem repeats (STRs), especially repeats of CpA (Weber and May, 1989; Litt *et al.*, 1989). To generate a genetic map, one selects potential genetic markers and tests them using DNA extracted from members of the kindreds being studied.

[0049] Genetic markers useful in searching for a genetic locus associated with a disease can be selected on an *ad hoc* basis, by densely covering a specific chromosome, or by detailed analysis of a specific region of a chromosome. A preferred method for selecting genetic markers linked with a disease involves evaluating the degree of informativeness of kindreds to determine the ideal distance between genetic markers of a given degree of polymorphism, then selecting markers from known genetic maps which are ideally spaced for maximal efficiency. Informativeness of kindreds is measured by the probability that the markers will be heterozygous in unrelated individuals. It is also most efficient to use STR markers which are detected by amplification of the target nucleic acid sequence using PCR; such markers are highly informative, easy to assay (Weber and May, 1989), and can be assayed simultaneously using multiplexing strategies (Skolnick and Wallace, 1988), greatly reducing the number of experiments required.

[0050] Once linkage has been established, one needs to find markers that flank the disease locus, i.e., one or more markers proximal to the disease locus, and one or more markers distal to the disease locus. Where possible, candidate markers can be selected from a known genetic map. Where none is known, new markers can be identified by the STR technique, as shown in the Examples.

[0051] Genetic mapping is usually an iterative process. In the present ~~invention~~ disclosure, it began by defining flanking genetic markers around the BRCA1 locus, then replacing these flanking markers with other markers that were successively closer to the BRCA1 locus. As an initial step, recombination events, defined by large extended kindreds, helped specifically to localize the BRCA1 locus as either distal or proximal to a specific genetic marker (Goldgar *et al.*, 1994).

[0052] The region surrounding BRCA1, until the ~~disclosure of the present invention~~ present, was not well mapped and there were few markers. Therefore, short repetitive sequences on cosmids subcloned from YACs, which had been physically mapped, were analyzed in order to develop new genetic markers. Using this approach, one marker of the present invention, 42D6, was discovered which replaced pCMM86 as the distal flanking marker for the BRCA1 region. Since 42D6 is approximately 14 cM from pCMM86, the BRCA1 region was thus reduced by approximately 14 centiMorgans (Easton *et al.*, 1993). The present ~~invention thus~~ disclosure began by finding a much more closely linked distal flanking marker of the BRCA1 region. BRCA1 was then discovered to be distal to the genetic marker Mfd15. Therefore, BRCA1 was shown to be in a region of 6 to 10 million bases bounded by Mfd15 and 42D6. Marker Mfd191 was subsequently discovered to be distal to Mfd15 and proximal to BRCA1. Thus, Mfd15 was replaced with Mfd191 as the closest proximal genetic marker. Similarly, it was discovered that genetic marker Mfd188 could replace genetic marker 42D6, narrowing the region containing the BRCA1 locus to approximately 1.5 million bases. Then the marker Mfd191 was replaced with tdj1474 as the proximal marker and Mfd188 was replaced with USR as the distal marker, further narrowing the BRCA1 region to a small enough region to allow isolation and characterization of the BRCA1 locus (see Figure 3), using techniques known in the art and described herein.

Physical Mapping

[0053] Three distinct methods were employed to physically map the region. The first was the use of yeast artificial chromosomes (YACs) to clone the region which is flanked by tdj1474 and U5R. The second was the creation of a set of P1, BAC and cosmid clones which cover the region containing the BRCA1 locus.

[0054] Yeast Artificial Chromosomes (YACs). Once a sufficiently small region containing the BRCA1 locus was identified, physical isolation of the DNA in the region proceeded by identifying a set of overlapping YACs which covers the region. Useful YACs can be isolated from known libraries, such as the St. Louis and CEPH YAC libraries, which are widely distributed and contain approximately 50,000 YACs each. The YACs isolated were from these publicly accessible libraries and can be obtained from a number of sources including the Michigan Genome Center. Clearly, others who had access to these YACs, without the ~~disclosure of the present invention~~ present, would not have known the value of the specific YACs we selected since they would not have known which YACs were within, and which YACs outside of, the smallest region containing the BRCA1 locus.

[0055] Cosmid, P1 and BAC Clones. In the present ~~invention~~ disclosure, it is advantageous to proceed by obtaining cosmid, P1, and BAC clones to cover this region. The smaller size of these inserts, compared to YAC inserts, makes them more useful as specific hybridization probes. Furthermore, having the cloned DNA in bacterial cells, rather than in yeast cells, greatly increases the ease with which the DNA of interest can be manipulated, and improves the signal-to-noise ratio of hybridization assays. For cosmid subclones of YACs, the DNA is partially digested with the restriction

enzyme Sau3A and cloned into the BamHI site of the pWE15 cosmid vector (Stratagene, cat. #1251201). The cosmids containing human sequences are screened by hybridization with human repetitive DNA (e.g., Gibco/BRL, Human C_ot-1 DNA, cat. 5279SA), and then fingerprinted by a variety of techniques, as detailed in the Examples.

[0056] P1 and BAC clones are obtained by screening libraries constructed from the total human genome with specific sequence tagged sites (STSs) derived from the YACs, cosmids or P1s and BACs, isolated as described herein.

[0057] These P1, BAC and cosmid clones can be compared by interspersed repetitive sequence (IRS) PCR and/or restriction enzyme digests followed by gel electrophoresis and comparison of the resulting DNA fragments ("fingerprints") (Maniatis *et al.*, 1982). The clones can also be characterized by the presence of STSs. The fingerprints are used to define an overlapping contiguous set of clones which covers the region but is not excessively redundant, referred to herein as a "minimum tiling path". Such a minimum tiling path forms the basis for subsequent experiments to identify cDNAs which may originate from the BRCA1 locus.

[0058] Coverage of the Gap with P1 and BAC Clones. To cover any gaps in the BRCA1 contig between the identified cosmids with genomic clones, clones in P1 and BAC vectors which contain inserts of genomic DNA roughly twice as large as cosmids for P1s and still greater for BACs (Stemberg, 1990; Sternberg *et al.*, 1990; Pierce *et al.*, 1992; Shizuya *et al.*, 1992) were used. P1 clones were isolated by Genome Sciences using PCR primers provided by us for screening. BACs were provided by hybridization techniques in Dr. Mel Simon's laboratory. The strategy of using P1 clones also permitted the covering of the genomic region with an independent set of clones not derived from YACs. This guards against the possibility of other deletions in YACs that have not been detected. These new sequences derived from the P1 clones provide the material for further screening for candidate genes, as described below.

Gene Isolation.

[0059] There are many techniques for testing genomic clones for the presence of sequences likely to be candidates for the coding sequence of a locus one is attempting to isolate, including but not limited to:

a. zoo blots
b. identifying HTF islands
c. exon trapping
d. hybridizing cDNA to cosmids or YACs.
e. screening cDNA libraries.

(a) Zoo blots. The first technique is to hybridize cosmids to Southern blots to identify DNA sequences which are evolutionarily conserved, and which therefore give positive hybridization signals with DNA from species of varying degrees of relationship to humans (such as monkey, cow, chicken, pig, mouse and rat). Southern blots containing such DNA from a variety of species are commercially available (Clonetech, Cat. 7753-1).

(b) Identifying HTF islands. The second technique involves finding regions rich in the nucleotides C and G, which often occur near or within coding sequences. Such sequences are called HTF (HpaI tiny fragment) or CpG islands, as restriction enzymes specific for sites which contain CpG dimers cut frequently in these regions (Lindsay *et al.*, 1987).

(c) Exon trapping. The third technique is exon trapping, a method that identifies sequences in genomic DNA which contain splice junctions and therefore are likely to comprise coding sequences of genes. Exon amplification (Buckler *et al.*, 1991) is used to select and amplify exons from DNA clones described above. Exon amplification is based on the selection of RNA sequences which are flanked by functional 5' and/or 3' splice sites. The products of the exon amplification are used to screen the breast cDNA libraries to identify a manageable number of candidate genes for further study. Exon trapping can also be performed on small segments of sequenced DNA using computer programs or by software trapping.

(d) Hybridizing cDNA to Cosmids, P1s, BACs or YACs. The fourth technique is a modification of the selective enrichment technique which utilizes hybridization of cDNA to cosmids, P1s, BACs or YACs and permits transcribed sequences to be identified in, and recovered from cloned genomic DNA (Kandpal *et al.*, 1990). The selective enrichment technique, as modified for the present purpose, involves binding DNA from the region of BRCA1 present in a YAC to a column matrix and selecting cDNAs from the relevant libraries which hybridize with the bound DNA, followed by amplification and purification of the bound DNA, resulting in a great enrichment for cDNAs in the region represented by the cloned genomic DNA.

(e) Identification of cDNAs. The fifth technique is to identify cDNAs that correspond to the BRCA1 locus. Hybridization probes containing putative coding sequences, selected using any of the above techniques, are used to screen various libraries, including breast tissue cDNA libraries, ovarian cDNA libraries, and any other necessary libraries.

[0060] Another variation on the theme of direct selection of cDNA was also used to find candidate genes for BRCA1 (Lovett *et al.*, 1991; Futreal, 1993). This method uses cosmid, P1 or BAC DNA as the probe. The probe DNA is digested with a blunt cutting restriction enzyme such as HaeIII. Double stranded adapters are then ligated onto the DNA and serve as binding sites for primers in subsequent PCR amplification reactions using biotinylated primers. Target cDNA is generated from mRNA derived from tissue samples, e.g., breast tissue, by synthesis of either random primed or oligo(dT) primed first strand followed by second strand synthesis. The cDNA ends are rendered blunt and ligated onto double-stranded adapters. These adapters serve as amplification sites for PCR. The target and probe sequences are denatured and mixed with human C_0t-1 DNA to block repetitive sequences. Solution hybridization is carried out to high C_0t-1/2 values to ensure hybridization of rare target cDNA molecules. The annealed material is then captured on avidin beads, washed at high stringency and the retained cDNAs are eluted and amplified by PCR. The selected cDNA is subjected to further rounds of enrichment before cloning into a plasmid vector for analysis.

Testing the cDNA for Candidacy

[0061] Proof that the cDNA is the BRCA1 locus is obtained by finding sequences in DNA extracted from affected kindred members which create abnormal BRCA1 gene products or abnormal levels of BRCA1 gene product. Such BRCA1 susceptibility alleles will co-segregate with the disease in large kindreds. They will also be present at a much higher frequency in non-kindred individuals with breast and ovarian cancer then in individuals in the general population. Finally, since tumors often mutate somatically at loci which are in other instances mutated in the germline, we expect to see normal germline BRCA1 alleles mutated into sequences which are identical or similar to BRCA1 susceptibility alleles in DNA extracted from tumor tissue. Whether one is comparing BRCA1 sequences from tumor tissue to BRCA1 alleles from the germline of the same individuals, or one is comparing germline BRCA1 alleles from cancer cases to those from unaffected individuals, the key is to find mutations which are serious enough to cause obvious disruption to the normal function of the gene product. These mutations can take a number of forms. The most severe forms would be frame shift mutations or large deletions which would cause the gene to code for an abnormal protein or one which would significantly alter protein expression. Less severe disruptive mutations would include small in-frame deletions and nonconservative base pair substitutions which would have a significant effect on the protein produced, such as changes to or from a cysteine residue, from a basic to an acidic amino acid or vice versa, from a hydrophobic to hydrophilic amino acid or vice versa, or other mutations which would affect secondary, tertiary or quaternary protein structure. Silent mutations or those resulting in conservative amino acid substitutions would not generally be expected to disrupt protein function.

[0062] According to the diagnostic and prognostic method ~~of the present invention~~, alteration of the wild-type BRCA1 locus is detected. In addition, the method can be performed by detecting the wild-type BRCA1 locus and confirming the lack of a predisposition to cancer at the BRCA1 locus. "Alteration of a wild-type gene" encompasses all forms of mutations including deletions, insertions and point mutations in the coding and noncoding regions. Deletions may be of the entire gene or of only a portion of the gene. Point mutations may result in stop codons, frameshift mutations or amino acid substitutions. Somatic mutations are those which occur only in certain tissues, e.g., in the tumor tissue, and are not inherited in the germline. Germline mutations can be found in any of a body's tissues and are inherited. If only a single allele is somatically mutated, an early neoplastic state is indicated. However, if both alleles are somatically mutated, then a late neoplastic state is indicated. The finding of BRCA1 mutations thus provides both diagnostic and prognostic information. A BRCA1 allele which is not deleted (e.g., found on the sister chromosome to a chromosome carrying a BRCA1 deletion) can be screened for other mutations, such as insertions, small deletions, and point mutations. It is believed that many mutations found in tumor tissues will be those leading to decreased expression of the BRCA1 gene product. However, mutations leading to non-functional gene products would also lead to a cancerous state. Point mutational events may occur in regulatory regions, such as in the promoter of the gene, leading to loss or diminution of expression of the mRNA. Point mutations may also abolish proper RNA processing, leading to loss of expression of the BRCA1 gene product, or to a decrease in mRNA stability or translation efficiency.

[0063] Useful diagnostic techniques include, but are not limited to fluorescent *in situ* hybridization (FISH), direct DNA sequencing, PFGE analysis, Southern blot analysis, single stranded conformation analysis (SSCA), RNase protection assay, allele-specific oligonucleotide (ASO), dot blot analysis and PCR-SSCP, as discussed in detail further below.

[0064] Predisposition to cancers, such as breast and ovarian cancer, and the other cancers identified herein, can be ascertained by testing any tissue of a human for mutations of the BRCA1 gene. For example, a person who has inherited a germline BRCA1 mutation would be prone to develop cancers. This can be determined by testing DNA from any tissue of the person's body. Most simply, blood can be drawn and DNA extracted from the cells of the blood. In addition, prenatal diagnosis can be accomplished by testing fetal cells, placental cells or amniotic cells for mutations of the BRCA1 gene. Alteration of a wild-type BRCA1 allele, whether, for example, by point mutation or deletion, can be detected by any of the means discussed herein.

[0065] There are several methods that can be used to detect DNA sequence variation. Direct DNA sequencing,

either manual sequencing or automated fluorescent sequencing can detect sequence variation. For a gene as large as BRCA1, manual sequencing is very labor-intensive, but under optimal conditions, mutations in the coding sequence of a gene are rarely missed. Another approach is the single-stranded conformation polymorphism assay (SSCA) (Orita *et al.*, 1989). This method does not detect all sequence changes, especially if the DNA fragment size is greater than 200 bp, but can be optimized to detect most DNA sequence variation. The reduced detection sensitivity is a disadvantage, but the increased throughput possible with SSCA makes it an attractive, viable alternative to direct sequencing for mutation detection on a research basis. The fragments which have shifted mobility on SSCA gels are then sequenced to determine the exact nature of the DNA sequence variation. Other approaches based on the detection of mismatches between the two complementary DNA strands include clamped denaturing gel electrophoresis (CDGE) (Sheffield *et al.*, 1991), heteroduplex analysis (HA) (White *et al.*, 1992) and chemical mismatch cleavage (CMC) (Grompe *et al.*, 1989). None of the methods described above will detect large deletions, duplications or insertions, nor will they detect a regulatory mutation which affects transcription or translation of the protein. Other methods which might detect these classes of mutations such as a protein truncation assay or the asymmetric assay, detect only specific types of mutations and would not detect missense mutations. A review of currently available methods of detecting DNA sequence variation can be found in a recent review by Grompe (1993). Once a mutation is known, an allele specific detection approach such as allele specific oligonucleotide (ASO) hybridization can be utilized to rapidly screen large numbers of other samples for that same mutation.

[0066] In order to detect the alteration of the wild-type BRCA1 gene in a tissue, it is helpful to isolate the tissue free from surrounding normal tissues. Means for enriching tissue preparation for tumor cells are known in the art. For example, the tissue may be isolated from paraffin or cryostat sections. Cancer cells may also be separated from normal cells by flow cytometry. These techniques, as well as other techniques for separating tumor cells from normal cells, are well known in the art. If the tumor tissue is highly contaminated with normal cells, detection of mutations is more difficult.

[0067] A rapid preliminary analysis to detect polymorphisms in DNA sequences can be performed by looking at a series of Southern blots of DNA cut with one or more restriction enzymes, preferably with a large number of restriction enzymes. Each blot contains a series of normal individuals and a series of cancer cases, tumors, or both. Southern blots displaying hybridizing fragments (differing in length from control DNA when probed with sequences near or including the BRCA1 locus) indicate a possible mutation. If restriction enzymes which produce very large restriction fragments are used, then pulsed field gel electrophoresis (PFGE) is employed.

[0068] Detection of point mutations may be accomplished by molecular cloning of the BRCA1 allele(s) and sequencing the allele(s) using techniques well known in the art. Alternatively, the gene sequences can be amplified directly from a genomic DNA preparation from the tumor tissue, using known techniques. The DNA sequence of the amplified sequences can then be determined.

[0069] There are six well known methods for a more complete, yet still indirect, test for confirming the presence of a susceptibility allele: 1) single stranded conformation analysis (SSCA) (Orita *et al.*, 1989); 2) denaturing gradient gel electrophoresis (DGGE) (Wartell *et al.*, 1990; Sheffield *et al.*, 1989); 3) RNase protection assays (Finkelstein *et al.*, 1990; Kinszler *et al.*, 1991); 4) allele-specific oligonucleotides (ASOs) (Conner *et al.*, 1983); 5) the use of proteins which recognize nucleotide mismatches, such as the *E. coli* mutS protein (Modrich, 1991); and 6) allele-specific PCR (Rano & Kidd, 1989). For allele-specific PCR, primers are used which hybridize at their 3' ends to a particular BRCA1 mutation. If the particular BRCA1 mutation is not present, an amplification product is not observed. Amplification Refractory Mutation System (ARMS) can also be used, as disclosed in European Patent Application Publication No. 0332435 and in Newton *et al.*, 1989. Insertions and deletions of genes can also be detected by cloning, sequencing and amplification. In addition, restriction fragment length polymorphism (RFLP) probes for the gene or surrounding marker genes can be used to score alteration of an allele or an insertion in a polymorphic fragment. Such a method is particularly useful for screening relatives of an affected individual for the presence of the BRCA1 mutation found in that individual. Other techniques for detecting insertions and deletions as known in the art can be used.

[0070] In the first three methods (SSCA, DGGE and RNase protection assay), a new electrophoretic band appears. SSCA detects a band which migrates differentially because the sequence change causes a difference in single-strand, intramolecular base pairing. RNase protection involves cleavage of the mutant polynucleotide into two or more smaller fragments. DGGE detects differences in migration rates of mutant sequences compared to wild-type sequences, using a denaturing gradient gel. In an allele-specific oligonucleotide assay, an oligonucleotide is designed which detects a specific sequence, and the assay is performed by detecting the presence or absence of a hybridization signal. In the mutS assay, the protein binds only to sequences that contain a nucleotide mismatch in a heteroduplex between mutant and wild-type sequences.

[0071] Mismatches, according to the present invention, are hybridized nucleic acid duplexes in which the two strands are not 100% complementary. Lack of total homology may be due to deletions, insertions, inversions or substitutions. Mismatch detection can be used to detect point mutations in the gene or in its mRNA product. While these techniques are less sensitive than sequencing, they are simpler to perform on a large number of tumor samples. An example of

a mismatch cleavage technique is the RNase protection method. In the practice of the present ~~invention~~ the method involves the use of a labeled riboprobe which is complementary to the human wild-type BRCA1 gene coding sequence. The riboprobe and either mRNA or DNA isolated from the tumor tissue are annealed (hybridized) together and subsequently digested with the enzyme RNase A which is able to detect some mismatches in a duplex RNA structure. If a mismatch is detected by RNase A, it cleaves at the site of the mismatch. Thus, when the annealed RNA preparation is separated on an electrophoretic gel matrix, if a mismatch has been detected and cleaved by RNase A, an RNA product will be seen which is smaller than the full length duplex RNA for the riboprobe and the mRNA or DNA. The riboprobe need not be the full length of the BRCA1 mRNA or gene but can be a segment of either. If the riboprobe comprises only a segment of the BRCA1 mRNA or gene, it will be desirable to use a number of these probes to screen the whole mRNA sequence for mismatches.

[0072] In similar fashion, DNA probes can be used to detect mismatches, through enzymatic or chemical cleavage. See, e.g., Cotton *et al.*, 1988; Shenk *et al.*, 1975; Novack *et al.*, 1986. Alternatively, mismatches can be detected by shifts in the electrophoretic mobility of mismatched duplexes relative to matched duplexes. See, e.g., Cariello, 1988. With either riboprobes or DNA probes, the cellular mRNA or DNA which might contain a mutation can be amplified using PCR (see below) before hybridization. Changes in DNA of the BRCA1 gene can also be detected using Southern hybridization, especially if the changes are gross rearrangements, such as deletions and insertions.

[0073] DNA sequences of the BRCA1 gene which have been amplified by use of PCR may also be screened using allele-specific probes. These probes are nucleic acid oligomers, each of which contains a region of the BRCA1 gene sequence harboring a known mutation. For example, one oligomer may be about 30 nucleotides in length, corresponding to a portion of the BRCA1 gene sequence. By use of a battery of such allele-specific probes, PCR amplification products can be screened to identify the presence of a previously identified mutation in the BRCA1 gene. Hybridization of allele-specific probes with amplified BRCA1 sequences can be performed, for example, on a nylon filter. Hybridization to a particular probe under stringent hybridization conditions indicates the presence of the same mutation in the tumor tissue as in the allele-specific probe.

[0074] The most definitive test for mutations in a candidate locus is to directly compare genomic BRCA1 sequences from cancer patients with those from a control population. Alternatively, one could sequence messenger RNA after amplification, e.g., by PCR, thereby eliminating the necessity of determining the exon structure of the candidate gene.

[0075] Mutations from cancer patients falling outside the coding region of BRCA1 can be detected by examining the non-coding regions, such as introns and regulatory sequences near or within the BRCA1 gene. An early indication that mutations in noncoding regions are important may come from Northern blot experiments that reveal messenger RNA molecules of abnormal size or abundance in cancer patients as compared to control individuals.

[0076] Alteration of BRCA1 mRNA expression can be detected by any techniques known in the art. These include Northern blot analysis, PCR amplification and RNase protection. Diminished mRNA expression indicates an alteration of the wild-type BRCA1 gene. Alteration of wild-type BRCA1 genes can also be detected by screening for alteration of wild-type BRCA1 protein. For example, monoclonal antibodies immunoreactive with BRCA1 can be used to screen a tissue. Lack of cognate antigen would indicate a BRCA1 mutation. Antibodies specific for products of mutant alleles could also be used to detect mutant BRCA1 gene product. Such immunological assays can be done in any convenient formats known in the art. These include Western blots, immunohistochemical assays and ELISA assays. Any means for detecting an altered BRCA1 protein can be used to detect alteration of wild-type BRCA1 genes. Functional assays, such as protein binding determinations, can be used. In addition, assays can be used which detect BRCA1 biochemical function. Finding a mutant BRCA1 gene product indicates alteration of a wild-type BRCA1 gene.

[0077] Mutant BRCA1 genes or gene products can also be detected in other human body samples, such as serum, stool, urine and sputum. The same techniques discussed above for detection of mutant BRCA1 genes or gene products in tissues can be applied to other body samples. Cancer cells are sloughed off from tumors and appear in such body samples. In addition, the BRCA1 gene product itself may be secreted into the extracellular space and found in these body samples even in the absence of cancer cells. By screening such body samples, a simple early diagnosis can be achieved for many types of cancers. In addition, the progress of chemotherapy or radiotherapy can be monitored more easily by testing such body samples for mutant BRCA1 genes or gene products.

[0078] The methods of diagnosis of the present ~~invention~~ are applicable to any tumor in which BRCA1 has a role in tumorigenesis. The diagnostic method of the present ~~invention~~ is useful for clinicians, so they can decide upon an appropriate course of treatment.

[0079] The primer pairs of the present ~~invention~~ are useful for determination of the nucleotide sequence of a particular BRCA1 allele using PCR. The pairs of single-stranded DNA primers can be annealed to sequences within or surrounding the BRCA1 gene on chromosome 17q21 in order to prime amplifying DNA synthesis of the BRCA1 gene itself. A complete set of these primers allows synthesis of all of the nucleotides of the BRCA1 gene coding sequences, i.e., the exons. The set of primers preferably allows synthesis of both intron and exon sequences. Allele-specific primers can also be used. Such primers anneal only to particular BRCA1 mutant alleles, and thus will only amplify a product in the presence of the mutant allele as a template.

[0080] In order to facilitate subsequent cloning of amplified sequences, primers may have restriction enzyme site sequences appended to their 5' ends. Thus, all nucleotides of the primers are derived from BRCA1 sequences or sequences adjacent to BRCA1, except for the few nucleotides necessary to form a restriction enzyme site. Such enzymes and sites are well known in the art. The primers themselves can be synthesized using techniques which are well known in the art. Generally, the primers can be made using oligonucleotide synthesizing machines which are commercially available. Given the sequence of the BRCA1 open reading frame shown in SEQ ID NO:1, design of particular primers is well within the skill of the art.

[0081] The nucleic acid probes provided by the present invention are useful for a number of purposes. They can be used in Southern hybridization to genomic DNA and in the RNase protection method for detecting point mutations already discussed above. The probes can be used to detect PCR amplification products. They may also be used to detect mismatches with the BRCA1 gene or mRNA using other techniques.

[0082] It has been discovered that individuals with the wild-type BRCA1 gene do not have cancer which results from the BRCA1 allele. However, mutations which interfere with the function of the BRCA1 protein are involved in the pathogenesis of cancer. Thus, the presence of an altered (or a mutant) BRCA1 gene which produces a protein having a loss of function, or altered function, directly correlates to an increased risk of cancer. In order to detect a BRCA1 gene mutation, a biological sample is prepared and analyzed for a difference between the sequence of the BRCA1 allele being analyzed and the sequence of the wild-type BRCA1 allele. Mutant BRCA1 alleles can be initially identified by any of the techniques described above. The mutant alleles are then sequenced to identify the specific mutation of the particular mutant allele. Alternatively, mutant BRCA1 alleles can be initially identified by identifying mutant (altered) BRCA1 proteins, using conventional techniques. The mutant alleles are then sequenced to identify the specific mutation for each allele. The mutations, ~~especially those~~ which lead to an altered function of the BRCA1 protein, ~~are~~ then used for the diagnostic and prognostic methods of the present ~~invention~~ disclosure.

Definitions

[0083] The present invention employs the following definitions:

[0084] **"Amplification of Polynucleotides"** utilizes methods such as the polymerase chain reaction (PCR), ligation amplification (or ligase chain reaction, LCR) and amplification methods based on the use of Q-beta replicase. These methods are well known and widely practiced in the art. See, e.g., U.S. Patents 4,683,195 and 4,683,202 and Innis *et al.*, 1990 (for PCR); and Wu *et al.*, 1989a (for LCR). Reagents and hardware for conducting PCR are commercially available. Primers useful to amplify sequences from the BRCA1 region are preferably complementary to, and hybridize specifically to sequences in the BRCA1 region or in regions that flank a target region therein. BRCA1 sequences generated by amplification may be sequenced directly. Alternatively, but less desirably, the amplified sequence(s) may be cloned prior to sequence analysis. A method for the direct cloning and sequence analysis of enzymatically amplified genomic segments has been described by Scharf, 1986.

[0085] **"Analyte polynucleotide"** and **"analyte strand"** refer to a single- or double-stranded polynucleotide which is suspected of containing a target sequence, and which may be present in a variety of types of samples, including biological samples.

~~**[0086]** **"Antibodies."** The present invention also provides polyclonal and/or monoclonal antibodies and fragments~~ thereof, and immunologic binding equivalents thereof, which are capable of specifically binding to the BRCA1 polypeptides and fragments thereof or to polynucleotide sequences from the BRCA1 region, particularly from the BRCA1 locus or a portion thereof. The term "antibody" is used both to refer to a homogeneous molecular entity, or a mixture such as a serum product made up of a plurality of different molecular entities. Polypeptides may be prepared synthetically in a peptide synthesizer and coupled to a carrier molecule (e.g., keyhole limpet hemocyanin) and injected over several months into rabbits. Rabbit sera is tested for immunoreactivity to the BRCA1 polypeptide or fragment. Monoclonal antibodies may be made by injecting mice with the protein polypeptides, fusion proteins or fragments thereof. Monoclonal antibodies will be screened by ELISA and tested for specific immunoreactivity with BRCA1 polypeptide or fragments thereof. See, Harlow & Lane, 1988. These antibodies will be useful in assays as well as pharmaceuticals.

[0087] Once a sufficient quantity of desired polypeptide has been obtained, it may be used for various purposes. A typical use is the production of antibodies specific for binding. These antibodies may be either polyclonal or monoclonal, and may be produced by *in vitro* or *in vivo* techniques well known in the art. For production of polyclonal antibodies, an appropriate target immune system, typically mouse or rabbit, is selected. Substantially purified antigen is presented to the immune system in a fashion determined by methods appropriate for the animal and by other parameters well known to immunologists. Typical sites for injection are in footpads, intramuscularly, intraperitoneally, or intradermally. Of course, other species may be substituted for mouse or rabbit. Polyclonal antibodies are then purified using techniques known in the art, adjusted for the desired specificity.

[0088] An immunological response is usually assayed with an immunoassay. Normally, such immunoassays involve ~~some purification of a source of antigen, for example, that produced by the same cells and in the same fashion as the~~

EXHIBIT F

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Datum/Date
17. 02. 09

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°.
K2709OPP(EP)S3	95305605.8 - 2405 / 0705903

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The University of Utah Research Foundation

Appeal number: **T 0666/05 - 3304**

Please find enclosed a copy of the decision dated 13-11-2008.

PROC DISP

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OPPO 02 - OPPO 03

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Case Number: T 0666/05 - 3.3.04

DECISION
of the Technical Board of Appeal 3.3.04
of 13 November 2008

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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted 09 June 2005 concerning maintenance of European patent No. 0705903 in amended form.**

Composition of the Board:

Chair:	U. Kinkeldey
Members:	M. Wieser
	D. S. Rogers
	G. Alt
	R. Moufang

Summary of Facts and Submissions

I. Appeals were lodged by the Patent Proprietor (Appellant I) and by Opponents 01 to 03 (Appellants II to IV) against the decision of the Opposition Division dated 9 June 2005 according to which European patent No. 0 705 903 could be maintained in amended form (Article 102(3) EPC 1973). The patent has the title "Mutations in the 17q-linked breast and ovarian cancer susceptibility gene" and claims priority from seven US applications, P1 to P7, of which the fourth P4 and the fifth P5 were filed on 29 November 1994 and 24 March 1995, respectively.

II. Six oppositions (Opponents 01 to 06) were filed against the patent covering the grounds of Article 100(a) in combination with Articles 52(2), 52(4), 53(a), 54, 56 and 57 EPC 1973, Article 100(b) in combination with Article 83 EPC 1973 and Article 100(c) in combination with Article 123(2) EPC 1973.

It is to be noted that the oppositions were filed before the entry into force of the EPC 2000 and therefore in the original notices of opposition all references to the Articles of the EPC were to the Articles of the EPC 1973. Taking into account the relevant transitional provisions, in this decision, instead of referring to Articles 52(2), 52(4), 53(a), 54, 56, 57, 83 and 123 EPC 1973, reference will be made to the corresponding Articles of the EPC 2000 that is Articles 52(2), 53(c), 53(a), 54, 56, 57, 83 and 123 EPC 2000 respectively, unless otherwise stated. Throughout this decision the EPC 2000 will be referred to as the EPC.

III. The Opposition Division decided that the subject-matter of claims 1 and 2 of the main request before it lacked novelty (Article 54 EPC) and, by exercising its discretion under Article 114(2) EPC, did not admit Patent Proprietor's auxiliary request I into the procedure, which was filed at the oral proceedings before it. Further it decided that the claims of auxiliary request II did not comply with Articles 123(2) and 84 EPC. However, the Opposition Division decided that claims 1 to 3 of Patent Proprietor's auxiliary request III, filed during the oral proceedings, met all requirements of the EPC.

IV. The Board dispatched a communication dated 21 January 2008, wherein the parties where asked whether they maintained their actual requests in the light of decision T 1213/05 of 27 September 2007, posted on 12 December 2007.

V. Oral proceedings before the Board took place on 12 and 13 November 2008.

Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of claims 1 to 9 of the main request filed with a letter dated 2 June 2008.

The Appellants II to IV (Opponents 01 to 03) requested that the decision under appeal be set aside and that the patent be revoked.

Opponents 04 to 06, which are parties as of right according to Article 107 EPC, also requested that the

decision under appeal be set aside and that the patent be revoked.

VI. Claim 1, 2 and 7 of the main request read as follows:

"1. A method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is germline alteration 185delAG -> ter39 in the BRCA1 gene in a tissue sample of said subject, said alteration indicating a predisposition to said cancer.

2. A method for diagnosing a breast or ovarian lesion of a human subject for neoplasia associated with the BRCA1 gene locus which comprises determining whether there is mutation 185delAG -> ter39 in the BRCA1 gene in a sample from said lesion.

7. A nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO:1 and containing the mutation 185delAG -> ter39."

Claims 3 to 6 refer to preferred embodiments of the methods according to claims 1 and 2. Claim 8 refers to a replicative cloning vector comprising the nucleic acid of claim 7 and claim 9 to a host cell transformed with the vector of claim 8.

VII. The following documents are mentioned in the present decision:

D1: Miki et al., Science (Oct. 1994) 266: 66-71

D5: Shattuck-Eidens et al., JAMA (Feb. 1995) 273: 535-541

D6: Simard et al., Nature Genetics (Dec. 1994) 8: 392-398

D9: Kelsell et al., Hum. Mol. Genet. (1993) 2: 1823-1828

D17: Information concerning GenBank Sequence, Accession number U14680

D29: Tonin et al., Am. J. Hum. Genet. (1995) 57: 189

D42: Feunteun et al., Am. J. Hum. Genet. (1993) 52: 736-742

D47: Extracts from the BIC database

D96: Editorial, Nature Genetics (Dec. 1994) 8: 310

D100: Declaration of Dr Critchfield of 22 November 2004

D115: Menczer et Ben-Baruch, Obstet. Gynecol. (1991) 77: 276-277

D116: Modan et al., JAMA (Dec. 1996) 276: 1823-1825

D117: Wooster et al., Science (Sep. 1994) 265: 2088-2090

D119: Overview of the frequency of BRCA1 mutations in European countries

D144: Declaration of Dr Critchfield of 9 October 2008

VIII. The submissions made by Appellant I can be summarized as follows:

Amendments (Article 123(2) and (3) EPC)

The amendments in claims 1 and 2 were supported by the application as filed, e.g. by the originally filed claims 17 and 18 in combination with Table 14 on page 57 of the description. To single out a single mutation from a list of thirty-four mutations resulted in a restriction of the scope of protection (Article 123(3) EPC) and could not be considered as an amendment violating the requirements of Article 123(2) EPC. The omission of a reference to SEQ ID NO: 1 and wild type allelic variants thereof did not introduce new matter. It was an established principle that a compound known in the art (the BRCA1 gene) needed not to be structurally defined in a claim if it could be referred to by using a generally accepted designation.

Clarity (Article 84 EPC)

The relevant date was the filing date of the fourth priority document P4. At that date the structural formula, i.e. the coding sequence of the BRCA1 gene, was known from the disclosure in document D1 in connection with document D17. Based on this disclosure in the prior art and in the patent in suit, the skilled

person was enabled to determine whether the mutation 185delAG -> ter39 was present in the BRCA1 gene. Thus the claims were clear and met the requirements of Article 84 EPC.

Priority right (Article 87 EPC 1973 and Articles 88 and 89 EPC)

The methods according to claims 1 and 2 relied on the detection of the mutation 185delAG -> ter39. The same invention was disclosed in priority document P4 (see claims 1 and 3 and Table 14 on page 92 of P4). Although the nucleic acid probe of claim 7, due to the term "having", might contain a nucleotide sequence in addition to the 15 to 30 nucleotides of SEQ ID NO:1 containing the 185delAG -> ter39 mutation, this additional sequence was not necessarily one derived from SEQ ID NO:1. Also priority document P4 used the term "having" in order to define probes (see page 29, lines 5 to 7 of P4). Therefore claims 1 to 9 were entitled to claim priority from priority document P4.

Novelty (Article 54 EPC)

As the claims were entitled to claim priority from priority document P4, there was no relevant prior art on file for the assessment of novelty. The requirements of Articles 54 EPC were thus met.

Inventive step (Article 56 EPC)

The closest state of the art was represented by document D1. The problem underlying the patent in suit was the identification of a mutation that allowed the

provision of an effective screening method. The identification of the 185delAG -> ter39 mutation, which was an extremely frequent mutation, to which none of the available prior art documents contained any information or hint, was considered to be a "lucky strike". At the best document D1 contained an invitation to start a scientific research program to find such mutation. As it was not predictable at all that such mutation existed, its detection was based on an inventive step as required by Article 56 EPC.

The objections raised under Articles 52(2) EPC, 52(4) EPC 1973, 53(a) and 57 EPC lacked substantiation and should be rejected by the Board.

IX. The submissions made by Appellants II to IV and Opponents 04 to 06 can be summarized as follows:

Amendments (Article 123(2) and (3) EPC)

To single out one specific mutation from a list of thirty four mutations was an amendment contravening the requirements of Article 123(2) EPC.

Claim 16 as granted contained a step of comparison with the reference molecule SEQ ID NO: 1 or a wild-type allelic variant thereof. The omission of this reference step violated the requirements of Article 123(3) EPC. This was because claim 1 now encompassed also the comparison with non-wild-type allelic variants of the gene. Contrary to Appellant I's argument, the BRCA1 gene was an unknown compound at the relevant priority date (P4) and thus needed to be structurally defined when mentioned in a patent claim.

Clarity (Article 84 EPC)

The diagnostic method of claim 1 did not refer to an identifiable reference sequence and thus missed an essential feature.

A further missing feature was the identification in the claim of the specific population group in which the germline alteration 185delAG -> ter39 appeared with high frequency, namely the Ashkenazi Jewish people.

The use of the term "BRCA1 gene" in claim 1 had the result that it was no longer clear what fell within the scope of the claim, as this term itself was not clear at the filing date of priority document P4.

Finally, claims 1 and 2 were not supported by the description.

Priority right (Article 87 EPC 1973 and Articles 88 and 89 EPC)

From priority document P4 it was not possible either to identify the definite BRCA1 cDNA sequence or the localization of the 185delAG -> ter39 mutation.

The claims could only enjoy priority right from priority document P5, being the earliest of the seven priority documents disclosing SEQ ID NOs: 1 and 2 corresponding exactly to SEQ ID NOs: 1 and 2 as disclosed in the application as filed.
Deciding differently would not only contradict decision T 1213/05 (supra) but also the gist of decision G 2/98 of the Enlarged Board of Appeal (OJ EPO 2001, 413).

Such possible contradiction could not be justified by the argument that present claim 1 did not refer to a substance, but to a diagnostic method using it. Anyhow, such argument would not apply to claim 7 referring to a nucleic acid probe and explicitly referring to SEQ ID NO: 1.

Novelty (Article 54 EPC)

As a consequence, documents D5 and D6, both published between priority documents P4 and P5, belonged to the state of the art and thus anticipated the claimed subject-matter.

Inventive step (Article 56 EPC)

Even if the claims were entitled to claim priority from priority document P4, there was no inventive step. The closest prior art was represented by document D1, disclosing the BRCA1 sequence and already showing several mutations thereof. The problem to be solved was therefore the provision of an alternative mutation of the BRCA1 gene. Upon combination of the teaching in document D1 with the disclosure in document D115 the finding of the 185delAG -> ter39 mutation was inevitable and any unexpected advantage represented simply a bonus effect which could not substantiate a finding of an inventive step according to EPO case law.

The inventors had carried out the necessary experimentation faster than others merely because they had been able to put more money and manpower into the project, but this did not justify the recognition of an inventive step. Suitable kindreds were also available

to other scientific groups, and sooner or later one of these groups would have been successful as well. Any problems that might have been encountered in the course of the project would have been overcome by the skilled person using conventional means.

The problem to be solved had been reformulated during the opposition procedure, namely to be the provision of a diagnostic method for detecting a particularly frequent mutation in the BRCA1 gene. This problem was not derivable from the application as originally filed. Accordingly the reformulation was not acceptable in the light of the established case law of the Boards of Appeal.

Moreover, the reformulated problem had not been solved over the entire scope of the claims, as the germline alteration 185delAG -> ter39 appeared with high frequency in a very limited part of the human population only. In the rest of the human population this mutation when used in a diagnostic method did not give rise to any "surprising effect" due to its low frequency.

Patentable inventions, exceptions to patentability, industrial applicability

Although the claimed diagnostic methods were practised on tissue samples, the logical link between the sample and the human body has not been broken. Claims 1 to 6 therefore did not refer to patentable inventions according to Article 53(c) EPC.

The commercial exploitation of the patent was unethical. The subject-matter of claims 1 to 6 contravened the requirements of Article 53(a) EPC.

Claim 7 referred to a fragment of the human genome which was not a patentable invention according to Article 52(2) EPC. The nucleic acid probe according to claim 7 had no industrial applicability, contrary to the requirements of Article 57 EPC.

Reasons for the Decision

For ease of reading if reference is made, either individually or collectively, to Appellants II to IV (Opponents 01 to 03) and the other parties (Opponents 04 to 06), such reference shall be to "the Opponents".

1. The appeals are admissible.

Main Request

Clarity (Article 84 EPC)

2. The claims of the main request differ from the claims as granted and it must thus be assessed whether they fulfil the requirements of Article 84 EPC in so far as the amendments are concerned.

3. The Opponents have argued that claims 1 and 2 were unclear, because they did not refer to the nucleotide sequence set forth in SEQ ID NO: 1 as the reference sequence, in contrast to the claims originally filed and granted. The term "BRCA1 gene" used in claims 1 and

2 was unclear, as the prior art disclosures of the exact sequence of this gene had changed over time.

4. As concerns the term "BRCA1 gene", the description of the patent in suit states that this term refers to "polynucleotides, all of which are in the BRCA1 region, that are likely to be expressed in normal tissue, certain alleles of which predispose an individual to develop breast, ovarian, colorectal and prostate cancer" (page 14, lines 45 to 47), and that "[t]he coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO:1" (page 14, lines 55 to 56).

Furthermore, documents D1 and D17, which were available to the public at the fourth priority date of the patent in suit, refer to the BRCA1 gene. The fourth priority document of the patent in suit is the earliest priority document in which the mutation 185delAG -> ter39 is mentioned (see Table 14 on page 92). The subject-matter of claims 1 and 2 of the main request relating to the determination of this mutation, can thus not be entitled to a priority date earlier than the fourth priority date, and this has not been contested by Appellant I. Document D1 describes the identification of the BRCA1 gene and discloses in Figure 2 the predicted amino acid sequence for BRCA1. In the legend to Figure 2, it is stated that the BRCA1 nucleotide sequence was deposited in GenBank with accession number U14680; this GenBank entry is part of document D17. The patent in suit also refers to said GenBank entry and states on page 43, lines 50 to 51 that the "sequence of the BRCA1 cDNA (up through the stop codon) has also been deposited with GenBank and assigned accession number U-14680".

In view of these disclosures in the patent in suit and in the prior art, the Board is convinced that the term "BRCA1 gene" would already have been clear to a skilled person at the earliest possible priority date. The skilled person would also know from his/her common general knowledge that the alteration termed "185delAG -> ter39" referred to a deletion of the nucleotides "AG" in position 185, which would result in a stop-codon in codon number 39. In the nucleotide sequence of the BRCA1 gene shown in SEQ ID NO: 1 of the patent in suit and in the GenBank entry U-14680 of document D17, the nucleotides "AG" do indeed occur in position 185.

5. With respect to the Opponents' argument that the prior art disclosures of the sequence of the BRCA1 gene had changed over time, the Board notes that no evidence has been presented by the Opponents that there have been any changes in the disclosures of the BRCA1 gene sequences in positions 185 and 186, which are the relevant positions when carrying out the methods of claims 1 and 2. Given the disclosures of the BRCA1 gene sequences in SEQ ID NO: 1 of the patent in suit and in document D17 of the prior art, the Board is convinced that it would be clear to the skilled person that the presence of the mutation 185delAG -> ter39 in the BRCA1 gene could be determined by establishing whether the nucleotides "AG" of the positions corresponding to numbers 185 and 186 are present or absent in the nucleotide sequence of the sample, and that there is thus no lack of clarity in claims 1 and 2.

6. The Opponents have further argued that claims 1 and 2 were not supported by the description and did not state the essential features of the invention, because these

claims did not state what the reference BRCA1 sequence was.

7. The Board cannot follow this argument but is convinced that the skilled person would know the BRCA1 gene sequence, both from the patent in suit and from the prior art, and would be able to use this knowledge to determine whether the mutation 185delAG -> ter39 is present or absent in a sample. Further information on how the claimed diagnostic methods can be carried out is disclosed for instance in the passage from page 20, line 7 to page 21, line 15 of the description of the patent in suit.

8. It has furthermore been argued by the Opponents that claims 1 and 2 did not state all the essential features of the claimed invention, contrary to Article 84 EPC. The mutation 185delAG -> ter39 was not the most important mutation in most European countries, as evidenced by document D119, but occurred at a high frequency only in people of Ashkenazi Jewish descent, as shown by document D29. Screening for this mutation would only make sense in a population where it was frequently occurring. According to the established case law of the Boards of Appeal, all features which are necessary for solving the technical problem with which the patent is concerned were to be regarded as essential features, which had to be indicated in the claims; therefore the target group had to be included into the relevant claims.

9. The Board cannot agree with the Opponents that claims 1 and 2 do not state all the essential features of the invention. In the Board's view the invention is not

directed to methods for screening a human population. Instead, the invention relates to methods for diagnosing either a predisposition for breast and ovarian cancer (claim 1) or a breast and ovarian lesion for neoplasia (claim 2) **in/of a human subject.** Therefore the Board is convinced that the determination of the presence of the mutation 185delAG -> ter39 in the BRCA1 gene in a sample of a human subject would allow the claimed diagnosis. Thus, the Board cannot recognize any lack of essential features in claims 1 and 2.

10. The Opponents also submitted that claim 7 lacked clarity, because due to the use of the term "having", which had to be interpreted as "comprising", the claim was indefinite and thus unclear.

11. The Board agrees that the term "having" in claim 7 has to be interpreted as meaning "comprising", but cannot recognize that this results in a lack of clarity of the claim. The skilled person reading the claim would understand that the claimed nucleic acid probe comprises 15 to 30 nucleotides of SEQ ID NO: 1 and contains the mutation 185delAG -> ter39, and can also comprise other, additional sequences.

12. Therefore, the requirements of Article 84 EPC are met.

Added matter (Article 123(2) EPC)

13. Article 123(2) EPC requires that a European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

In accordance with the established case law of the Boards of Appeal, the content of an application is the disclosure that is directly and unambiguously derivable from this application.

14. Claim 1 of the main request relates to a "method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is germ line alteration 185delAG -> ter39 in the BRCA1 gene in a tissue sample of said subject, said alteration being indicative of a predisposition to said cancer".

15. Claim 17 of the application as filed relates to a "method for diagnosing a predisposition for breast and ovarian cancer in a human subject which comprises determining whether there is a germ line alteration in the sequence of the BRCA 1 gene in a tissue sample of said subject compared to the nucleotide sequence set forth in SEQ. ID No: 1 or a wild-tyle [*sic*] allelic variant thereof, said alteration indicating a predisposition to said cancer being selected from the mutations as set forth in Tables 12, 12A and 14".

In Table 14 of the application as filed, the mutation 185delAG -> ter39 is one of the mutations listed.

Claim 1 of the main request thus differs from claim 17 of the application as filed in that only one of the mutations set forth in Tables 12, 12A and 14, i.e. the mutation 185delAG -> ter39, is mentioned, and in that it lacks the phrase "compared to the nucleotide

sequence set forth in SEQ. ID No: 1 or a wild-tyle [*sic*] allelic variant thereof".

16. The Opponents have argued that the selection of only one specific mutation out of the long list of mutations set forth in Tables 12, 12A and 14 was not directly and unambiguously derivable from the application as filed, which only disclosed methods for testing for a plurality of mutations, for instance in the passages on page 2, lines 3 to 7; page 5, lines 2 to 8 and 45 to 52, and page 19, lines 3 to 9 of the application as filed (published version), which referred to the plural form of "alleles" and "mutations". Therefore, claim 1 did not comply with Article 123(2) EPC.

17. The Board cannot follow this argument, because claim 17 of the application as filed states that the claimed method comprises determining whether there is **a germ line alteration** in the sequence of the BRCA1 gene, **said alteration** being selected from the mutations set forth in Tables 12, 12A and 14. Determining in the claimed method only one of any of the specific mutations listed in Tables 12, 12A and 14, for instance the second mutation of Table 14, 185delAG -> ter39, is thus disclosed in the application as filed.

18. The Opponents have furthermore argued that claim 1 contravened Article 123(2) EPC because the application as filed only disclosed methods comprising a step of comparison with the nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof, which step was not stated in claim 1 of the main request.

19. The Board considers that the expression "compared to the nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof" in claim 17 as filed does not define an actual step of comparison to be carried out in the claimed methods, but only serves as a reference in the definition of the alteration that is to be determined (see also point (28) infra). When determining whether there is mutation 185delAG -> ter39 in a tissue sample, the skilled person would always establish whether or not the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene are absent in the sequence of the patient's sample, and there would be no difference if the method was carried out in accordance with the method of claim 17 as filed or in accordance with the method of claim 1 of the main request. Therefore, the subject-matter of claim 1 is directly and unambiguously derivable from the application as filed.

20. Accordingly, the subject-matter of claim 2 can be derived from claim 18 of the application as filed. As concerns the dependent claims 3 to 6, the subject-matter of claim 3 can be derived from claims 19 to 21 and 23 as filed, claim 4 can be derived from claims 22 and 23 as filed, claim 5 can be derived from claim 26 as filed, and claim 6 can be derived from claim 25 as filed.

21. With respect to claim 7, the Opponents have argued that the length of the claimed "nucleic acid probe having 15 to 30 nucleotides of SEQ ID NO: 1 and containing the mutation 185delAG -> ter39" was not disclosed in the application as filed, and that, therefore, the claim did not comply with Article 123(2) EPC.

22. Claim 4 of the application as filed relates to a "nucleic acid probe wherein the nucleotide sequence is a portion of a nucleic acid as claimed in any one of claims 1 to 3 including a mutation or polymorphism compared to the nucleotide sequence set forth in SEQ.ID No: 1 selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19", but does not specify a length of 15 to 30 nucleotides. With respect to the disclosure of this length, the Board can follow Appellant I's argument that because the application as filed discloses on page 14, lines 19 to 22 the broad range of "at least about five codons (15 nucleotides)", and page 11, lines 13 to 15 discloses the single value of "30 nucleotides", the range of "15 to 30 nucleotides" was directly and unambiguously derivable from the application as filed, in accordance with the established case law of the Boards of Appeal (see for instance decisions T 201/83, OJ EPO 1984, 481, point (7) and T 925/98 of 13 March 2001, point (2)). Thus, claim 7 fulfils the requirements of Article 123(2) EPC.

23. The subject-matter of claims 8 and 9 is disclosed in claims 5 and 7 of the application as filed, respectively.

24. Consequently, claims 1 to 9 comply with Article 123(2) EPC.

Extension of scope (Article 123(3) EPC)

25. According to Article 123(3) EPC, a patent may not be amended in such a way as to extend the protection it confers.

26. Claims 16 and 17 as granted relate to diagnostic methods which comprise determining whether there is a alteration in the sequence of the BRCA 1 gene in a tissue sample compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof, said alteration being selected from a list of 34 specific mutations, one of which is the mutation 185delAG -> ter39.

Claims 1 and 2 of the main request relate to diagnostic methods which comprise determining whether there is the mutation 185delAG -> ter39 in the BRCA 1 gene in a tissue sample. In contrast to claims 16 and 17 as granted, claims 1 and 2 of the main request do not contain the expression "compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof".

27. The Opponents have argued that, due to the absence of said expression in the claims of the main request, there was an extension of scope of protection, contrary to Article 123(3) EPC, firstly because the methods now claimed lacked a comparison step with the full-length sequence, which step was mandatory in the methods of claims 16 and 17 as granted, and secondly because the reference for determining the mutation in the methods of the main request now also included non-wild-type allelic variants of the nucleotide sequence set forth

in SEQ ID NO: 1, and was thus broader than in the claims as granted.

28. The Board does not share the Opponents' interpretation of the claims as granted and considers that the expression "compared to the nucleotide sequence set forth in SEQ ID NO: 1 or a wild-type allelic variant thereof" in claims 16 and 17 as granted does not mean that the claimed methods actually comprise a step of "comparing" the entire sequence of the BRCA1 gene with the sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof (see point (19) above). Instead, SEQ ID NO: 1 is used in said claims only as a reference for defining the specific mutations listed, inter alia the mutation 185delAG -> ter39. The determination of this mutation is the same in the methods of the claims as granted and in the methods of the claims of the main request which do not refer to SEQ ID NO: 1; in both cases, a skilled person would establish whether or not the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene are absent in the sequence of the patient's sample.

29. The Board's interpretation that claims 16 and 17 as granted do not comprise a mandatory step of comparing the entire sequence of the BRCA1 gene present in the patient's sample with the sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof is further supported by dependent claims 20 to 22 and 24 as granted.

Claims 20 and 21 as granted, which are directly or indirectly dependent on claims 16 and 17, state that an oligonucleotide BRCA1 gene probe is contacted with mRNA or genomic DNA from the sample, and hybridization of

said probe is determined. Claim 22, which is dependent on claims 20 and 21, defines the probe as "an allele-specific probe for a mutant BRCA1 allele". The skilled person would understand that a method in which an allele-specific probe is used to determine a specific mutation would not comprise the comparison of the full-length gene sequence of the patient with SEQ ID NO: 1 or a wild-type allelic variant thereof as a mandatory feature.

Furthermore, claim 24 as granted, which is dependent on claims 16 and 17, states that "all or part of the BRCA1 gene in said sample is amplified and the sequence of said amplified sequence is determined". The Board considers that the amplification of only part of the BRCA1 gene would not make sense to a skilled person if the method required that the entire gene sequence would have to be compared with the sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof. Although it may theoretically be possible to interpret the expression "part of the BRCA1 gene" in claim 24 as granted as referring only to the case where all exon sequences are amplified, which would then allow the comparison with the entire sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof, the Board is convinced that this would not be the skilled person's understanding of claim 24 read in combination with independent claims 16 and 17.

30. The Board thus concludes that the methods of claims 16 and 17 as granted do not comprise a mandatory comparison step with the entire nucleotide sequence of SEQ ID NO: 1 or a wild-type allelic variant thereof, and that the lack of such a step in the methods of

claims 1 and 2 of the main request cannot result in an extension of scope of protection.

31. The Board can also not recognize any extension of the scope of protection due to a broadening of the definition of the reference sequence used. It follows from the definition given on page 14, lines 45 to 51 of the patent in suit, that the term "BRCA1 gene" referred to in claims 1 and 2 of the main request encompasses all allelic variations of the DNA sequence, including mutated, non-wild type forms, which are not encompassed by the expression "nucleotide sequence set forth in SEQ ID No: 1 or a wild-type allelic variant thereof" referred to in claims 16 and 17 as granted. However, this difference does not affect the scope of the claims, since in order to determine whether the mutation 185delAG -> ter39 is present in the sequence of a patient's sample, the skilled person would only establish whether the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene are absent or not. For this determination, it does not matter whether SEQ ID NO: 1 or wild-type allelic variants thereof are used as the reference nucleotide sequence or whether the reference sequence would contain additional mutations.

32. The Board cannot follow the Opponents' argument that claims 1 and 2 of the main request now covered the case where a comparison of the sequence of the patient's sample was made with a 185delAG -> ter39 mutant sequence and would thus entail a different, i.e. false result, in contrast to the methods of claims 16 and 17 as granted. The Board is convinced that a skilled person aiming at diagnosing a patient by determining whether there is the mutation 185delAG -> ter39 in the

BRCA1 gene in a tissue sample would not make this determination on the basis of a reference sequence already having the mutation that is to be determined. This would go against his/her common general knowledge and would not make any sense. According to established case law of the Boards of Appeal, a skilled person should try to arrive at an interpretation of a claim which is technically sensible and takes into account the whole disclosure of the patent (see decisions T 190/99 of 6 March 2001, point (2.4) and T 1241/03 of 1 September 2005, point (9)).

33. In view of the above, the requirements of Article 123(3) EPC are fulfilled.

Priority right (Article 87 EPC 1973 and Articles 88 and 89 EPC)

34. Documents D5 and D6 are scientific publications dated February 1995 and December 1994, respectively, thus published between the filing dates of the fourth priority document P4 (US 348824; 29 November 1994) and the fifth priority document P5 (US 409305; 24 March 1995). It is undisputed that the disclosure in these documents, if it belonged to the state of the art under Article 54(2) EPC, would be highly relevant for the issues of novelty (Article 54 EPC) and/or inventive step (Article 56 EPC) of the claimed subject-matter.

Documents D5 and D6 would not belong to the state of the art under Article 54(2) EPC if the claims were entitled to claim priority from the fourth priority document P4.

35. The right to priority is governed by Article 87 EPC 1973, which requires that the European patent (application) and the application whose priority is claimed relate to the same invention. Article 88(3) EPC further specifies that, if one or more priorities are claimed in respect of a European patent application, the right of priority shall cover only those elements of the application which are included in the respective priority application(s).

36. According to the Opinion G 2/98 of the Enlarged Board of Appeal (OJ EPO 2001, 413, point (9)), the requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC 1973, means that the priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

37. The fourth priority document P4 discloses a method for diagnosing a predisposition to breast and ovarian cancer in a human comprising the detection of an alteration in the BRCA1 gene, said alteration indicating a predisposition to said cancer and being selected from the group consisting of the mutations set forth in Table 14 (see page 5, lines 26 to 29 and claims 1 and 3), whereby the first mutation of the list in Table 14 is the mutation 185delAG -> ter39.

However, the nucleotide sequence of the cDNA coding for BRCA1 as disclosed in SEQ ID NO: 1 of the fourth

priority document P4 deviates from the corresponding sequence disclosed in SEQ ID NO: 1 of the patent in suit by 15 nucleotide residues. These deviations in the BRCA1 coding sequence are listed in Exhibit 1 (Table 1) of document D144 submitted by Appellant I with his letter dated 10 October 2008. Nine of these deviations lead to an amino acid change in the amino acid sequence of SEQ ID NO: 2, while six are "silent deviations" which do not result in amino acid changes. Thus, the 1863 amino acid long sequence of the BRCA1 protein shown in SEQ ID NO: 2 of the fourth priority document P4 deviates from the corresponding sequence disclosed in SEQ ID NO: 2 of the patent in suit in 9 amino acid positions. None of the 15 nucleotide changes is an insertion or a deletion or results in a stop codon. Within the BRCA1 coding sequence, the first of the 15 deviations occurs in nucleotide position 1364, corresponding to codon number 415.

The earliest priority document disclosing the nucleotide sequence coding for BRCA1 and the amino acid sequence of the encoded protein, which are identical to SEQ ID NOs: 1 and 2 disclosed in the patent in suit and in the application as filed, is the fifth priority document P5.

38. The Opponents have argued that because of the above mentioned differences in the nucleotide and amino acid sequences between the fourth priority document P4 and the patent in suit, only the fifth priority could be accorded to the claims of the main request.

39. With respect to claim 1, the Opponents have argued that in view of said sequence differences, the meaning of

the term "BRCA1 gene" differed between the fourth priority document, P4, and the patent in suit, and because the BRCA1 gene was a technical feature of the claim, the claimed invention could not be directly and unambiguously derived from the fourth priority document P4.

40. The Board cannot follow this line of argument. The invention claimed in claim 1 is a diagnostic method which comprises determining whether there is germline alteration 185delAG -> ter39 in the BRCA1 gene. In order to determine in the claimed method whether there is the mutation 185delAG -> ter39, it is not required to determine any kind of difference between the patient's nucleotide or amino acid sequence and a reference sequence. It is only required to determine whether there is a deletion of the nucleotides "AG" in positions 185 and 186 of the BRCA1 gene. Neither this mutation 185delAG -> ter39, nor the nucleotides of the BRCA1 gene in the relevant positions 185 and 186 have changed between the fourth priority document P4, the fifth priority document P5 and the patent in suit. In fact, the first nucleotide in the BRCA1 sequence which deviates between the fourth priority document P4 on the one hand and the fifth priority document P5 and the patent in suit on the other hand is in position 1364, thus more than 1000 nucleotides downstream of the positions that are looked at in the claimed method. The above mentioned sequence differences thus do not have any impact on the actual invention claimed. The mutation to be detected with the method of claim 1 is exactly the same, irrespective of whether the sequence information disclosed in the fourth priority document

P4, the fifth priority document P5 or the patent in suit is used as a reference.

41. The Opponents have also argued that SEQ ID NO: 1 of the fourth priority document P4 did not have the nucleotides "AG" in position 185, and that there was a severe ambiguity within this priority document because the footnote 2 of Table 14 referred to the BRCA1 sequence in GenBank under accession number U14680. The Opponents submitted that from its first release onwards, this GenBank entry had disclosed the "correct" BRCA1 sequence disclosed in the fifth priority document and the patent in suit which thus differed from the sequence of SEQ ID NO: 1 of the fourth priority document. There was thus no clear and unambiguous disclosure of the invention now claimed in the fourth priority date.

42. The Board notes that SEQ ID NO: 1 of the fourth priority document P4 lacks the 56 nucleotides that are present at the 5' end of SEQ ID NO: 1 of the patent in suit, resulting in a different numbering of the nucleotides. In SEQ ID NO: 1 of the fourth priority document P4, the nucleotides "AG" that are deleted in the mutation 185delAG -> ter39 occur in position 129 instead of position 185. By contrast, Table 14 of the fourth priority document P4 refers to the mutation 185delAG -> ter39, and states in footnote 2 that "[n]ucleotides refer to the BRCA1 cDNA sequence in GENBANK under Accession No. U-14680". It has not been contested by any of the parties that in this sequence as released before the fourth priority date, nucleotide position 185 corresponds to the "AG" that is deleted in

the mutation 185delAG -> ter39 as disclosed in the patent.

The Board considers that a skilled person reading the fourth priority document would have easily recognized by a simple sequence comparison that the nucleotides in SEQ ID NO: 1 of this priority document and in the sequence of GenBank entry U14680 are differently numbered, and that position 185 of the mutation in Table 14 would correspond to position 129 of SEQ ID NO: 1. In this way, the skilled person would have been able to identify the exact location of the 185delAG -> ter39 mutation also in the sequence of SEQ ID NO: 1. The Board is therefore convinced that the skilled person would not have had problems to perform the method of claim 1 on the basis of the information given in the fourth priority document P4.

43. It was a matter of dispute between the parties whether the GenBank entry U14680 when it first became available to the public on 8 October 1994 disclosed a BRCA1 nucleotide sequence which contained the same sequencing "errors" as the nucleotide sequence of SEQ ID NO: 1 of the fourth priority document P4, or the "correct" nucleotide sequence as shown in SEQ ID NO: 1 of the fifth priority document and the patent in suit. Since, however, the sequence deviations under discussion do in any case not occur in the region of the mutation 185delAG -> ter39, and thus do not affect the claimed invention, the issue of the exact disclosure of the GenBank entry U14680 of 8 October 1994 is not relevant for the present case and need not be decided by the Board.

44. The Board is thus convinced that the invention of claim 1 is directly and unambiguously derivable from the fourth priority document P4 and enjoys the fourth priority date.

45. In view of page 5, lines 27 to 29 and page 37, lines 4 to 6 of the fourth priority document P4, the reasons given above as to why the subject-matter of claim 1 enjoys the fourth priority date apply analogously also for the subject-matter of claim 2. Furthermore, the subject-matter of claims 3 to 6 is disclosed in claims 5, 7, 8 and 10 and on page 18, lines 10 to 20 of the fourth priority document P4.

46. With respect to claim 7, the Opponents have argued that its subject-matter was not entitled to the fourth priority date because due to the use of the term "having", which had to be interpreted as meaning "comprising", the claimed nucleic acid probe could also comprise those nucleotides of SEQ ID NO: 1 which differed between the fourth priority document P4 and the patent in suit. SEQ ID NO: 1 was thus a technical feature of the claim, which feature was not disclosed in the fourth priority document P4.

47. It has not been contested by Appellant I that the term "having" in claim 7 is to be interpreted as meaning "comprising", and the Board concurs with this interpretation. Therefore, claim 7 does indeed encompass nucleic acid probes which, in addition to the "15 to 30 nucleotides of SEQ ID NO: 1", comprise any other nucleotide sequences. These sequences include parts of SEQ ID NO: 1 which lie outside the region of the mutation 185delAG -> ter39 and which differ

between the fourth priority document P4 and the patent in suit, or any other additional sequences unrelated to the BRCA1 gene.

48. The Board considers that these additional, non-defined sequences, whose presence in the claimed nucleic acid probe is entirely optional, do not define the actual invention that is claimed. The claimed invention is defined as a nucleic acid probe which has 15 to 30 nucleotides of SEQ ID NO: 1 and contains the mutation 185delAG -> ter39. With respect to these features defining the claimed invention, the disclosures of the fourth priority document P4, the fifth priority document P5 and the patent in suit are identical, the first nucleotide deviation in the sequence of SEQ ID NO: 1 occurring in position 1364. Therefore, the Board is convinced that the invention of claim 7 enjoys the fourth priority date.

49. As concerns claims 8 and 9, their subject-matter is disclosed on page 26, lines 8 to 11 of the fourth priority document.

50. The Board thus concludes that the subject-matter of claims 1 to 9 of the main request enjoys the fourth priority date and that, consequently, documents D5 and D6 do not constitute prior art under Article 54(2) EPC.

51. It was repeatedly argued by the Opponents that to decide along the lines argued above would be incompatible with decision T 1213/05 (supra). However, with respect to the question of priority rights, the situation in the present case differs from the one dealt with in decision T 1213/05 (supra) in the context

of auxiliary request II then before that Board, which concerned product claims and where the amino acid sequence of SEQ ID NO: 2 was a technical feature of the claimed invention (see points 19 to 34 of said decision).

In the present case, the claimed invention relates to the determination of a specific mutation, 185delAG -> ter39, and to certain probes containing said mutation, and this invention does not differ between the fourth priority document P4, the fifth priority document P5 and the patent in suit, for the reasons given above.

Novelty (Article 54 EPC)

52. As a consequence of the above decision on right to priority, documents D5 and D6, which are the only documents the Opponents relied on in the written procedure when objecting to the novelty of the claimed subject-matter, do not belong to the state of the art under Article 54(2) EPC.

53. The Opponents have thus not objected to the novelty of the claimed subject-matter on the basis of any document which belongs to the state of the art under Article 54(2) EPC.

As the Board also has no objections in this respect, the subject-matter of claims 1 to 9 is considered to be novel and to meet the requirements of Article 54 EPC.

Inventive step (Article 56 EPC)

54. The closest prior art is represented by document D1 which discloses the identification of the BRCA1 gene by positional cloning. Table 2 of the document discloses four predisposing mutations in BRCA1. The mutation 185delAG -> ter39 is not mentioned in document D1.

55. Having regard to document D1, the technical problem to be solved is the provision of a mutation that allows the development of an effective screening for inherited breast and ovarian cancer.

56. The Board is satisfied that this problem has been solved by the specific mutation of the method according to claim 1.

56.1 Paragraph [0276] on page 60, lines 43 to 51 of the patent in suit states that the mutation 185delAG -> ter39 is a predisposing mutation that is relatively common, occurring in 12 % of the probands studied. The same paragraph further states that "[m]any of the probands screened to date for BRCA1 mutations were selected for having a high prior probability of having such mutations. Thus the mutations found in this set may not be representative of those which would be identified in other sets of patients. However, the two most frequent BRCA1 mutations (5382 ins C and 185 del AG) have been found multiple times in targeted screening in sets of probands who were either unselected for family history or ascertained with minimal family history." The patent in suit discloses that the mutation 185delAG -> ter39 occurs at a

relatively high frequency and thus allows effective screening of a human subject.

56.2 Opponents have argued that according to the post-published document D29, the mutation 185delAG -> ter39 was only predominant in people of Ashkenazi Jewish descent, and could not generally be considered as a particularly frequent mutation. Since the high frequency of the mutation in the Ashkenazi Jewish population was not disclosed in the patent in suit, this advantageous property could not be used in the formulation of the technical problem or support the acknowledgment of an inventive step.

56.3 The Board agrees that the high frequency of the mutation 185delAG -> ter39 in the Ashkenazi Jewish population, which is not disclosed in the patent in suit, cannot support the finding that the technical problem has been solved. However, the Board takes the position that on the basis of the evidence on file, in particular document D100, a declaration of Dr Critchfield, the mutation 185delAG -> ter39 is to be considered as a frequent mutation also with respect to the general population. According to document D100, the frequency of the mutation 185delAG -> ter39 was 8.92 % in samples of Ashkenazi ancestry analyzed for mutations in BRCA1 at Myriad (see page 3, point 6), and 0.47 % in non-Ashkenazi samples (see page 3, point 8). It is further stated in point 8 of this document that "[o]ther than the **185delAG** and 5385insC mutations, the mutation with the highest frequency in the non-Ashkenazi samples analyzed at Myriad is the C61G mutation with a frequency of **0.30%**. Thus, the **185delAG** mutations is **1.6** times more prevalent than the C61G

mutation among the **non-Ashkenazi** samples analyzed at Myriad". The Board concludes from this data that although the mutation 185delAG -> ter39 is considerably less frequent in non-Ashkenazi samples when compared to samples from people of Ashkenazi ancestry, the mutation is to be considered as a frequent one also in people who are not of Ashkenazi descent. Document D100 thus supports the statement in the patent in suit that the mutation 185delAG -> ter39 is a frequent one and thus allows effective screening.

56.4 Opponents have furthermore argued that the technical problem had not been solved over the whole scope of the claims, because the frequency of the mutation 185delAG -> ter39 varied dramatically from country to country, as evidenced by document D119 which gives an overview of BRCA1 mutation spectra in different European countries. This document showed that the frequency of the mutation 185delAG -> ter39 is relatively high in some countries, for instance in Spain (15 %) and in the United Kingdom (19 %), but very low in other European countries including Italy, Belgium, Germany, Switzerland and Austria. With respect to these latter countries, screening for the mutation 185delAG -> ter39 would not be useful and in no way cost-effective. An advantageous effect thus only existed for a very limited part of the human population, and not over the whole scope of the claim.

56.5 The Board cannot follow this line of argument since although the mutation 185delAG -> ter39 occurs less frequently in some countries than in others, this cannot prejudice the fact that this mutation is a frequent one in the general human population.

Furthermore, the determination of the presence of said mutation in the BRCA1 gene of a human subject according to the method of claim 1 would always allow the diagnosis of a predisposition for breast and ovarian cancer, irrespective of the country from which the human subject originates.

57. The relevant question for assessing inventive step is whether or not, at the fourth priority date, the provision of a diagnostic method for finding the mutation 185delAG -> ter39 would have been obvious for a skilled person faced with the problem posed.

58. The Board agrees with the Opponents and Appellant I that the skilled person in the present case would be a team of experts including at least a molecular geneticist and a medical doctor having access to patient samples.

59. It has been pointed out in a number of decisions of the Boards of Appeal in the technical field of bio-technology that, in evaluating the attitude of the skilled person, one should not confuse the "hope to succeed", which is linked to the wish that a result be achieved, with the "reasonable expectation of success", which is linked to the ability to reasonably predict, based on the particular technical circumstances, a successful conclusion of the project within acceptable time limits (see decisions T 296/93 of 28 July 1994, point (7.4.4), T 923/92 of 8 November 1995, point (51), T 223/96 of 29 January 1999, point (23) and T 1213/05, supra, point (77)). In this respect, each case has to be assessed on its own merits, and any hindsight has to be avoided.

60. The Board notes that from the content of document D1, there was still a considerable degree of uncertainty with respect to the mutations that predispose individuals to BRCA1-linked breast and ovarian cancer and to the development of BRCA1 screening methods. Although at the time of its publication, the document was seen by the scientific community as disclosing the identification of the BRCA1 gene, the authors of the document themselves expressed some caution in this regard by giving their publication the title "A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1". At the end of document D1 (page 71, column 1, paragraph 1), it is stated: "The large size and fragmented nature of the coding sequence will make exhaustive searches for new mutations challenging. Nevertheless, the percentage of total breast and ovarian cancer caused by mutant BRCA1 alleles will soon be estimated, and individual mutation frequencies and penetrances may be established. This in turn may permit accurate genetic screening for predisposition to a common, deadly disease."

The Board furthermore observes that document D1 does not give any information on the frequencies of the mutant alleles listed in Table 2 in BRCA1 predisposed individuals. It was found out only later, i.e. after the fourth priority date, that the mutation indicated in Table 2 as occurring in kindred 1910 is a relatively frequent mutation (see the comments on mutation "5385insC" in document D100).

61. The Board considers that the skilled person, departing from the disclosure of document D1, would have readily undertaken to identify BRCA1 predisposing mutations

suitable for effective screening in the hope to succeed. This hope is expressed also by the authors of the document by stating in the above quoted passage that "the percentage of total breast and ovarian cancer caused by mutant BRCA1 alleles will soon be estimated, and individual mutation frequencies and penetrances may be established". However, in the same paragraph, the authors of document D1 describe the task of carrying out exhaustive searches for new mutations as being "challenging", in view of the large size and fragmented nature of the coding sequence. The Board is therefore convinced that, in view of the disclosure in document D1, the skilled person, taking a conservative attitude, would not have reasonably expected to successfully identify a mutation that allows the development of an effective screening for inherited breast and ovarian cancer within acceptable time limits. From the skilled person's perspective at the fourth priority date of the patent in suit, finding such a mutation would not only involve a substantial amount of "challenging" work, but would also require a "lucky strike", which could in no way be predicted on the basis of document D1.

62. Opponents have argued that finding the mutation 185delAG -> ter39 was obvious because, starting from document D1, the skilled person would immediately have carried out an extensive screening of the available patient samples and, by doing so, would have inevitably arrived at said mutation. This was evidenced by the fact that the well-documented families "BOV3" known from document D9 (also mentioned in post-published document D5, Table 3) and "2979" known from document

D42 - access to these families was available at the fourth priority date - contained the mutation 185delAG -> ter39, as confirmed by document D47. By following the suggestion in document D1 to find mutations, catalogue them and determine their frequencies, the skilled person would also have obtained the information of the frequency of the mutation 185delAG -> ter39. Also, the more frequent a mutation was, the higher was the chance to find it. To carry out the screening involved nothing but repetitive work, which would have inevitably resulted in the claimed invention. The finding of the mutation 185delAG -> ter39 was thus a "one-way street" situation, not a lucky strike. This was also supported by the post-published document D96, which stated that within days after the disclosure of the complete nucleotide sequence of BRCA1 in GenBank, oligonucleotide primers had been prepared to start the genetic analysis, and that less than a week later, some groups had already found sequence changes in their own patient samples (see column 1, last paragraph of the document).

63. The Board cannot follow this line of argument as it is based on an *ex post facto* analysis, which should be avoided in the assessment of inventive step (see Case Law of the Boards of Appeal of the European Patent Office, 5th edition 2006, chapter I.D.5.). It is only with the benefit of hindsight that one can now know what the skilled person would have had to do at the relevant time in order to arrive at the claimed subject-matter. This does, however, not reflect the skilled person's circumstances at the fourth priority date, which should not be confused with the circumstances of those scientists that, in the hope to

succeed, eagerly undertook the "challenging" search for BRCA1 predisposing mutations and, by doing so, might have arrived at the claimed invention.

64. Opponents have further argued that the claimed subject-matter was obvious over a combination of documents D1, D115 and D117. Document D115 disclosed that a familial aggregation of ovarian cancer occurs in the Israeli Jewish population, and the skilled person would have considered this population as a suitable group for BRCA1 mutation analysis in order to find further predisposing mutations. Upon screening these Israeli Jewish women, the skilled person would inevitably have identified 185delAG -> ter39 as a predisposing mutation. This was evidenced by the post-published document D116 which showed that said mutation was detected in 38.9 % of ovarian cancer patients with familial history and 13.1 % of family history-negative ovarian cancer cases in this population (see abstract, section results). Although document D115 did not mention the term "BRCA1", there would have been no doubt for the skilled person that said population was appropriate for the further screening for BRCA1 mutations, because it was known from document D117 that the BRCA2 gene was linked to susceptibility to hereditary breast cancer only, i.e. not ovarian cancer.

65. The Board considers that the Opponents' argumentation is again based on an *ex post facto* analysis and that in the absence of a reasonable expectation of success (see points 59 to 61 above), the skilled person would not have undertaken the screening of the population of document D115.

66. Opponents have also argued that the detection of the mutation 185delAG -> ter39 was made easy by the disclosure of the mutation 188del11 in document D1 in view of the proximity of the two mutations in exon 2.

67. However, in the Board's judgment, the skilled person could not expect from the disclosure of the mutation 188del11 in document D1 to find a further predisposing mutation in this area of exon 2, let alone a mutation that would allow effective screening. Therefore, the Opponents' argument fails.

68. Opponents have further argued that document D6 disclosing the mutation 185delAG -> ter39 had been submitted for publication on 3 November 1994 (as was indicated on the last page of the document), thus shortly after the publication of document D1. According to the Opponents, this demonstrated that it had not been difficult to identify the mutation.

69. The Board cannot see how the submission for publication of the mutation 185delAG -> ter39 in document D6 (the authors of which include three of the inventors of the patent in suit) shortly after the publication of document D1 could in any way prejudice the inventiveness of claim 1. The Board takes the position that, in view of what has been said points at (54) to (67) above, it is only with the benefit of hindsight that one could conclude that it would have been straightforward to arrive at the claimed invention.

70. In view of the above considerations, the subject-matter of claim 1 is considered to involve an inventive step. Since claim 2 also requires the determination of the

mutation 185delAG -> ter39 in the claimed method, the reasons given above as to why the subject-matter of claim 1 involves an inventive step apply analogously also for the subject-matter of claim 2. Claims 3 to 5 are dependent on claims 1 and 2 and their subject-matter thus likewise involves an inventive step. The nucleic acid probe of claim 7 is considered to involve an inventive step because it must contain the mutation 185delAG -> ter39. The same applies to the replicative cloning vector of claim 8 comprising an isolated nucleic acid according to claim 7, and to the host cells of claim 9 which are in vitro transformed with a vector of claim 8.

Consequently, the subject-matter of claims 1 to 9 fulfils the requirements of Article 56 EPC.

Sufficiency of disclosure (Article 83 EPC)

71. The Opposition Division decided in point (14) of the appealed decision that the patent disclosed a method for diagnosing a predisposition for breast and ovarian cancer based on the determination of the mutation 185delAG -> ter39 in a manner sufficiently clear and complete for it to be carried out by a skilled person.

72. None of the Opponents has submitted any evidence or argument to further substantiate this issue during the present appeal proceedings.

73. The Board, having no reason to deviate from the decision taken by the Opposition Division in this respect, decides that the requirements of Article 83 EPC are met.

Patentable invention (Article 52(2) EPC)

74. In the notice of opposition, dated 22 February 2002, Opponent 06 argued that the sequences of the probes according to present claim 7 occur in nature and are therefore a discovery rather than an invention. In view of Article 52(2) EPC, said probes were thus not patentable. During the oral proceedings, this point was not further pursued by any of the Opponents.

75. According to the case law of the Boards of Appeal (see decision T 272/95 of 23 October 2002), Article 52(2)(a) EPC is to be interpreted in accordance with the implementing Rule 29(2) EPC (corresponding to Rule 23e(2) EPC 1973) which states:

"(2) An element isolated from the human body or otherwise produced by means of a technical process including the sequence or partial sequence of a gene may constitute a patentable invention, even if the structure of that element is identical to that of a natural element".

76. Claims 7 relates to a nucleic acid **probe** comprising partial DNA sequences of the human BRCA1 gene, which is described in the patent in suit as having been obtained by technical processes. This probe is thus an isolated element of the human body as defined in Rule 29(2) EPC and thus patentable subject-matter. Accordingly, the subject-matter of claim 7 does not fall within the category of inventions which may not be patentable as being discoveries (Article 52(2)(a) EPC).

Exceptions to patentability (Article 53(a) and (c) EPC)

77. Opponent 04 in the notice of opposition, dated 25 February 2002, and Opponent 06 argued that methods for diagnosing a predisposition for breast and ovarian cancer or for diagnosing a breast or ovarian lesion for neoplasia in/of a human subject should not be regarded as patentable invention according to Article 52(4) EPC 1973 (now Article 53(c) EPC). During the oral proceedings, this point was not further pursued by any of the Opponents.

78. Article 53(c) EPC (which corresponds to Article 52(4) EPC 1973) states that European patents shall not be granted in respect of methods for treatment of the human or animal body by surgery or therapy and diagnostic methods **practised on the human or animal body.**

The Enlarged Board of Appeal in its Opinion G 1/04 (OJ EPO 2006, 334) said that Article 52(4) EPC 1973 excludes diagnostic methods practised on the human or animal body only if the method steps of technical nature belonging to the preceding steps which are constitutive for making a diagnosis as an intellectual exercise are performed on a living human or animal body (see point (6) of the reasons).

79. According to present claims 1 to 6, all method steps of technical nature are performed on a tissue sample of a human subject. The Opponents' argument must therefore fail. The claims do not refer to subject-matter not patentable according to Article 53 (c) EPC (Article 52(4) EPC 1973).

80. Furthermore, Opponent 04 argued that the subject-matter of the claims contravened the requirements of Article 53(a) EPC. If the patent was granted, patients were no longer able to have their genetic information read and interpreted by the organisation of their choice and it could not be guaranteed that criminal and medical gene databases were kept strictly separate, which was an accepted ethical principle in the member states of the EPO.

81. Opponent 06 argued that the socio-economic consequences of the patenting of the claimed subject-matter should be considered by the Board under Article 53(a) EPC, because in the present case, these consequences touched ethical issues. Patenting of the claimed subject-matter would not only result in increased costs for patients, but would also influence the way in which diagnosis and research would be organized in Europe, which would be clearly to the detriment of patients and doctors. The fact that a particular group of patients, i.e. patients suspected to carry a predisposition to breast cancer, would be faced with severe disadvantages and would become dependent on the patent proprietor, was contrary to human dignity. Therefore, the claimed subject-matter constituted an exception to patentability under Article 53(a) EPC.

A further indication that the legislator intended to enforce a critical examination of this aspect was seen in the transfer of Article 52(4) EPC 1973 to Article 53 EPC, referring to exceptions to patentability.

82. This Board, in a different composition, already in decision T 1213/05 (supra) has dealt with the socio-

economic and ethical consequences of the patenting of diagnostic methods involving the use of human genetic material.

The Board in the present composition follows decision T 1213/05 (supra, see especially points (52) and (53)) and, on this basis, rejects Opponents' objection under Article 53(a) EPC.

Industrial applicability (Article 57 EPC)

83. Claim 7 refers to a nucleic acid probe defined by a nucleotide sequence.

According to Appellants II to IV the possible uses of such probes were not industrial applications in the sense of Article 57 EPC in connection with Rule 29(3) EPC, which required that, with regard to inventions concerning the human body and its elements, the industrial application of a sequence or a partial sequence must be disclosed in the patent application.

The capacity of a single stranded DNA sequence to hybridize with a complementary single-stranded sequence was a consequence of the physico-chemical properties of each single-stranded DNA molecule and was thus a universal characteristic thereof. Such universal characteristic could not be accepted as a basis for an industrial application within the meaning of Article 57 and Rule 29(3) EPC.

During the oral proceedings, this point was not further pursued by any of the Opponents.

84. This Board, in a different composition, already in decision T 1213/05 (supra, see especially point (62)) has dealt with the industrial applicability of nucleic acid probes.

The Board found, and the present Board agrees with this position, that the provision of a probe useful in a diagnostic method cannot be considered to be merely a research tool for the detection of complementary single stranded DNA molecules, but that such probe can also be commercially applied for a diagnostic purpose, in the present case to detect the presence of a BRCA1 allele predisposing an individual to cancer.

85. Accordingly, the requirements of Article 57 EPC are met.

Adaptation of description

86. The description has been correctly adapted to the subject-matter of claims 1 to 9.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent in the following version:

Description: Pages 3, 3a, 4 to 24 and 138 submitted at the oral proceedings on 13 November 2008; pages 25 to 137 of the patent specification as granted.

Claims: 1 to 9 of the main request, filed with a letter dated 2 June 2008.

Figures: 1 to 10 on pages 151 to 169 of the patent specification as granted.

The Registrar: The Chair:

P. Cremona U. Kinkeldey

EXHIBIT G

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Datum/Date
12. 12. 07

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n° //Patent Nr./Patent No./ Brevet n°.
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Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
The University of Utah Research Foundation, et al

Appeal number: **T 1213 / 05 - 3304**

Please find enclosed a copy of the decision dated 27-09-2007.

PROC DISP

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04 and 05

Appeal number: **T 1213 / 05 - 3304**

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An die Erben von Herrn Dr. Wilhelms, Rolf E.
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ALLEMAGNE

Datum/Date
12. 12. 07

Zeichen/Ref./Réf.	Anmeldung Nr./Application No./Demande n°./Patent Nr./Patent No./ Brevet n°.
OPPO 07	95305601.7 - 2405 / 0705902

Anmelder/Applicant/Demandeur//Patentinhaber/Proprietor/Titulaire
The University of Utah Research Foundation, et al

Appeal number: **T 1213 / 05 - 3304**

Please find enclosed a copy of the decision dated 27-09-2007.

PROC DISP

The Registrar - P. Cremona
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Datum/Date
12. 12. 07

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Case Number: T 1213/05 - 3.3.04

D E C I S I O N
of the Technical Board of Appeal 3.3.04
of 27 September 2007

Appellant I: (Patent Proprietor)
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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted 19 September 2005 concerning maintenance of European patent No. 0705902 in amended form.**

Composition of the Board:

Chair: U. Kinkeldey
Members: M. Wieser
D. Rogers
B. Claes
G. Weiss

Summary of Facts and Submissions

I. Appeals were lodged by the Patent Proprietor (Appellant I) and Opponent 01 (Appellant II) against the interlocutory decision of the Opposition Division dated 19 September 2005 according to which European patent No. 0 705 902 could be maintained in amended form on the basis of claims 1 to 3 of the auxiliary request before it (Articles 102(3) and 106(3) EPC). The patent has the title "17q-Linked breast and ovarian cancer susceptibility gene" and claims priority from eight US applications (P1 to P8), of which the second (P2) and the fifth (P5) were filed on 2 September 1994 and 24 March 1995, respectively.

II. Eight oppositions had been filed against the patent covering the grounds of Article 100(a) EPC in combination with Articles 52(2) and (4), 53(a), 54, 56 and 57 EPC, and Article 100(b) and (c) EPC.

III. The Opposition Division decided that the main request before it did not meet the requirements of Articles 123(2) and (3) and 84 EPC.

IV. The Board expressed its preliminary opinion in a communication dated 27 February 2007.

V. With letter dated 8 June 2007, the Board was informed that Opponent 7 had passed away.

VI. Oral proceedings before the Board took place from 24 to 27 September 2007.

Appellant I requested that the decision under appeal be set aside and that the patent be maintained on the basis of a main request (claims 1 - 29 filed with a letter dated 30 January 2006), or auxiliary request I (claims 1 - 14 filed with a letter dated 30 January 2006), or auxiliary request II (claims 1 - 32 filed on 25 September 2007 at the Oral Proceedings), or to dismiss the appeal of Appellant II (which corresponds to upholding the claims held allowable by the Opposition Division - hereafter referred to as "auxiliary request III"). Further, Appellant I requested to refer three questions to the Enlarged Board of Appeal.

Appellant II requested that the decision under appeal be set aside, that the patent in suit be revoked and to refer five questions to the Enlarged Board of Appeal.

Opponents 2 to 5, parties as of right, requested that the decision under appeal be set aside and that the patent be revoked.

Opponents 6 and 8, parties as of right, requested that the appeal of Appellant I be dismissed.

VII. Claim 1 of the main request read as follows:

"An isolated nucleic acid which comprises a coding sequence for the human BRCA1 polypeptide, wherein said polypeptide

- has 1863 amino acids,
- has a molecular weight of 208 kilodaltons, and
- comprises the amino acid sequence of SEQ ID NO: 82,

said coding sequence being comprised in a genomic DNA which is obtainable by:

(a) providing a human genomic library;

(b) screening the genomic library using a probe selected from the group consisting of:

(i) the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TCG A

and

(ii) the DNA sequence of any one of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 67, 72 and 81

and

(c) producing a genomic DNA comprising said coding sequence;

wherein said genomic DNA comprising said coding sequence is more than 100 kb in length;
and wherein the first exon within said genomic DNA immediately follows the nucleotide sequence corresponding to SEQ ID 35; or

said coding sequence being comprised in a cDNA which is obtainable by:

(aa) providing a cDNA library using human mRNA from

breast, thymus, testis or ovary;

(bb) screening the cDNA library using a probe having the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TCG A

and

(cc) producing a cDNA comprising said coding sequence;

wherein said coding sequence comprises the following nucleotides sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TCG A

and

wherein upon hybridization of a Northern blot with a fragment of said cDNA a single transcript of 7.8 kb is identified in breast, thymus, testis and ovary tissue."

VIII. Claim 2 of auxiliary request I read as follows:

"A hybridization probe wherein the sequence of said probe comprises a portion of a coding sequence for a mutant BRCA1 polypeptide, which is

(i) a DNA sequence comprising the nucleotide sequence set forth in SEQ ID NO: 1 from nucleotide 120 to nucleotide 5708 or an allelic variant thereof having one of the following mutations defined with reference to SEQ ID NO: 1:
(a) T substituted for C at position 4056;
(b) an extra C at nucleotide position 5385; and
(c) G substituted for T at position 5443; or

(ii) a corresponding RNA,
said coding sequence portion including a mutation compared to the nucleotide sequence set forth in SEQ ID NO: 1 from nucleotide 120 to nucleotide 5708 as defined in any of (a) to (c),

with the proviso that said coding sequence portion does not comprise positions 1364, 1369, 1454, 1492, 1494, 1571, 1581, 2201, 2430, 2731, 3499, 4060, 4535, 4689 and 5609 of SEQ ID NO: 1."

IX. Claims 1 and 2 of auxiliary request II, which are identical to claims 1 and 2 as granted, read as follows:

"1. An isolated nucleic acid which comprises a coding sequence for the BRCA1 polypeptide defined by the amino acid sequence set forth in SEQ ID NO:2, or an amino acid sequence with at least 95% identity to the amino acid sequence of SEQ ID NO:2.

2. An isolated nucleic acid as claimed in claim 1 which is a DNA comprising the nucleotide sequence set forth in SEQ ID NO:1 from nucleotide 120 to nucleotide 5708 or a corresponding RNA."

X. The three claims of auxiliary request III read as follows:

"1. A nucleic acid probe wherein the nucleotide sequence of said probe comprises the following DNA sequence:

AG GAA AGT TCT GCT GTT TTT AGC AAA AGC GTC CAG
AAA GGA GAG CTT AGC AGG AGT CCT AGC CCT TTC ACC
CAT ACA CAT TTG GCT CAG GGT TAC CGA AGA GGG GCC
AAG AAA TTA GAG TCC TCA GAA GAG AAC TTA TCT AGT
GAG GAT GAA GAG CTT CCC TGC TTC CAA CAC TTG TTA
TTT GGT AAA GTA AAC AAT ATA CCT TCT CAG TCT ACT
AGG CAT AGC ACC GTT GCT ACC GAG TGT CTG TCT AAG
AAC ACA GAG GAG AAT TTA TTA TCA TTG AAG AAT AGC
TTA AAT GAC TCG A

or a DNA probe comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 66, 67, 72 and 81."

"2. A replicative cloning vector which comprises (a) an isolated DNA according to claim 1 and (b) a replicon operative in a host cell for said vector."

"3. Host cells in vitro transformed with a vector as claimed in claim 2."

XI. The following documents are mentioned in the present decision:

D1: Miki et al., Science (Oct. 1994) 266: 66-71

D3: Friedman et al., Nature Genetics (Dec. 1994) 8: 399-404

D4: Castilla et al., Nature Genetics (Dec. 1994) 8: 387-391

D10: Kelsell et al., Hum. Mol. Genet. (1993) 2: 1823-1828

D11: Albertsen et al., Nature Genetics (Aug. 1994) 7: 472-479

D17: Simard et al., Nature Genetics (Dec. 1994) 8: 392-398

D22: Smith et al., Genes Chrom. Cancer (1994) 10: 71-76

D31: Clone Genbank Accession L18209 information

D52: Goldgar et al., Am. J. Hum. Genet. (1993) 52: 743-748

D88: Simard et al., Hum. Mol. Genet. (1993) 2: 1193-1199

D112: Feunton et al., Am. J. Hum. Genet. (1993) 52: 736-742

D120: Declaration Dr Shattuck

D122: Cropp et al., Cancer Res. (1994) 54: 2548-2551

D125: Positional Cloning of BRCA1

D128: Amplimer UM44_

D129: Couch et al., Genomics (1994) 24: 419-424

D136: Declaration Dr Matthijs

D154: Davies, K. and White, M.; Breakthrough - The race to find the Breast Cancer Gene, 1995, Ed. John Wiley & Sons, Inc., New York

D159: Personal Communication Couch

D160: Amplimer UM44_ History

D164: Documentation on "Human Genome Sequence Quality Standards", http://www.genome.gov/pfv.cfm?pageID=10000923

D165: Schmutz et al., Nature (2004) 429: 346-368

D166: Bermuda Standards, http://www.gene.ucl.ac.uk/hugo/bermuda2.htm

D172: Declaration Dr Critchfield

D173: Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998, OJ EPO 2/1999, 101

D174: Judgment of the Court of Justice of the European Communities dated 9 October 2001; Case C-377/98

D175: Opinion of Advocate General Jacobs delivered on 14 June 2001, Case C-377/98

XII. The submissions by Appellant I, insofar as they are relevant to the present decision, can be summarized as follows:

Main request

Amendments (Article 123(2) EPC)

The subject-matter of claim 1 was directly and unambiguously derivable from the application as filed. The skilled person reading the application would realize that the probes specified in claim 1 could be used for the screening of genomic or cDNA libraries. In fact any part of the BRCA1 sequence would be useful for this purpose. Using the product-by-process format did not change the nature of the invention, as the product was still the same as in the application as filed. In view of the major technical contribution of the invention, allowing a product-by-process definition would be a fair solution in order to provide the entitlement to the second priority (P2).

Auxiliary request I

Amendments (Article 123(2) EPC)

The disclaimers in claims 2, 3, 6, 8, 12 and 13 were allowable under Article 123(2) EPC since they merely served to restore the second priority. The disclaimers had been drafted on the basis of a comparison between the second priority document and the European application, not on the basis of the prior art.
The list of situations in which disclaimers were held allowable in decisions G 1/03 and G 2/03 (OJ EPO 2004, 413) was not exhaustive, and was therefore not in contradiction to allowing the present disclaimers under Article 123(2) EPC. Furthermore, the disclaimers did not provide a technical contribution, since none of the sequence positions disclaimed were involved in causing breast cancer.

Auxiliary request II

The filing of a new request the claims of which were almost identical to the claims as granted had to be allowed even at a late stage of the proceedings.

As priority document (P2) disclosed the same invention as defined in the claims of auxiliary request II, the claims were entitled to claim priority from priority document (P2). Although priority document (P2) referred to SEQ ID NOs: 1 and 2 which deviated from SEQ ID NO's: 1 and 2 disclosed in the application as filed, it disclosed in an enabling form the same diagnostic target as defined in claim 1 of auxiliary request II.

If a parameter which was used to define a substance in a claim was known to vary within margins of experimental errors, the occurrence of variation in such a parameter between a priority document and the corresponding later application did not necessarily abrogate entitlement to the claimed priority.

For further detailed submissions see "Reasons for the Decision" (points (19) and following).

Auxiliary request III

Articles 123(2)(3), 84, 52(2), 53(a), 57, 83 and 87 to 89 EPC

The amendments complied with Article 123(2) and (3) EPC, and the claims were clear under Article 84 EPC.

The objections raised by Opponents under Article 52(2) and Article 53(a) EPC lacked substantiation and should be rejected by the Board.

The probes according to claim 1 could be used as diagnostic tools which had to be considered as being an industrial application in the sense of Article 57 and Rule 23e(3) EPC.

The claimed subject-matter was disclosed in a manner sufficiently clear and complete for it to be carried out by a skilled person (Article 83 EPC).

The claimed subject-matter was furthermore directly and unambiguously derivable from the second priority document (Articles 87 to 89 EPC).

Novelty (Article 54 EPC)

Document D11 was not prejudicial to the novelty of the probe of claim 1. Firstly, it had not been sufficiently proven by document D136 that the first sequence mentioned in claim 1 was indeed present in YAC clone 22HE5, as correctly pointed out in the decision of the Opposition Division. Secondly, document D11 only disclosed a library of clones which could not destroy the novelty of the probe specified in claim 1.

Inventive step (Article 56 EPC)

In view of the uncertainties with respect to the chromosomal localisation of the BRCA1 gene at the second priority date, it was problematic to select a closest prior art document. The technical problem to be solved was the provision of probes for the BRCA1 gene to detect breast cancer. The positional cloning of the BRCA1 gene was very complex and involved many uncertainties, and there could not have been a reasonable expectation of success. During the cloning procedure, the inventors had to take a multitude of decisions many of which had the potential of leading to ultimate failure. Picking the right breast and ovarian cancer families (kindreds) was one of the crucial points that led to success. The solution to the technical problem as provided by the claimed subject-matter was thus not obvious over the prior art.

XIII. The submissions by Appellant II and by the parties as of right, Opponents 2 to 8, insofar as they are relevant to the present decision, can be summarized as follows:

Main request

Amendments (Article 123(2) EPC)

The product-by-process definition in claim 1 was not acceptable under Article 123(2) EPC, and the combination of features mentioned in claim 1 was not disclosed in the application as filed.

Auxiliary request I

Amendments (Article 123(2) EPC)

The disclaimers in claims 2, 3, 6, 8, 12 and 13 did not comply with Article 123(2) EPC since they provided a technical contribution to the claimed subject-matter. Furthermore, the reasons for which Appellant I attempted to restore the second priority by use of said undisclosed disclaimers were to overcome a non-accidental disclosure and/or an inventive step objection. This was not acceptable in view of decisions G 1/03 and G 2/03.

Auxiliary request II

The request, submitted at the oral proceedings before the Board, should not be admitted into the proceedings as being late filed. Should the Board admit the request the case had to be remitted to the department of first instance.

The claims of auxiliary request II could only enjoy priority right from priority document (P5), being the earliest of the eight priority documents disclosing SEQ

ID NO's: 1 and 2 corresponding exactly to SEQ ID NO's: 1 and 2 as disclosed in the application as filed.

Auxiliary request III

Amendments (Articles 123(2)(3) and 84 EPC)

Claim 1 did not comply with Article 123(2) EPC since the legend to Figure 7 on page 4, lines 30 to 32 of the application (published version), which referred to "a probe consisting of nucleotide positions 3631 to 3930 of BRCA1", did not indicate that the positions of the numbering of SEQ ID NO: 1 were meant.

Patentable inventions (Article 52(2)(a) EPC)

The claimed subject-matter was not patentable under Article 52(2)(a) EPC since the sequences of the probes according to claim 1 occurred in nature and were thus a discovery rather than an invention.

Exceptions to patentability (Article 53(a) EPC)

No proof had been provided by Appellant I showing that previous informed consent to the commercial exploitation of the invention by patents had been given by the donors of the cells critical for the invention, and that a benefit sharing agreement had been made. Therefore, the claimed invention was unethical and excluded from patentability in view of Article 53(a) EPC. Furthermore, the consequences of the patenting of the claimed invention had to be taken into account when examining the patentability under Article 53(a) EPC.

For further detailed submissions see "Reasons for the Decision" (points (46) and following).

Industrial applicability (Article 57 EPC)

The nucleotide probes according to claim 1 were useful for research purposes only which could not be considered as being an industrial application in the sense required by Article 57 and Rule 23e(3) EPC.

Sufficiency of disclosure (Article 83 EPC)

Since the patent did not disclose a technical application of the claimed subject-matter it did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a skilled person as required by Article 83 EPC.

Right to priority (Articles 87 to 89 EPC)

The subject-matter of claim 1 was not entitled to the second priority date, since there was no indication on page 6, lines 24 to 28 of the second priority document that by referring to "a probe consisting of nucleotide positions 3575 to 3874 of BRCA1", the positions of the numbering of SEQ ID NO: 1 were meant.

Novelty (Article 54 EPC)

The YAC clone 22HE5 mentioned in Figure 2 of document D11 was prejudicial to the novelty of claim 1. Evidence for this was provided in document D136. Claim 1 encompassed any nucleic acid probe comprising the mentioned sequence, and thus lacked novelty over any

isolated and individualized section of DNA comprising this sequence, such as YAC clone 22HE5.

Inventive step (Article 56 EPC)

The closest prior art was represented by document D11, and the technical problem to be solved was the identification and isolation of the BRCA1 gene.

Starting from document D11, the skilled person would have had a high expectation of success that the BRCA1 gene could be identified and isolated merely by the application of conventional positional cloning techniques. Arriving at the claimed subject-matter was obvious from document D11 in combination with common general knowledge, or, alternatively, from document D11 in combination with either document D128 or document D31.

The inventors had carried out the necessary experimentation faster than others merely because they had been able to put more money and manpower into the project, but this did not justify the recognition of an inventive step. Suitable kindreds were also available to other scientific groups, and sooner or later one of these groups would have been successful as well. Any problems that might have been encountered in the course of the project would have been overcome by the skilled person using conventional means.

Reasons for the Decision

1. The appeals are admissible.

Main request

Amendments (Article 123(2) EPC)

2. Claim 1 is directed to a nucleic acid which comprises a coding sequence for the human BRCA1 polypeptide, whereby the claimed product is defined by features of the polypeptide as well as by features of a process of genomic DNA and cDNA library screening (product-by-process).

3. Article 123(2) EPC requires that a European patent application or a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. In accordance with the established case law of the Boards of Appeal, the content of an application comprises the disclosure that is directly and unambiguously derivable from this application.

4. The Board considers that in the case of a product-by-process definition, the process defined in a claim also has to be directly and unambiguously derivable from the application as filed in order for the claim to comply with Article 123(2) EPC. This has not been contested by Appellant I.

4.1 As concerns the process steps of screening a genomic or cDNA library, page 14, lines 13 to 15 of the application (published version) of the patent in suit

states that "cDNA or genomic libraries of various types may be screened as natural sources of the nucleic acids of the present invention", and lines 17 to 18 mention that clones are "probed for the presence of desired sequences". Further, it is stated in lines 19 to 20 that the "DNA sequences used in this invention will usually comprise at least about five codons (15 nucleotides), more usually at least about 7-15 codons, and most preferably, at least about 35 codons".

4.2 On page 19 of the application as published, under the heading "Methods of Use: Nucleic Acid Diagnosis and Diagnostic Kits" it is stated that "in order to detect the presence of a BRCA1 allele predisposing an individual to cancer, a biological sample such as blood is prepared and analyzed for the presence or absence of susceptibility alleles of BRCA1" (lines 3 to 4). Further on the same page, PCR-based methods of target amplification and of detection of target sequences using nucleic acid probes are described. In lines 55 to 56 of the same page it is then stated that "[e]xamplary probes are provided in Table 9 of this patent application and additionally include the nucleic acid probe corresponding to nucleotide positions 3631 to 3930 of SEQ ID NO:1". The latter probe ("Northern probe") was also used for RNA hybridization (see page 4, lines 30 to 34 and Figure 7) and its sequence is the one stated in points (b)(i) and (bb) of claim 1. The probes in Table 9 represent intron borders and include the probes of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 67, 72 and 81 referred to in point (b)(ii) of claim 1. However, there is no disclosure on page 19 of the application as published of using these probes in the screening of genomic or cDNA libraries.

4.3 Claim 13 of the application as published is directed to a "nucleic acid probe suitable for a use as claimed in claim 11", wherein the nucleotide sequence of said probe may comprise the DNA sequence of the "Northern probe" or a sequence set forth in Table 9. As claim 11 is directed to an isolated DNA, not to a use, claim 13 should apparently refer to claim 12, the latter being directed to a "[u]se of an isolated nucleic acid (...) as a hybridization probe **to detect in a sample** (i) a DNA (...)" (emphasis added by the Board). Again, there is no suggestion of using the specified probes in the screening of genomic or cDNA libraries.

4.4 Appellant I has argued that it did not matter technically for which purpose the probes were disclosed, as any probe could be taken for the screening of a genomic or cDNA library. However, the Board considers that it is the actual teaching of the application as filed which is relevant, and that, therefore, the general disclosure of screening a genomic or cDNA library with a probe defined as comprising "at least about five codons" (see page 14, lines 13 to 20) cannot be combined with the more specific disclosure of using the "Northern probe" or a probe as set forth in Table 9 for **a different purpose**, namely the detection of DNA in a sample (page 19 and claim 13), without contravening Article 123(2) EPC.

4.5 Appellant I has further referred to Exhibits 1 to 20 as filed during the first instance proceedings with letter of 19 November 2004 as showing support for claim 1 of the main request in the application as filed. Exhibits 7, 8 and 15 relating to the steps of library screening as mentioned in points (b) and (bb) of claim 1

suggested that because the Northern blot probe sequence and the intron border DNA sequences fall into the definition given on page 14, lines 19 to 20 of the application as published (see point 4.1 above), this would provide a direct and unambiguous disclosure of these probes for screening a genomic or cDNA library. The Board cannot follow this reasoning since the specific probes mentioned in claim 1, steps (b) and (bb), have not been disclosed for use in screening a genomic or cDNA library.

5. The Board concludes that in claim 1, step (b), the screening of the genomic library using any one of the probes specified in points (i) and (ii), and step (bb), the screening of a cDNA library using a probe having the specified DNA sequence, are not directly and unambiguously derivable from the application as filed.

6. Consequently, the subject-matter of claim 1 of the main request does not comply with Article 123(2) EPC.

Auxiliary request I

Amendments (Article 123(2) EPC)

7. Claim 2 of auxiliary request I contains the disclaimer "with the proviso that said coding sequence portion does not comprise positions 1364, 1369, 1454, 1492, 1494, 1571, 1581, 2201, 2430, 2731, 3499, 4060, 4535, 4689 and 5609 of SEQ ID NO: 1". Claims 3, 6, 8, 12 and 13 contain similar disclaimers. Said disclaimers cannot be found in the application as filed.

8. Appellant I has submitted that the nucleotide and amino acid sequences disclosed in SEQ ID NOs: 1 and 2 of the second priority document have turned out to contain sequencing errors, and that the correct sequences as stated in the patent in suit are only disclosed in the fifth priority document (see grounds of appeal dated 30 January 2006, point 6.1.2.3). The disclaimers exclude those positions within SEQ ID NO: 1 by which this nucleotide sequence differs between the second priority document and the application as filed. The disclaimers have been incorporated into the claims in order to safeguard the second priority (see grounds of appeal, point 6.2.2.3).

9. Decisions G 1/03 and G 2/03 (OJ EPO 2004, 413) of the Enlarged Board of Appeal (EBA) provide criteria for allowing under Article 123(2) EPC a disclaimer which is not disclosed in the application as filed. According to these decisions, a disclaimer may be allowable in order to restore novelty by delimiting a claim against the state of the art under Article 54(3) and (4) EPC and against an accidental anticipation under Article 54(2) EPC, but not against a non-accidental anticipation under Article 54(2) EPC; an anticipation is said to be accidental if it is so unrelated to and remote from the claimed invention that the person skilled in the art would never have taken it into consideration when making the invention. A disclaimer which is or becomes relevant for the assessment of inventive step or sufficiency of disclosure adds subject-matter contrary to Article 123(2) EPC.

10. Appellant I has submitted that the sole reason for introducing the disclaimers was to validly claim the

second priority, not to establish novelty and inventive step. The Board cannot follow this argumentation, since the issue of the right to priority cannot be seen in isolation from the effect it has on novelty and inventive step by virtue of Article 89 EPC, according to which the date of priority shall count as the date of filing of the European patent application for the purpose of Article 54(2) EPC. There is no provision in the EPC, that in order to obtain a patent, a priority has to be validly claimed. Therefore, the actual reason why Appellant I aims at claiming the second priority by the introduction of disclaimers has to be seen in prior art published between the second and fifth priority date, notably document D1. It is undisputed that document D1 is not an accidental disclosure and would become highly relevant for the evaluation of novelty and/or inventive step of the claimed subject-matter (see point (35) below). Hence, the Board considers that the disclaimers are in fact necessary to either restore novelty over a non-accidental disclosure or to establish an inventive step. These are, however, the areas excluded from the allowability under Article 123(2) EPC by the decisions of the EBA.

11. Consequently, the subject-matter of the claims of auxiliary request I does not comply with Article 123(2) EPC.

Auxiliary request II

Admission into the proceedings

12. Claims 1 and 2 of auxiliary request II are identical to claims 1 and 2 as granted (see section (IX) above).

13. Auxiliary request II, which was not before the Opposition Division, was filed by Appellant I on the second day of the oral proceedings. Appellant II and Opponents 2 to 6 and 8 objected to its late introduction into the proceedings. Furthermore, in the case the Board should allow auxiliary request II into the proceedings, they requested that the case be remitted to the department of first instance for further consideration according to Article 111(1) EPC.

14. According to the case law of the Boards of Appeal, a Patent Proprietor during opposition and opposition/appeal proceedings is entitled to amend a request already made; in particular he can reinstate the patent in the form in which it was granted, provided this does not constitute an abuse of the procedure. In requesting that the patent be maintained in a limited form the Patent Proprietor merely tries to delimit the patent to meet objections expressed by the EPO or the opponents. However, the Patent Proprietor does not, by virtue of such limitation, irrevocably abandon subject-matter covered by the patent as granted but not by the request as thus limited (cf decision T 123/85, OJ EPO 1989, 336).

15. Appellant I has filed auxiliary request II at the oral proceedings, after having been informed by the Board that the claims of his main request and of auxiliary request I contravened the requirements of Article 123(2) EPC. Reinstatement of the patent in a form which almost precisely corresponds to the form in which it was granted is considered to be a straightforward response

to the course of the oral proceedings and does not amount to an abuse of the procedure.

16. In general, to expedite the proceedings, parties to appeal proceedings are supposed to submit all facts, evidence and requests at the outset, or - if this is not possible - as soon as they can. They should not be filed piecemeal, this principle being enshrined in Articles 10a and 10b of the Rules of Procedure of the Boards of Appeal.

17. According to Article 114(2) EPC the European Patent Office may disregard facts or evidence which are not submitted in due time by the parties concerned. Thus, the Board may exercise its discretion when deciding on whether to admit late submissions.

The decision to admit a new request into the proceedings should take into account, amongst other factors, a general interest in the appeal proceedings being conducted in an effective manner while still being brought to a close within a reasonable time (cf decision T 633/97 of 19 July 2000, point (2) of the reasons for the decision).

The Board takes the view that the new auxiliary request II filed by Appellant I in response to the decisions announced by the Chair in the oral proceedings under Article 123(2) EPC with regard to his main request and auxiliary request I, whereby this auxiliary request II almost entirely corresponds to the claims as granted, does not raise additional technical or legal issues that neither the Board nor the other parties could have been expected to deal with. In fact, the question

whether or not the claims of auxiliary request II are entitled to a certain priority date, which is the core issue to be decided in the light of the disclosure in document D1 published between the third and fourth claimed priority dates of the patent in suit (see points (19) to (34) below), was known to the parties to be of outstanding importance during the opposition procedure and had already been extensively discussed by all parties involved in the context of the main request.

Therefore, in order to conduct the appeal proceedings in an effective and fair manner, the Board exercised its discretion and admitted Appellant I's auxiliary request II into the proceedings.

18. Remittal to the department of first instance lies within the discretion of the Board (cf decision T 249/93 of 27 May 1998, point (2) of the reasons for the decision). It is acknowledged that there is no absolute right for a party to have every aspect of a case examined in two instances (see for example decision T 133/87 of 23 June 1988). Other criteria, e.g. the general interest that proceedings are brought to a close within an appropriate period of time, have also to be taken into account.

Taking into consideration that the parties already had the opportunity to argue the issue of priority right (Articles 87 to 89 EPC) of the subject-matter of the claims of the patent as granted in the opposition procedure, the Board, using its discretion, decided not to remit the case to the department of first instance.

Priority right (Articles 87 to 89 EPC)

19. Document D1 is a scientific publication dated 7 October 1994, thus published between the filing date of the third priority document (P3)(US 308104; 16 September 1994) and the fourth priority document (P4)(US 348824; 29 November 1994) of the patent in suit. Document D1 is authored by a group of 45 persons, among them the 10 inventors of the patent. It is undisputed that the disclosure in this document, if it belonged to the state of the art under Article 54(2) EPC, would be highly relevant for the issues of novelty (Article 54 EPC) and/or inventive step (Article 56 EPC) of the subject-matter of Appellant I's auxiliary request II.

Document D1 would not belong to the state of the art under Article 54(2) EPC, if the claims of auxiliary request II were entitled to claim priority from US 308104 (P3), the third priority document.

The third priority document (P3) discloses on pages 94 to 98 SEQ ID NO: 1 showing the nucleotide sequence coding for BRCA1 and on pages 98 to 103 SEQ ID NO: 2 showing the amino acid sequence of the protein. SEQ ID NOs: 1 and 2 are identically disclosed on pages 90 to 94 and 94 to 99 of the second priority document (P2), US 300266; 2 September 1994. Therefore, when comparing the disclosure in the application as originally filed underlying the patent in suit, with the disclosure in the documents from which priority is claimed, the Board will refer to the second priority document (P2), which is the earliest priority document from which these sequences can be derived.

20. The BRCA1 coding sequence disclosed in SEQ ID NO: 1 of priority document (P2) deviates from the BRCA1 coding sequence disclosed in the application as filed by 15 nucleotide residues. Nine of these deviations lead to an amino acid exchange in SEQ ID NO: 2 while six are so-called "silent deviations". The earliest priority document disclosing the nucleotide sequence coding for BRCA1 and the amino acid sequence of the protein which are exactly identical to SEQ ID NOs: 1 and 2 disclosed on pages 58 to 67 and pages 67 to 73 of the application as filed is the fifth priority document (P5) (see pages 114 to 123 and 123 to 129 of US 409305; 24 March 1995).

21. The EBA in the Opinion G 2/98 (OJ EPO 2001, 413) came to the conclusion that the requirement for claiming priority in respect of "the same invention", referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

When examining whether a narrow or strict interpretation of the concept of "the same invention" referred to in Article 87(1) EPC should be applied, the EBA considered that a narrow and strict interpretation of the concept of "the same invention", equating it with the concept of "the same subject-matter" referred to in Article 87(4) EPC, was entirely consistent with Articles 4F and 4H of the Paris Convention (points (2) to (5) of the reasons for the Opinion). This followed

from the very aim and object of the right of priority: the protection from novelty destroying disclosures during a period of twelve months from the date of filing of the first application is satisfied only in case of the filing of a subsequent application relating to the same invention.

In point (8.3) of the reasons the EBA considered an issue that had been raised in decision T 73/88 (OJ EPO 1992, 557), which, in order to assess whether a claim in a later European patent application was in respect of the same invention as the priority application pursuant to Article 87(1) EPC, made a distinction between technical features which are related to the function and effect of the invention and technical features which are not. This approach was said to be problematic because there are no suitable and clear, objective criteria for making such a distinction; it could thus give rise to arbitrariness. Different deciding bodies might thus arrive at different results when assessing these facts and circumstances. Furthermore, as pointed out in the referral of the President of the EPO underlying the Opinion, it had to be borne in mind that the assessment by these different deciding bodies of whether or not certain technical features were related to the function and effect of the claimed invention might completely change in the course of proceedings. This was the case, in particular, if new prior art was to be considered, with the possible consequence that the validity of a hitherto acknowledged right of priority could be put in jeopardy. Such dependence would, however, be at variance with the requirement of legal certainty.

Finally in point (9) of the reasons the EBA stated:

"... an extensive or broad interpretation of the concept of "the same invention" referred to in Article 87(1) EPC, making a distinction between technical features which are related to the function and effect of the invention and technical features which are not, with the possible consequence that a claimed invention is considered to remain the same even though a feature is modified or deleted, or a further feature is added (cf point 8.3 supra), is inappropriate and prejudicial to a proper exercise of priority rights. Rather, according to that analysis, a narrow or strict interpretation of the concept of "the same invention", equating it to the concept of "the same subject-matter" referred to in Article 87(4) EPC (cf point (2) supra), is necessary to ensure a proper exercise of priority rights ...".

22. In application of the Opinion G 2/98 (supra) of the EBA, the Boards of Appeal, in a number of decisions, have defined the concept of "the same invention" in the field of biotechnology and especially in connection with inventions referring to nucleotide sequences.

Decision T 351/01 of 2 July 2003 was concerned with a patent referring to a polynucleotide encoding a biologically active tissue factor protein (TFP). The polynucleotide was defined in claim 1 by a reference to Figure 2. The figure showed a polynucleotide comprising the coding sequence for TFP, which was about 900 nucleotides long (and the deduced TFP amino acid sequence) and in addition non-coding portions at both ends of the coding region.

The patent claimed priority from priority documents I and II which disclosed a polynucleotide having the same function, namely coding for TFP, but whose structure differed from that of the polynucleotide of claim 1 by five bases all found outside of the coding region. The Board concluded, that, in the light of the EBA's Opinion G 2/98 (supra), the Respondents' (Patent Proprietor's) arguments to the avail that the claimed invention was the TFP coding sequence which was the same in all the documents and that the differences observed in the non-coding portion were irrelevant, were not convincing. Claim 1 was directed to a polynucleotide as defined in Figure 2, i.e. to a polynucleotide which had the sequence from the first to the last nucleotide depicted in the figure. This sequence like the one reported in Figure 2 of the first and second priority documents encoded a TFP. However, it was structurally different. Thus, it could not be seen as the same subject-matter. For this reason, it was decided that claim 1 did not enjoy priority rights from the filing dates of either of priority documents I or II.

23. Decisions T 70/05 of 7 February 2006 and T 30/02 of 9 October 2006 both were concerned with the entitlement of a prior art document to the claimed priority date.

In decision T 70/05 (supra) the amino acid sequence of a death-domain-containing receptor disclosed in the priority document and in the application as filed differed at nine of 181 positions. In accordance with the "narrow or strict interpretation" laid down in Opinion G 2/98 (supra) the Board decided that claim 1

referring to the receptor defined by specific full-length sequence ("amino acid residues 1 to 181 of SEQ ID NO: 1") could not enjoy the claimed priority right. In point (20) of the reasons for the decision the Board stated:

"It is also the board's opinion that, based on a disclosure of a "wrong" nucleotide or amino acid sequence in the priority document - independently of the reasons for the possible mistakes, either arising from unintended sequencing or typing errors or else arising from a conscious choice to file an application at a very early stage and thus, comprising doubtful or incomplete data - it would not be fair to acquire a right over a broad area from which, only later on, the "correct" sequence might be selected and disclosed in a patent application. The possible advantages conferred by such a practice would only encourage and, in the long term, lead to a mischievous use of priority rights."

24. In decision T 30/02 a novelty attack was based on prior art document D16, which was only comprised in the state of the art if it enjoyed priority from document D15. Document D16 disclosed a recombinant DNA sequence encoding a xylanase characterised by a partial nucleotide sequence (SEQ ID NO: 13) which differed from SEQ ID NO: 7 of claim 1 of the patent in suit only in so far as it included two additional guanine residues at its 3' end. A DNA molecule comprising the sequence defined in SEQ ID NO. 13 of document D16 could be expected to hybridize to a DNA molecule comprising the sequence of SEQ ID NO: 7, thus rendered the patent in suit not novel.

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However, the earlier application, document D15, did not contain SEQ ID NO: 13 of document D16 but only a Figure 9 showing a partial DNA sequence which was identical to SEQ ID NO: 13 of document D16 except for that it lacked the two guanine residues at the 3' end.

When answering the question whether or not the skilled person may have recognized the DNA of SEQ ID NO. 13 and of Figure 9 of document D15 as representing the "same subject-matter" and, thus, the "same invention" within the meaning of Article 87 EPC, as required in the Opinion G 2/98 (supra), the Board decided that the presence of two additional guanine residues in SEQ ID NO: 13 resulted in a different molecule that was not directly and unambiguously derivable from the earlier application, so that the priority right was not validly claimed.

25. Decision T 30/02 refers in point (15) of the reasons to decision T 923/92 (OJ EPO 1996, 564).

In this earlier decision the Board decided that a claim referring to a process comprising the preparation of a protein which was defined by its function and by an amino acid sequence 1 to 527 as depicted in Figure 5, did not enjoy priority from documents (P1) and (P2) which contained a Figure 5 that differed from Figure 5 of the patent in suit in respect of three amino acid positions 175, 178 and 191.

In point (16) of the decision the Board stated, that the primary amino acid sequence of a protein (or the nucleotide sequence of a DNA) constituted a true

technical feature and relying on a given sequence rather than on another one for the definition of the subject-matter of an invention in a claim made a critical difference.

In point (13), the Board commented on the relevance of decision T 65/92 (this decision is relied upon by the Appellant I in the present case in order to substantiate his line of argumentation (see point (28) below)) in the following way:

"In decision T 65/92 (supra), the board decided that a difference in the reported upper limit of the molecular weight of the glycosylated form of a polypeptide between the priority document and the European patent application (all other measured parameters being identical) did not reflect a true structural difference between the products of the two applications, especially in view of the fact that the molecular weight is able to be determined only approximately. Contrary to that, in the present case, the primary structure of human t-PA is not a parameter which is determined approximately, unless one relies on a general formula, which is not the case here."

26. The present Board endorses the decisions discussed in points (22) to (25) above, taking into account the technical situation underlying each individual case.

It has to be decided whether or not the specific technical situation in the present case requires the Board to develop, as Appellant I put it, "a more pragmatic approach" with regard to the issue of

priority rights concerning the concept of "the same invention".

27. Indeed, Appellant I, in the written procedure and during oral proceedings, submitted various arguments why the Board in the present case should not follow the gist of the decisions discussed in points (22) to (25) above, but should come to the conclusion that the BRCA1 coding sequence disclosed in the application as filed enjoys priority from priority document (P2), although it deviates from the BRCA1 coding sequence disclosed in priority document (P2) by 15 nucleotide residues.

28. Appellant I provided calculations, showing that the 5592 nucleotides (including stop codon) of the coding sequences of BRCA1 according to priority document (P2) and the application as filed shared a sequence identity of 99,73%. He argued that "silent mutations" would not generally be expected to disrupt protein function, so that the actually relevant sequence identity referred to 9 deviations out of 5592 nucleotides, i.e. 99,84%.

Appellant I took the view, that, if parameters (here: the nucleic acid sequence) which are used to define a substance (here: a nucleic acid) in a claim are known to vary within margins of commonly encountered experimental errors, the occurrence of variation in such a parameter between a disclosure in a priority document and the corresponding later application did not necessarily abrogate entitlement to the claimed priority. Appellant I referred in this respect to decision T 65/92 of 13 June 1993, wherein the Board acknowledged the entitlement to the claimed priority for a claim referring to a protein defined by reference

to its molecular weight, although the molecular weight ranges in the priority document and in the claim under consideration were not identical. The difference in molecular weight was considered to fall within the experimental error of the method for determination and was considered to have no influence on the fact that the priority document and the patent application related in substance to the same subject-matter. A similar approach had been taken in decision T 1147/98 of 14 July 2000.

Appellant I argued, that DNA sequencing was a measuring method which regularly produced experimental errors and was unable to produce 100% accurate data. This was acknowledged for example in documents D164 to D166, wherein it was stated that, although the sequence accuracy of so-called "finished sequences" should be no less than 99,99%, also preliminary results of sequencing projects were very useful, so that such "working drafts" having sequence accuracy between 90 and 99% should also be published. Therefore, as DNA sequencing had a certain margin of experimental error this should be taken into account when considering the validity of a priority claim directed to subject-matter referring to a DNA sequence. Legal certainty for third parties, an issue relied upon by Appellant II, was considered to be a function of the technology it referred to and the need for it could not be higher than experimental certainty.

The skilled person was aware of the possibility of sequencing errors and would have realized that the BRCA1 coding sequence of priority document (P2), containing two ambiguities ("N" at positions 1571 and

4535), was a preliminary version from which he/she would have been able to inevitably arrive at the correct sequence by using routine methods, like PCR, library screening, or sub-cloning.

As it was clear that a skilled person would have interpreted priority document (P2) and the application as filed as relating in substance to the same BRCA1 coding sequence, the sequence deviations did not negatively affect entitlement to the claimed priority date.

29. The argument, that a claim which explicitly refers to a **DNA sequence comprising a coding sequence for a specific polypeptide** should be entitled to claim priority from an earlier application disclosing a DNA sequence deviating from the claimed one within the margin of error of the used sequencing method, is not compatible with the EBA's conclusion in Opinion G 2/98 (supra) that the requirement for claiming priority of "the same invention", referred to in Article 87(1) EPC, means that priority of a previous application in respect of a claim in a European patent application in accordance with Article 88 EPC is to be acknowledged only if the skilled person can derive the subject-matter of the claim directly and unambiguously, using common general knowledge, from the previous application as a whole.

Indeed, also decision T 70/05 (supra) has applied the principles set out in the Opinion of the EBA G 2/98 (supra), and held that no priority right can be claimed from an earlier application disclosing an amino acid or nucleotide sequence which differs from the sequence in

a later application only by unintended sequencing or typing errors.

Furthermore, with regard to Appellant I's reflections on the interrelation between legal certainty and experimental certainty, the Board considers that the acknowledgement of an "allowable" margin of error for a specific detection method would be open for interpretation and would lead to ambiguity and vagueness.

30. Appellant I argued that the nucleic acid of claim 1 was a tool for diagnosis of predisposition to breast or ovarian cancer. In order to assess whether the claims were entitled to claim priority from priority document (P2), it had to be established whether priority document (P2) in this respect disclosed the same invention as defined in the claims of auxiliary request II. Thus, it had to be decided whether priority document (P2), despite its reference to the deviated amino acid sequence of SEQ ID NO: 2, disclosed in an enabling form the same diagnostic tool as defined in claim 1 of auxiliary request II.

The technical problem underlying the patent in suit was the provision of the isolated BRCA1 gene as a tool to diagnose a predisposition to breast or ovarian cancer. The sequence deviations between priority document (P2) and the application as filed were irrelevant for solving this problem since in more than 180.000 tests carried out in the past twelve years there had never been allocated any relevance for the diagnosis of breast or ovarian cancer predisposition. Moreover, as soon as the inventors had published the BRCA1 coding

sequence in October 1994 in document D1, which sequence corresponds to the "deviating" sequence disclosed in priority document (P2), other scientists, using this sequence, were able to provide accurate detection of BRCA1 mutations and diagnosis of predisposition to breast and ovarian cancer. This was evident from the disclosure in documents D3, D4 and D17, all published before the present inventors revised the BRCA1 coding sequence to be identical to the one disclosed in the application as filed.

31. The Board emphasizes again that claims 1 and 2 refer to a DNA sequence comprising a coding sequence for a specific polypeptide.

To adopt the approach, that a decision on whether or not a claim to a DNA sequence in respect of "the same invention" as a priority document disclosing a deviating DNA sequence, can only be taken after it has been decided whether the deviations have an effect on the function of the claimed DNA sequence (here: as a diagnostic target or tool), is not compatible with the Opinion G 2/98 (supra) of the EBA, which stated in point (9) of the reasons for the decision that, making a distinction between technical features which are related to the function and effect of the invention and technical features which are not, with the possible consequence that a claimed invention is considered to remain the same even though a feature is modified or deleted, or a further feature is added, is inappropriate and prejudicial to a proper exercise of priority rights.

The Board considers, that a narrow interpretation of the concept of "the same invention" equating it with the concept of "the same subject-matter", as developed by the EBA, is the correct approach to take. Thus, the Board considers, that the DNA sequence disclosed in SEQ ID NO: 1 and the amino acid sequence deduced therefrom disclosed in SEQ ID NO:2 of priority document (P2) do not refer to "the same invention" as the DNA sequence and the amino acid sequence disclosed in SEQ ID NOs: 1 and 2 of the application as filed.

32. Appellant I argued that the respective technical situation in the decisions cited in points (22) to (25) above (i.e. decision T 923/93, T 351/01, T 30/02 and T 70/05) was fundamentally different from the situation underlying the patent in suit.

Decision T 923/93 (supra) only referred to deviations in the amino acid sequence of a protein having a defined biological function. In the case underlying decision T 30/02 (supra) two additional guanine residues resulted in the encoded xylanase being structurally different. No evidence had been provided that this structural difference did not cause a functional difference. Decision T 70/05 (supra) was concerned with a case which contained no information concerning the effect of sequence deviations between a prior art document and its priority document. Finally in case T 351/01 (supra) the Board was confronted with deviations between a polynucleotide sequence in the patent and in the priority documents, wherein said deviations were in the non-coding part. However in the case underlying decision T 351/01 (supra), as well as in all other cases, the parties had not put forward

arguments about the origin and the lack of relevance of the deviations.

Thus, the present case differed from all these cases in so far as Appellant I had provided arguments that the deviations were within the margin of error of the sequencing method and that said deviations had no effect on the successful use of the DNA sequence in diagnosis of cancer in 180.000 cases.

33. The Board repeats that the Opinion of the EBA G 2/98 (supra) held, that an approach which makes a distinction between technical features which are related to the function and effect of an invention and technical features which are not is problematic, can give rise to arbitrariness and is therefore inappropriate and prejudicial to a proper exercise of priority rights.

This principle has been followed in decisions concerning the field of DNA technology (see points (22) to (25) above). In decision T 351/01 (supra) the Board denied the right to priority in a case where the sequence deviations between the priority document and the patent were situated in the non-coding region, thus not having any effect on the sequence and thus function of the encoded protein. In decision T 70/05 (supra) it was explicitly stated, that no priority right could be claimed from an earlier application disclosing an amino acid or nucleotide sequence which differs from the sequence in a later application only by unintended sequencing or typing errors.

The submission of arguments referring to this issue, which according to Appellant I distinguishes the present case from the cases discussed above, is not automatically considered as proof that the Opinion G 2/98 and the case law of the Boards of appeal applying it are based on an incorrect interpretation of the law.

34. Furthermore, the Board observes that the case law of the Boards of Appeal with regard to the entitlement to priority of a claim referring to a nucleotide or amino acid sequence is uniform and definite. The arguments presented by Appellant I, therefore, cannot convince the Board that there is a special situation involved in the underlying case which could justify a deviation from this case law. Accordingly, the Board arrives at the decision that the subject-matter of the claims of Appellant I's auxiliary request II is only entitled to claim priority from the fifth priority document (P5), (US 409305; 24 March 1995).

Novelty (Article 54 EPC)

35. As a consequence of the above decision on right to priority document D1 belongs to the state of the art under Article 54(2) EPC.

At the oral proceedings, Appellant I stated that document D1 was novelty destroying for the subject-matter of claim 1 of auxiliary request II.

In view of this statement the Board sees no reason to further examine the claims of this request.

Referral of questions to the EBA (Article 112(1)(a) EPC)

36. Appellant I requested to refer the following questions to the EBA according to Article 112(1)(a) EPC:

"(1) If a priority document and a European patent application as filed concern the same physical entity but describe it in deviating form relying on the same physical characterisation method, can a claim to the physical entity enjoy priority under Article 87 EPC since it relates to the same invention according to G 2/98, when said descriptions only deviate within the margin of error of the physical characterization method employed at the time when the physical entity was characterized?

(2) More precisely, if a claim defines an invention by reference to a nucleotide sequence (or an amino acid sequence translated therefrom) does this subject-matter enjoy priority under Article 87 EPC as interpreted by G 2/98 from a disclosure in a priority document of a nucleotide sequence (or amino acid sequence translated therefrom) differing to an extent which is within the margin of error of the sequencing method employed at the time the nucleotide sequence was determined, provided that there is no reasonable doubt with regard to the physical identity of the molecule described in the priority document and referred to in the claim under consideration?

(3) If the answers to questions 1 and 2 are no, are the answers any different if it has been established that the deviations are technically irrelevant for the use of the invention in normal practice?"

37. Article 112(1)(a) EPC stipulates that the Board of Appeal, following a request from a party to the appeal, shall refer any question to the EBA if it considers that a decision is required in order to ensure uniform application of the law, or if an important point of law arises.

38. The questions proposed by Appellant I do not relate to a uniform application of the law, as this Board does not take a view of the law which would deviate from earlier cases (see points (22) to (25) above).

39. The second alternative according to Article 112(1)(a) EPC concerns the possibility of questions to be referred to the EBA in case there exists an important point of law.

Question (1) as formulated by Appellant I relies on the hypothesis that the "**same physical entity**" described in a priority document and in a European patent application in deviating form, relying on the same method of characterization, relates to "**the same invention according to G 2/98**", when said deviating description only results from the margin of error of the physical characterization method. Based on this assumption it is asked whether a claim to the physical entity in the European patent application can validly claim priority from the priority document.

This question, in a more precise form, is repeated in question (2), where the answer is made dependent on the further hypothetical provision "**... that there is no reasonable doubt with regard to the physical identity**

of the molecule described in the priority document and referred to in the claim under consideration."

In question (3) it is asked whether the answers to questions (1) and (2) depend on whether or not the deviations are technically relevant, which in the present case means, whether or not the deviations have an influence on the ability of BRCA1 to be used as a diagnostic tool.

40. The EBA in its Opinion G 2/98 (supra) has already decided that a narrow and strict interpretation of the concept of "the same invention" is to be applied, equating it with the concept of "the same subject-matter" referred to in Article 87(4) EPC. The EBA in its Opinion did not provide any basis for speculation that this narrow interpretation should, in a specific technical field, be replaced by an approach which takes into consideration possibly unintended errors resulting from specific physical characterization methods. Moreover the EBA has stated that a distinction between technical features which are related to the function and effect of the invention and technical features which are not is problematic and has to be avoided.

41. Questions that are based on hypothetical considerations are not suitable for a referral (cf decision T 118/89 of 19 September 1990). Furthermore, no referral based on questions already decided by the EBA can be permitted (cf decision T 82/93, OJ EPO 1996, 274).

In view of the above, Appellant I's request for referral of questions to the EBA is refused.

Auxiliary request III (Claims as maintained by the Opposition Division)

Amendments (Articles 123(2)(3) and 84 EPC)

42. The Board considers that the probe with the nucleotide sequence specified in claim 1 is directly and unambiguously derivable from the application as filed, particularly from page 4, lines 31 and 32 of the published version. The skilled person would understand this passage as referring to the numbering of the sequence presented in SEQ ID NO: 1, particularly in view of page 13, lines 50 to 51 stating that the "coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO: 1", and claim 13 of the application as filed. The sequences of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 67, 72 and 81 are directly and unambiguously derivable from Table 9 on pages 44 and 45 of the application as published.

Claims 1 to 3, therefore, comply with Article 123(2) EPC.

As the subject-matter of claims 1 to 3 has been restricted in comparison to that of the claims as granted, the requirements of Article 123(3) EPC are also met.

The claims are clear and supported by the description as required by Article 84 EPC.

Patentable inventions (Article 52(2)(a) EPC)

43. It has been submitted by the Opponents that the sequences of the probes according to claim 1 occur in nature and are therefore a discovery rather than an invention. In view of Article 52(2) EPC, said probes were thus not patentable. During the oral proceedings, this point was not further pursued by any of the Opponents.

44. According to the case law of the Boards of Appeal (see decision T 272/95 of 23 October 2002), Article 52(2)(a) EPC is to be interpreted in accordance with the implementing Rule 23e(2) EPC which states:

"(2) An element isolated from the human body or otherwise produced by means of a technical process including the sequence or partial sequence of a gene may constitute a patentable invention, even if the structure of that element is identical to that of a natural element".

45. Claims 1 to 3 relate to nucleic acid **probes** comprising partial DNA sequences of the human BRCA1 gene, which are described in the patent in suit as having been obtained by technical processes (see especially page 5, paragraph [0024], and Table 9). These probes are thus isolated elements of the human body as defined in Rule 23e(2) EPC and thus patentable subject-matter. Accordingly, the subject-matter of claims 1 to 3 does not fall within the category of inventions which may not be patentable as being discoveries (Article 52(2)(a) EPC).

Exceptions to patentability (Article 53(a) EPC)

46. Appellant II and Opponent 02 presented different lines of argumentation why the claimed subject-matter was excluded from patentability under Article 53(a) EPC.

47. Appellant II submitted that no proof had been provided by Appellant I that the donors of the cells that had been critical to identify the BRCA1 gene had given a previous informed consent to the use of said cells. In the opinion of Appellant II, such previous informed consent would have had to include an explicit consent to the commercial exploitation of the research results by patents as well as a benefit sharing agreement, in particular with respect to members of kindreds 2082 and 2080, the cell donations of which had been essential in arriving at the claimed invention. In the absence of such proof, it had to be assumed that the initial obtaining of these research results involved severe ethical violations, and thus a violation of "ordre public" or morality as referred to in Article 53(a) EPC.

48. The Board observes that the EPC contains no provision establishing a requirement for applicants to submit evidence of a previous informed consent or a benefit sharing agreement. According to Rule 23b(1) EPC, the Directive 98/44/EC on the Legal Protection of Biotechnological Inventions (document D173; hereafter referred to as "the Directive") shall be used as a supplementary means of interpretation of the relevant provisions of the Convention and of Chapter VI ("Biotechnological inventions") of Part II of the Implementing Regulations. Recital (26) of the Directive states:

"Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, **in accordance with national law**" (emphasis added by the Board).

49. The legislator has thus not provided for a procedure of verifying the informed consent in the framework of the grant of biotechnological patents under the EPC.

50. The Court of Justice of the European Communities in the judgment in case C-377/98 dated 9 October 2001 concerning the application for annulment of the Directive by the Kingdom of the Netherlands, supported by Italy and Norway (document D174) has dealt with a similar argument. There the applicant had submitted in its fifth plea that the absence in the Directive of a provision requiring verification of the consent of the donor or recipient of products obtained by biotechnological means undermined the right to self-determination. The Court rejected this plea stating that reliance on the fundamental right of human integrity was "clearly misplaced as against a directive which concerns only the grant of patents and whose scope does not therefore extend to activities before and after that grant, whether they involve research or the use of the patented products" (point (79) of the judgment). The Court furthermore stated that "[t]he grant of a patent does not preclude legal limitations or prohibitions applying to research into patentable products or the exploitation of patented products, as the 14th recital of the preamble to the Directive

points out. The purpose of the Directive is not to replace the restrictive provisions which guarantee, outside the scope of the Directive, compliance with certain ethical rules which include the right to self-determination by informed consent" (point (80) of the judgment).

The Board furthermore notes that also the "Opinion of Advocate General Jacobs" delivered on 14 June 2001 in case C-377/98 (document D175), stated in point (211) that "[i]n my view, however, although the requirement of consent to all potential uses of human material may be regarded as fundamental, patent law is not the appropriate framework for the imposition and monitoring of such a requirement".

51. Accordingly, the Board does not accept Appellant II's argument that the claimed subject-matter is not patentable under Article 53(a) EPC.

52. Opponent 02 argued that the socio-economic consequences of the patenting of the claimed subject-matter should be considered by the Board under Article 53(a) EPC, because in the present case, these consequences touched ethical issues. Patenting of the claimed subject-matter would not only result in increased costs for patients, but would also influence the way in which diagnosis and research would be organized in Europe, which would be clearly to the detriment of patients and doctors. The fact that a particular group of patients, i.e. patients suspected to carry a predisposition to breast cancer, would be faced with severe disadvantages and would become dependent on the patent proprietor, was contrary to human dignity. Therefore, the claimed subject-matter

constituted an exception to patentability under Article 53(a) EPC.

53. In order to deal with the objection of Opponent 02 it is helpful to look at the pertinent wording of Article 53(a) EPC:

"European patents shall not be granted in respect of inventions the... exploitation of which would be contrary to "ordre public" or morality...".

It is important to note that Article 53(a) EPC refers to the "exploitation of the invention", not about the "exploitation of the patent".

The objections raised by Opponent 02 are directed to the possible consequences of the exploitation of the patent in suit. It thus seems that such an objection, which goes to the exploitation of the patent and not to the exploitation of the invention, does not fall within Article 53(a) EPC. Thus, Opponent 02's objections under Article 53(a) EPC must be rejected upon this basis.

In an attempt to evade this legal consequence of the wording of Article 53(a) EPC, Opponent 02 sought to argue that the exploitation of the patent, in this case, could be assimilated to the exploitation of the invention, and thus the exploitation of the patent *per se* was contrary to "ordre public" and morality. Opponent 02 stressed that this invention concerned breast and ovarian cancer and had a significant impact on public health, thus in these special circumstances the Board should apply Article 53(a) EPC to the exploitation of the patent. The Board accepts that

public health care is a sensitive area, however the Board sees no basis in the EPC to distinguish in this respect between inventions concerning different technical fields. Such an approach has been confirmed by the EBA in its decision G 1/98 (OJ EPO 2000, 111; point (3.9) of the reasons) where the EBA stated that the EPO has not been vested with the task of taking into account the economic effects of the grant of patents in specific areas and restricting the field of patentable subject-matter accordingly.

In the Board's opinion the possible consequences of exploitation of the patent identified by Opponent 02 are the result of the exclusionary nature of the rights granted by a patent, that is the right to stop competitors from using the invention.

The objection of Opponent 02, reduced to its essence, is that the inevitable consequences of the exploitation of the patent in suit are contrary to "ordre public" or morality. Logically, such an objection applies to the exploitation of any patent, as the nature of the consequences of the exploitation of a patent (which derive from the exclusionary nature of private property rights), are the same for all patents.

Thus, for the reasons stated above, the Board rejects this objection.

54. Opponent 02 has further argued that the implementation of the Directive in the national law of France and Germany had made it clear that socio-economic and ethical concerns about the patenting of human genes had to be taken into account. The French legislator had

explicitly provided that not genes as such, but only functions derived from genes should be patentable, and the German legislator had provided a separate legislation for the patenting of human genes in view of ethical concerns.

55. Opponent 02 therefore seems to imply that the correct implementation of the Directive requires the importation of socio-economic concerns into the text of the Directive, upon the basis that certain EU member states have adopted this approach to implementing the Directive.

The Board does not agree with this position. The content of national legislation does not form part of the legal order established by the EPC and is thus irrelevant to the issue of how the EPC should be interpreted.

Opponent 02 also referred to the resolution of the European Parliament, P6_TA(2005)0407 of 26 October 2005 "Patents on biotechnological inventions" ("the Resolution"). Opponent 02 argued that the Resolution could be used to interpret the Directive and thus introduce socio-economic and ethical issues into the EPO's patent granting process.

Opponent 02 referred in the Oral Proceedings, in particular, to recitals J and L and paragraphs 4 and 5 of the Resolution. These state:

"J. whereas the Directive allows the patenting of human DNA only in connection with a function, but it is unclear whether a patent on DNA covers only

the application in this function or whether other functions are also covered by the patent,

L. whereas over-generous granting of patents can stifle innovation,

4. Considers that the Directive provides the framework for this in most cases, but that it still leaves important questions open, such as the patenting of human DNA;

5. Calls on the European Patent Office and the Member States to grant patents on human DNA only in connection with a concrete application and for the scope of the patent to be limited to this concrete application so that other users can use and patent the same DNA sequence for other applications (purpose-bound protection)".

Recitals J, L and paragraph 4, can be considered as general statements of fact and/or opinion. Paragraph 5 is the only part of the Resolution relied on by Opponent 02 that calls for action on the part of the EPO. The wording of paragraph 5 contains no suggestion that the EPO has been, or should be, vested with the task of taking into account the socio-economic effects of the grant of patents in specific areas and restricting the field of patentable subject-matter accordingly. Thus the Resolution provides no support for Opponent 02's already rejected objection under Article 53(a) EPC (see point (53) above), or for any further objection based upon some general duty to take into account the socio-economic effects of the grant of

patents in specific areas and to restrict the field of patentable subject-matter accordingly.

56. No arguments or evidence have been brought forward to the Board showing that the **publication or exploitation** of the claimed probes, vectors and cells is contrary to "ordre public" or morality. Furthermore, Rule 23e(2) EPC (cf point (44) above), which implements Article 53(a) EPC (see decision T 272/95, supra), does not exclude the subject-matter of claim 1 from patentability under Article 53(a) EPC.

57. The Board thus concludes that the subject-matter of claims 1 to 3 is not excluded from patentability under Article 53(a) EPC.

Referral of questions to the EBA (Article 112(2)(a) EPC)

58. Appellant II requested to refer the following questions to the EBA according to Article 112(1)(a) EPC:

"- In the case of patent applications which depend on donations of biological material of human origin in a critical way, is it necessary in view of Article 53(a) EPC that the previous informed consent of the donors of critical material is proven in the application proceedings by documents (or other means of proof)?

If the answer to the question is "yes":

- Should the previous informed consent in view of Article 53(a) EPC include an explicit consent to the commercial exploitation of the donations with the aid of patents?

and:

- Should the previous informed consent in view of Article 53(a) EPC include a benefit sharing agreement?"

59. The questions suggested by Appellant II do not concern the uniform application of the law, since this Board does not take a view of the law different to any earlier case.

Furthermore, when examining whether an important point of law arises which may justify the referral of the questions to the EBA, the Board observes that the EPC contains no provisions concerning a necessity on behalf of patent applicants or proprietors of providing any kind of proof about a previous informed consent in the proceedings before the EPO. When the legislator amended the Implementing Regulations of the EPC by adding Rules 23(b) to 23(e), it did not choose to introduce such provisions, in accordance with Recital (26) of the Directive, which in the context of previous informed consent makes reference to national law (cf point (48) above). The legal situation is thus considered to be clear in this regard, and the Board concludes that no important point of law arises.

Therefore, Appellant II's request for referral of questions to the EBA is refused.

Industrial applicability (Article 57 EPC) and Sufficiency of disclosure (Article 83 EPC)

60. Claim 1 of auxiliary request III refers to a nucleic acid probe defined by its nucleotide sequence.

According to Appellant II the possible uses of such probes were the cloning of BRCA1, the detection of BRCA1 or of mutations thereof in Southern blots and the detection of BRCA1 transcripts in Northern blots. These were not industrial applications in the sense of Article 57 EPC in connection with Rule 23e(3) EPC, which required that, with regard to inventions concerning the human body and its elements, the industrial application of a sequence or a partial sequence must be disclosed in the patent application.

The capacity of a single stranded DNA sequence to hybridize with a complementary single-stranded sequence was a consequence of the physico-chemical properties of each single-stranded DNA molecule and was thus a universal characteristic thereof. It could not have been the intention of the legislator to accept such universal characteristic as basis for an industrial application within the meaning of Article 57 and Rule 23e(3) EPC, as this would have the consequence that each and every single-stranded DNA was industrially applicable thereby depriving Rule 23e(3) EPC of any range of application.

61. Opponent 02, although referring to the requirements of Article 83 EPC, argued that the subject-matter of claim 1 did not meet the patentability requirements of the EPC, as it referred to a sequence for which no use

and no function was indicated which meant that it lacked any technical application.

62. It is not disputed between the parties that the patent in suit discloses that the present invention relates to the human breast cancer predisposing gene BRCA1, some alleles of which cause susceptibility to cancer, particularly breast and ovarian cancer (see paragraph [0017] of the patent in suit). In view of the provision of such a diagnostic target, a probe sequence specifically hybridizing to the BRCA1 gene, or as in the case of the probes according to claim 1 specifically hybridizing to the transcribed mRNA, is considered to be useful for diagnostic purposes. Therefore, the probes according to claim 1 do not only serve as research tools for the detection of complementary single stranded DNA molecules as argued by Appellant II, they also can be commercially applied for diagnostic purposes in order to detect the presence of BRCA1 allele predisposing an individual to cancer. The probes are explicitly disclosed in the patent as being useful in nucleic acid diagnosis and diagnostic kits (see paragraphs [0149], [0155] and [0156] of the patent in suit) and furthermore can be used to detect the length of a BRCA1 transcript and thereby detect larger deletions in the gene.

63. In the letter dated 18 January 2006, Appellant II argued, that the results obtainable by using the claimed probes at the relevant date were speculative and could not be considered to result in a specific, substantial and plausible diagnostic test. On pages 11 to 14 of said letter he referred to document D154 and

extensively cited contemporary statements ("zeitgenössische Aussagen").

64. These statements were made by a number of scientists who all were involved in research projects dealing with BRCA1. Although none of the statements contains an exact date, Appellant II considers all of them to date from autumn 1994. The statements draw a picture of the situation in the scientific community in 1994. They describe the aims and strategies of the different working groups, they express doubts and critics on the results of other groups and even refer to rivalries between specific groups. They do not, however, allow one to convincingly draw the conclusion, that the subject-matter of claim 1 of auxiliary request III lacks industrial applicability.

65. Appellant II has repeatedly referred to a decision of the Opposition Division published in the Official Journal of the EPO (2002, page 293), which concerned a patent application disclosing a list of speculative functions of a claimed protein. The Board notes however that the technical circumstances underlying this decision are different from the present ones, so that for this reason alone it can have no bearing on the present case.

66. The Board considers decision T 898/05 of 7 July 2006 to be relevant to the present case. It refers to the nucleotide sequence and the encoded amino acid sequence of the human transmembrane receptor Zcytor1, which is proposed for use in different screening methods for receptor ligands as well as for agonists and antagonists of the natural ligand. For the agonists as

well as for the antagonists several therapeutic applications are indicated. The Board when analysing the relevant case law of the Boards of Appeal with regard to the requirements of Article 57 EPC (cf Case Law of the Board of Appeal of the EPO, 5th Edition 2006, Chapter I.E.1), considers that this Article refers to the concepts of "financial (commercial) gain" (cf decision T 144/83, OJ EPO 1986, 301) and "profitable use" (cf decision T 870/04 of 11 May 2005). The Board came to the conclusion that these concepts were not to be understood in the narrow sense of an actual or potential profit or of a commercial interest, but rather they had to be "...understood in the wider sense that the invention claimed must have such a sound and concrete technical basis that the skilled person can recognize that its contribution to the art could lead to practical exploitation in industry."

The Board continued that it is necessary to disclose in definite technical terms the purpose of an invention and how it can be used in industrial practice to solve a given technical problem, this being the actual benefit or advantage of exploiting the invention. It was concluded that a product which is definitely described and plausibly shown to be usable, i.e. in the case of decision T 898/05 for curing a disease, might be considered to meet the requirements of Article 57 and Rule 23e(3) EPC (cf points (1) to (8) of the reasons for the decision).

67. This Board considers that the nucleic acid probes of claim 1 of auxiliary request III are definitely described and plausibly shown in the patent to be useful in the diagnosis of cancer, particularly breast

or ovarian cancer and finds itself therefore confronted with a technical situation corresponding to the one underlying decision T 898/05 which it considers to be based on a correct interpretation of the law.

Accordingly, the requirements of Article 57 and Rule 23e(3) EPC are met by the subject-matter of clams 1 to 3 of auxiliary request III.

68. Appellant II, in a letter dated 14 July 2007, has further requested to refer two question to the EBA pursuant to Article 112(1)(a) EPC. The Board notes that the first question concerned Appellant I's main request only, which was found by the Board not to meet the requirements of Article 123(2) EPC (see points (2) to (6) above). Thus, it is the second question that will be addressed in the present decision. It read as follows:

"Do sequences or partial sequences of a gene, the function of which is merely declared to be a probe, fulfil the requirement of industrial applicability according to Rule 23e(3) and Article 57 EPC?"

69. The question proposed by Appellant II (see point (68) above) does not relate to a uniform application of the law, as this Board does not take a view of the law different to earlier cases.

When examining whether an important point of law may justify the referral of the question to the EBA in accordance with Article 112(1) EPC, the Board notes that Rule 23e(3) EPC requires that the industrial application of a sequence must be disclosed **in the**

patent application. The same wording can be found in Article 5.3 and recital (22) of the Directive. The Board, having found that the **patent application** discloses an industrial application of the claimed nucleic acid probe, namely its use in diagnosis of cancer, considers Appellant II's question wherein it is assumed that the claimed sequence "is merely declared to be a probe", which, therefore, denies its use as a diagnostic tool, as being hypothetical and not relating to the facts of the present case. Such questions however, shall not be referred to the EBA (cf decision T 118/89 supra). Appellant II's request is therefore rejected.

70. The Board is moreover convinced in view of the above considerations that the patent contains sufficient information to allow a skilled person to make and technically apply the subject-matter of claims 1 to 3, so that, contrary to the argumentation brought forward by Opponent 02, the requirements of Article 83 EPC are met.

Right to priority (Articles 87 to 89 EPC)

71. The second priority document (P2) refers at page 6, lines 24 to 26 to "a probe consisting of nucleotide positions 3575 to 3874 of BRCA1" which was used for hybridization in a blot containing RNA from different tissues, and at page 24, lines 14 to 15 to the "coding sequence for a BRCA1 polypeptide is shown in SEQ ID NO: 1". The Board can follow Appellant I's argumentation that a skilled person would understand that the nucleotide positions mentioned on page 6 are the positions of SEQ ID NO: 1, since in the only other

nucleotide sequence disclosed in the second priority document (P2) being long enough, i.e. SEQ ID NO: 13, positions 3575 to 3874 lie in the intron (denoted in lower case letters). A skilled person would realize that it did not make sense to use an intron sequence to hybridize in a Northern blot to an RNA molecule from which the introns are spliced out.

Nucleotide positions 3575 to 3874 of SEQ ID NO: 1 of the second priority document (P2) have been shown by Appellant I to be identical to nucleotide positions 3631 to 3930 of SEQ ID NO: 1 of the application, which sequence is specified in claim 1. This has not been disputed by any of the other parties. Furthermore, page 27, line 21 explicitly refers to "probes comprising (...) polynucleotides of the present invention". Therefore, the Board considers that a nucleic acid probe comprising the DNA sequence specified in claim 1 is directly and unambiguously derivable from the second priority document (P2).

Moreover, the Board is convinced that a nucleic acid probe comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs: 35, 38, 41, 42, 47, 57, 62, 67, 72 and 81 is directly and unambiguously derivable from Table 9 on pages 73 and 74 of the second priority document.

The Board thus considers that the second priority is validly claimed for the subject-matter of claims 1 to 3.

Novelty (Article 54 EPC)

72. Opponents have argued that the YAC clone 22HE5 mentioned in Figure 2 of document D11 was prejudicial to the novelty of the subject-matter of claim 1. It had been shown by document D136 that this YAC clone contained exon 11 along with other exons of BRCA1, and the first sequence mentioned in claim 1 also related to exon 11.

73. The Board cannot follow this line of argument, since it has not actually been proven by document D136 or any other document on file that the YAC clone 22HE5 mentioned in document D11 contains any of the sequences specified in claim 1. According to the established case law of the Boards of Appeal (see e.g. decision T 464/94 of 21 May 1997), it is not appropriate to base a decision on the novelty of a claimed invention on considerations of likelihood. Rather, in order to revoke a patent for lack of novelty, the deciding body must be certain that based on the arguments and evidence submitted, the claimed subject-matter lacks novelty. In the absence of the required proof, the Board must thus conclude that the subject-matter of claim 1 is novel over document D11. In this respect, the Board concurs with the opinion expressed by the Opposition Division in the decision under appeal.

Inventive step (Article 56 EPC)

74. The closest prior art is considered to be represented by document D11 which discloses a physical map of the BRCA1 region on chromosome 17q12-21, said map comprising a contig of 137 overlapping YAC and P1

clones. The location of the BRCA1 gene is indicated to be proximal (centromeric) to the marker D17S78 and distal (telomeric) to the marker D17S776 (see Figure 2 of document D11).

74.1 Appellant I argued that considering document D11 as the closest prior art was based on hindsight and therefore inappropriate. As shown in Exhibit 22 submitted with letter of 24 July 2007, the prior art documents D52, D88, D10, D22, D112 and D122 had suggested chromosomal regions for BRCA1 different to that disclosed in document D11, and it only turned out later that the region for BRCA1 indicated in document D11 was correct.

74.2 The Board notes that documents D52, D88 and D10, which were published earlier than document D11, suggest regions for the BRCA1 gene that are larger in size but include the one suggested in document D11. As document D11 had already narrowed down the BRCA1 region, the Board considers that the skilled person would have preferred to start from this smaller region rather than from those regions suggested in documents D52, D88 and D10.

74.3 Document D22, which was published three months before document D11, suggests that the BRCA1 gene lies distal to the marker D17S702 and proximal to the marker EDH17B. The analyses of the results from "family 64" gave rise to the suggestion that the marker EDH17B could be the distal boundary for the BRCA1 gene (which information is in contradiction to that of document D11). At the end of document D22 a section "Note Added in Proof" states: "Subsequent analysis of the offspring of individual 309 in family 64 has indicated that the

ovarian cancer case did not inherit the putative linked haplotype. This suggests that either the ovarian cancer is a sporadic case or that the family is not linked to 17q12-21." The Board notes that in view of this statement, the skilled person would not have relied on the information that the marker EDH17B is the distal boundary, and would have given more weight to the information given in document D11.

74.4 Document D112, which was published more than a year before document D11, suggests a location for the breast-ovarian cancer locus between the markers D17S588 and D17S579. It is stated on page 742, first paragraph: "[I]n contrast, the recombination that places the cancer gene below D17S579 is evident only in woman 25. She developed breast cancer at age 57 years, an age significantly higher than the mean age at onset (41.5 years) of breast cancer in the family. None of her five daughters (ages between 20 and 37 years) is affected. If this case of breast cancer is sporadic, the recombinant has not mapping value". Because of this statement, the skilled person would have been reluctant to rely on the information concerning the marker D17S579. Since this information is furthermore in contradiction to that of document D11, the Board considers that the skilled person would not have started from document D112 as the closest prior art.

74.5 Document D122 provides information which, contrary to the other documents mentioned above, is not based on linkage studies with breast/ovarian cancer families, but on examination of sporadic breast cancers for deletions as measured by loss of heterozygosity. The smallest common region that was deleted occurred

between the markers D17S846 and D17S746. The document discusses possible reasons for an inconsistency with the results of another publication, one such reason being that "the locus we have defined may be relevant only in sporadic breast cancer and not in hereditary breast cancer" (page 2549, column 2, lines 4 to 6). The possibility of two separate loci on 17q12-21 important in breast cancer development, BRCA1 and a second locus defined by loss of heterozygosity, is also discussed in document D11 (see page 477, column 1, lines 36 to 44), as the region identified in the earlier document D122 does not overlap with that identified in document D11. Since the data of document D112 are not based on linkage studies with affected families, the Board considers that a skilled person would have given more weight to the information disclosed in document D11.

74.6 In view of these considerations, the Board concludes that while the correct chromosomal region including the BRCA1 gene was indeed in doubt at the second priority date, document D11 would have been selected by the skilled person as the most promising starting point.

75. Having regard to the closest prior art document D11, the technical problem to be solved is the provision of nucleic acid probes which are suitable to identify the BRCA1 gene.

The Board is satisfied that this problem has been solved by the nucleic acid probes according to claim 1. The probe with the sequence first mentioned in claim 1 has been shown to detect a single transcript in Northern blots (see Figure 7 of the patent in suit), and the sequences of SEQ ID NOs: 35, 38, 41, 42, 47,

57, 62, 66, 67, 72 and 81 consist of fragments of the BRCA1 gene (i.e. SEQ ID NO: 1) representing intron/exon junctions (see Table 9 of the patent in suit), which are likewise suitable to detect the BRCA1 gene.

76. In order to be able to provide nucleic acid probes suitable to detect the BRCA1 gene, a skilled person starting from the disclosure of document D11 would first have to identify the BRCA1 gene and isolate (at least part of) its sequence. The key question is therefore whether at the second priority date, a skilled person would have reasonably expected to be able to identify and isolate the BRCA1 gene.

77. A number of decisions of the Boards of Appeal in the technical field of biotechnology have pointed out that, in evaluating the attitude of the skilled person, one should not confuse the "hope to succeed", which is linked to the wish that a result be achieved, with the "reasonable expectation of success", which is linked to the ability to reasonably predict, based on the particular technical circumstances, a successful conclusion of the project within acceptable time limits (see decisions T 296/93, OJ EPO 1995, 627, T 923/92, OJ EPO 1996, 564, and T 223/96 of 29 January 1999). In this respect, each case has to be assessed on its own merits, and any hindsight has to be avoided.

78. It is evident that the skilled person, departing from the disclosure of document D11, would have readily undertaken to identify the BRCA1 gene in the hope to succeed. The question remains, however, whether, when evaluating realistically the chances of success at the

second priority date, he or she would have had a reasonable expectation of achieving the desired result.

79. For the reasons given hereinafter, the Board found the arguments concerning this question as put forward by Appellant I more convincing than those put forward by Appellant II and the remaining Opponents.

79.1 In order to identify the BRCA1 gene, for which no information about its protein product was available at the relevant priority date, a skilled person would have been aware that a positional cloning approach had to be applied. As a first step in such an approach, polymorphic markers are identified by linkage analysis using DNA of well-documented families (kindreds) with inherited cases of the disease in question (here: breast cancer), in order to narrow the putative chromosomal region containing the gene to a manageable size of about 600 kb (see for instance documents D120 and D125).

79.2 In the present case, the closest prior art document D11 had already narrowed the relevant chromosomal region down to approximately 1.5 Megabases (Mb) and provided a physical map of this region. Although this region was the most promising starting point, there was however no certainty that it did indeed contain the BRCA1 gene (see points (74.1) to (74.6) above). A skilled person would have been well aware that any cloning efforts starting from the wrong chromosomal region would evidently result in ultimate failure.

79.3 Furthermore, there was no certainty that suitable polymorphic markers could indeed be identified in order to further narrow down the relevant chromosomal region. In order to be successful, it would not only be necessary to find polymorphic markers that map to the region, but also to have well-documented kindreds with cases of inherited breast cancer at hand, which would need to contain individuals with recombination events located such that they would provide the necessary mapping information. Apart from the substantial amount of experimentation involved in the linkage analysis, success thus required a substantial amount of luck which a skilled person could not reasonably predict.

79.4 If refining the chromosomal region containing the BRCA1 gene to a sufficiently small size would have been successful, the next steps would be to identify gene sequences within that chromosomal region and to look for a gene which contains a causal mutation, i.e. a mutation existing within that gene which is found to co-segregate with breast cancer in a statistically significant manner, but not with control or non-cancer patients. Finding such a mutation would not only involve substantial amounts of work, but would also require a "lucky strike", which could in no way be predicted even if well-documented breast cancer kindreds were available.

80. Considering the uncertainties of the project as outlined above, the Board concludes that at the second priority date, a person skilled in the art would not have reasonably expected to successfully arrive at the cloning of the BRCA1 gene within acceptable time limits merely by way of routine experimentation. The Board is

convinced that solving the technical problem was a major breakthrough which was not obvious to the skilled person.

81. The Opponents have argued that the claimed subject-matter was obvious to the skilled person because document D11 referred to sequence information relating to clone extremities which were available from GenBank and directly from the authors. One of these sequences had the accession number L18209 and contained a CpG island, as was evidenced by document D31, which corresponded to the promoter region of the BRCA1 gene. It would thus have lead the skilled person to the identification of the BRCA1 gene.

In this regard, the Board considers that the Opponents have not sufficiently proven if or what information on the sequence termed L18209 was available to the public at the second priority date. Document D31 is a print-out of a database entry which carries the date 10 October 1995, and cannot thus constitute evidence as to what was available to the public on 2 September 1994, the second priority date. Document D11 itself neither mentions the term "L18209", nor does it provide information about its sequence. For these reasons the argumentation based on sequence L18209 must fail.

82. Opponents have also argued that in order to further narrow down the BRCA1 region identified in document D11 to a size of approximately 650 kb, the marker D17S1141, also known as UM44_, would have been available to the skilled person. This would then have easily led to the identification of the BRCA1 coding region. Document D128, a print-out of the gdb database, disclosed this

marker as having been available from Dr Chamberlain as of 18 February 1994. Documents D159 and D160, also print-outs of database entries, provided additional evidence that the marker was publicly available. The post-published document D129 described the marker in detail.

Concerning the question whether a disclosure available from the internet, like for example the database entry of document D128, is part of the state of the art under Article 54(2) EPC, a strict standard of proof is to be applied (see decision T 1134/06 of 16 January 2007). In the present case, the Board does however not consider it necessary to investigate the question whether document D128 was indeed available to the public at the second priority date, because even if it was, the Board could not follow Opponents' line of argument that the claimed subject-matter lacked an inventive step under Article 56 EPC. The reason for this is that the skilled person would not have known from the supposed disclosure of document D128 that the marker D17S1141 was suitable to narrow down the approximately 1.5 Mb BRCA1 region as identified in document D11. This fact only became known to the skilled person after the second priority date. As pointed out in numerous decisions by the Boards of Appeal, any *ex post facto* analysis has to be strictly avoided in the assessment of inventive step (see Case Law of the Boards of Appeal of the European Patent Office, 5th edition 2006, chapter I.D.5.).

83. For these reasons, the subject-matter of claim 1 is considered to involve an inventive step. Since claim 2 relates to a replicative cloning vector comprising a

DNA according to claim 1, and since claim 3 relates to a host cell transformed with a vector of claim 2, the Board likewise considers the subject-matter of claims 2 and 3 to involve an inventive step.

84. In view of the above, the claims of auxiliary request III are allowable.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chair:

P. Cremona U. Kinkeldey

EXHIBIT H

MAX-PLANCK-GESELLSCHAFT

Genetic Inventions and Patent Law

An Empirical Survey of Selected German R & D Institutions

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Genetic Inventions and Patent Law

- An Empirical Survey of Selected German R & D Institutions -

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Foreword

The impact of intellectual property rights (IPR), especially patents, on the progress of life sciences and biotechnology has been at the center of interest of the public at large and the academic community for some time. Politicians have focussed on this issue in the course of their deliberations related to the implementation of Directive 98/44 of the European Parliament and the Council on the Legal Protection of Biotechnological Inventions of July 1998, due by July 31, 2000, but missed by the vast majority of the EU Member States. One key reason for the hesitation observed was the rule in Article 5 (2) of the Directive providing, ***inter alia***, for product patents on DNA sequences of human origin if isolated from the human body or otherwise technically produced.

Since concerns related to product patents on DNA sequences have been expressed and supported by a number of well-known scientists, who predicted a serious negative impact of such patents on further developments in the area of genomics and life sciences in general, the OECD Working Party on Biotechnology took up this issue and organized an expert workshop on "Genetic Inventions, Intellectual Property Rights, and Licensing Practices", which was hosted by the Federal Ministry for Education and Research in January 2002 in Berlin and opened by Minister Edelgard Bulmahn. In order to provide the workshop with the reliable empirical data necessary for discussions and further OECD actions, the German Federal Ministry for Education and Research commissioned an empirical survey of selected German R&D institutions, which was carried out in 2001 by Henrik Holzapfel and Matthias Lindenmeir under my supervision. The results of that survey were presented at the OECD Berlin Workshop and briefly summarized in the OECD publication "Genetic Inventions, Intellectual Property Rights and Licensing Practices – Evidence and Policies" (Paris 2002, pp. 45-49). Due to repeated enquiries for more information on that survey, we decided to publish it in full length with some additional general comments. We are very indebted to the Federal Ministry for Education and Research for the financial support that enabled this publication.

Joseph Straus

Table of Contents

Abbreviations

AIPA	American Inventors Protection Act
DNA	Deoxyribonucleic Acid
e.g.	for example
EC	European Community
EPC	European Patent Convention
EPO	European Patent Office
EST	Expressed Sequence Tag
EU	European Union
GenTG	Gentechnikgesetz
HGP	Human Genome Project
i.e.	id est
IIC	International Review of Industrial Property and Copyright Law
IP	Intellectual Property
IPR	Intellectual Property Rights
JPO	Japan Patent Office
Ltd	Limited
NIH	National Institute of Health
OECD	Organization for Economic Cooperation and Development
PCT	Patent Cooperation Treaty
pp.	following pages
R&D	Research and Development
rDNA	Recombinant DNA
SNP	Single Nucleotide Polymorphisms
U.S.	United States
USPTO	United States Patent and Trademark Office
UTTOs	University Technology Transfer Organizations
Vol	Volume

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I. Introduction

As diverse a definition of biotechnology[1] could be as sundry seems to be any biotech subcategory like genetic engineering combined with intellectual property rights, and here especially with patent law and licensing features. Granting of patents on genetic inventions was one of the first and most controversial legal and societal developments of biotechnology. The issue was raised when Genentech first filed patent applications on genes encoding already well known examined proteins. In 1991, when the NIH sought patents on ESTs[2], the stormy debate refreshed anew and is continuing today when innovations in DNA sequencing technology made high-throughput sequencing feasible and in response genomics companies start in race filing tsunamis of whole gene patent applications[3]. However, there has to be mentioned, that it is not solely the patent and licensing systems that determine how consecutive biotech research at universities, start-ups and even giant pharmaceutical companies is transferred to both the public and private sectors, but it is also essential to keep in mind that in the life cycle of genetic engineering, from research to the market-place, there are other fundamental legal regulations (e.g. Genetechnikgesetz in Germany) that are critically important for facilitating, constraining and guiding the evolution of gene research[4]. Besides, to understand systems of reward exchange in research and development one has to consider that in the biotechnology and pharmaceutical industries, where joint ventures, licensing, and other transactions are common, there might be many traps for the careless patent owner and licensor. Enforcing patent rights in a proper way defines a valuable asset and could help a company to establish a profitable transaction pipeline.

[1] The US Definition of Biotechnology, proposed at the OECD Meeting, Paris, May 2003: "A diverse collection of technologies that both capitalize on the attributes of manipulate organisms, tissues, or cellular, sub-cellular, or biomolecular components to discover new knowledge, to solve problems and create models thereof, goods, products, services and therapies".

[2] Cf. Straus, J., Intellectual Property in Human Genome Research Results, OECD STI Review No. 19 (1996), pp. 46, 50 ss.

[3] Nuffield Council on Bioethics, "The ethics of patenting DNA", Nuffield Foundation (2002), paragraphs 3.42 and 5.38.

[4] Gentechnikgesetz (GenTG), introduced in Germany 1990 with the purpose of control of risk and dangers through genetic engineering.

Although, the numbers of patent applications and patent grants on genetic inventions show a significant increase[5], only little information is openly accessible about the interrelationship between patent law and the licensing practices to whom and under what contractual conditions they take place and about the general impact of patent law on scientific research. Transfer of research and technology and transformation into the development and marketing process underwent severe changes during recent years, where only powerful pharmaceutical companies could afford widespread internal research and development activities. Medium sized smaller companies are forced to enter into R&D partnerships as the mandatory financial input volume seems to explode. In response to this development complementary research platform technologies have to be licensed in to compete with other players and to gain access to novel enabling technologies assigned to modify the own in-house production activities, e.g. with "in-silico" genomics. The individual contributions to the complex genomics evolution are mostly covered by patents, implicating that a company involved in R & D activities will be compelled to acquire licenses with the side-effect of piling up additional financial obligations[6].

Whether patent law, often denounced as being inhibitive to the scientific progress, indeed has such a negative impact on the dynamics of research and development has so far not been well investigated. This the more, since the information pipelines in this area are mainly kept dry.

Nevertheless, for clarifying the alleged and the real impact of patent law in focus through an empirical study on "Genetic Inventions and Patent Law" the impetus was to gain information from an objective viewpoint concentrating on the challenges of potential patentees for patenting genetic inventions and to provide evidence about the licensing practices in respect of genetic inventions. Furthermore, it was to elucidate whether specific problems arise from the application of patent law on genetic inventions, in particular from patents on DNA-sequences.

[5] World Health Organisation. Advisory Committee on Health Research. Genomics and World Health. 2002: http//www3.who.int/whosis/genomics/pdf/genomics_report.pdf.

[6] European Commission, Community research, Workshop Report on Managing IPR in a knowledge-based economy-Bioinformatics and the influence of public policy, Brussels, November 2001.

II. Conception of the Survey

In co-operation with the Federal Ministry of Education and Research a sample group consisting of pharmaceutical companies, biotechnological companies, biotechnological research institutions and clinical institutions associated with universities performing research and development in the field of genetic engineering was selected.
It has been agreed upon to conduct personal interviews with the representatives of these genomics-associated firms and institutions. All of them were involved in this interrelational interface between genomics and the patenting and licensing systems as potential proprietors of patents, licensees and/or licensors, or even as plaintiffs and defendants in legal conflicts.
The applied questionnaire encompassed five key-categories:

1. Formal business profile of company.

This category included questions on the marketed product, yearly turnover, financial background, merger acquisitions and cooperative structures with other companies.

2. Patents

This category focused on the number of filed and granted patents, especially claiming DNA sequences and taking into account the significance of own patents as well as the competitors` patents interacting with the company's business.

3. Licenses

In analogy to the second key-category, the number of granted and refused in-licenses were ascertained. Questions on applications for compulsory licenses and cross-licenses were posed.

4. Patents and R&D

The main points here were questions on the annual investments in R&D, policies controlling situations where any dependent patents were available and dominated by competitor's patents, or how research tools for the own R&D are tackled. Other questions included the scientific publications and the impact of patent law on time, quality and quantity of publishing research findings. Developments based on patents and R&D, as e.g. spin-offs of genomics R&D were also examined.

5. Patents and Patent Litigation

This category dealt with the possibility of law-suits in the light of alleged patent infringements and potential consequences thereof for R&D. The influence of in-depth knowledge of patent law also in relation to external legal consultation taken. A broader survey should have been gained through questions on special patent characteristics of genetic patents. Other issues here were the justification of absolute protection of a substance, independence of disclosed use and the comparison of the legal framework for R&D in the field of biotechnology in Germany and other countries.

6. The Method Applied

The interviews have been conducted in a seven-months period from July 2001 to January 2002. Taking into account the differing activities and needs of the individual interview partners for each key category the questionnaire was adaptively modified, being in this very sense of a questionnaire more of a guideline than a strict frame for each interview performed. This procedure seemed to be appropriate in order to discuss delicate questions of patent law and biotechnology with the addressees directly and to avoid any misunderstandings. Moreover, an individual personal conversation enabled further investigation of topics that had been raised unexpectedly. Due to an extensive method of investigation and the given personnel and financial resources the number of institutions to

be interviewed was limited. Bearing this aspect in mind, the significance of statistical data obtained has to be considered in the light of this flexible way of interviewing and reflecting as well the relatively small sample group. This notwithstanding, the primer to identify and judge trends and developments could be accomplished.

III. Results of the Survey

1. Financial Dependency on Patents and Patent Lawsuits

In recent years investors have been piling into biotechnology stocks creating a new emerging stock sector with all the ups and downs of the indices. When it came to the situation that pressure had been exerted on the EPO or the USPTO to restrict their practices for granting gene-related patents, mainly those companies were at risk of sliding biotech indices having patent portfolios stiffed with broad claims on DNA or DNA fragments like ESTs[7]. However, even if the patent offices grant broad claims on genes, such patent-owners might be exposed to costly law-suits to defend them for the future. Another economic aspect might be influenced by such patents creating a prospect function, so-called pioneer patents, that introduce new and promising technologies and thereby stimulate greater venture support through the investors[8]. But it might not only be the patent portfolio setting the venture capital on a high scale, what matters could also be the existence of real products tightly associated to patents. Although it is hard to quantify and evaluate such dynamics the economic importance of patents is undisputed as our findings suggest.

[7] Seen as an effect of the introduction of the new "written description guidelines" by the USPTO.

[8] Kenneth W. Dam, "The Economic Underpinnings of Patent Law", Journal of Legal Studies, Vol. 23, (1994), 247-271.

a. Pharmaceutical Companies

The interviewed pharmaceutical companies did not believe that patent applications and patent lawsuits in the field of biotechnology specifically affected their stock exchange rate or the acquisition of venture capital, even if considerable turnover was generated in marketing biotechnological or biotechnologically made products. Large pharmaceutical companies rather regard patent rights as a mechanism for prevailing research in specific scientific field and as pawn in negotiations with potential partners. The decisive variable there was seen in a successful end-product, related or not related to in-house patents.

b. Biotechnological Companies

Biotech companies without or with few ready for sale products stated that patent applications, patent grants or patent lawsuits affected their stock exchange range or the acquisition of venture capital substantially. In the first place because a fundamental pioneer patent in most cases was the essential asset for start up companies. In the second place every lawsuit filed against a company forced downs of the stock exchange rates markedly. The development of the stock exchange rate was particularly essential for small companies, because among those stock transfers were a common mode for merging with other companies.

One principal issue here was to bridge the gap between the potential of science and the expectations of the investors implicated by legal proceedings. There existed criticism that venture capital firms could asses properly the implications of neither patent applications nor of patent lawsuits, i.e. some investors were blinded by high numbers of patent applications not recognizing that the majority of applications belonged to a single family of gene sequences. Companies could possibly take advantage of this fact by primarily filing a multitude of patent applications in order to combine various applications into a single patent in order to save patent office's fees. Besides that from the investor's perspective the prospects of a pending lawsuit due to patent infringement or patent invalidity were overshadowed by the mere fact of filing an action. On the contrary it was pointed out that the scrutiny preceding the entry into the stock market was more profound.

Two biotechnological companies, that had been active in the market for a longer time, felt that in the long run qualities like qualification of the employees, after-sales service and quality management will increase in importance compared to the patent portfolio.

2. Significance of Patents for the Co-operation or Merging of Companies

In the face of increasing costs and risks of high-tech innovations, one means of transacting knowledge could be through alliances between companies in form of sporadic associations or even stable joint ventures as active promoters for acquisition, development and exchange of technology.

Despite this positive list of benefits through allying the disadvantages may also lay at hand, since a company as alliance partner would consequently agree or may be obliged to transfer control over internal activities and technological resources[9]. This could turn out as a mechanism where a cooperating partner company could be cast for the part of the dependent partner risking the loss of technological knowledge to those partners which without alliance would be competitors itself.

In an increasing manner, the value and the importance of intangible assets, among them the traditional intellectual property assets like patents, seem to be the incentives for mergers, acquisitions and takeovers.[10] The critical point in such a manifestation of corporate restructuring through merging is the issue that the consecutive acquisition of patents as intangible assets could lead to antitrust violations by eliminating competition between major players within a certain domain. However, it is anticipated, that in the global development of a knowledge-based economy the driving force for future merger and acquisitions proceedings might be dominantly manifested in the technological value of patents[11].

[9] Sergio Speranza, Strategic alliances and licensing the transmission of knowledge, Les Nouvelles, Vol. 35 No. 2. (2000), pp. 82-85.

[10] Lanning G. Bryer and Scott J. Lebson, Intellectual Property Assets in Mergers and Acquisitions, Les Nouvelles, Vol. 35, No. 3. (2000), pp. 124-128.

[11] Biotechnology Statistics in OECD Member Countries: Compendium of Existing National Statistics, Second Ad Hoc Meeting On Biotechnology Statistics, Paris, OECD, 3-4 May 2001.

a. Pharmaceutical Companies

Some pharmaceutical companies pursued a strategy of "buy, not make", i.e. they bought intermediary products, production assets as well as research tools from biotechnological companies or used external services for screening or purification procedures.

In this respect intellectual property issues were of limited significance as far as the ownership of patents could not be secluded from the – not legally protected – know-how that was acquired by realizing the patented invention. Sometimes the know-how was regarded as even more crucial:

The question was rather who could implement a certain method than who had the permission to do this. However as permission and ability regularly coincide the intellectual property situation was attributed at least a secondary importance.

Whether relevant patent rights existed and whether the contractor owned these patent rights was not always examined meticulously. A slightly different situation was observed in respect of research tools such as expressed sequence tags (ESTs) or single nucleotide polymorphisms (SNPs). Costly developments of pharmaceuticals and diagnostics relied on these research tools. To avoid a tiring "rat race", the pharmaceutical companies tried to monopolize the innovative activity based on such research tools. For this purpose the intellectual property issues were screened more accurately and an exclusive license was sought.

b. Biotechnological Companies

Some biotechnological companies admitted that co-operations with other companies had failed or were complicated because of unresolved intellectual property questions.

c. Co-operations

As regards the ownership of prospective patents co-operations between companies including joint research projects differed to a high degree, depending on individual

circumstances. In most cases the parties agreed on the distribution of intellectual property prior to the co-operation, at least on a preliminary basis. According to the ex-post estimates of the value of the invention, the preliminary arrangement could be subject to changes.

Predominantly the co-operating parties agreed upon which one should become sole proprietor of expected patents, combined with the obligation to license the invention for free or within an agreed range of royalties to partners in the co-operation. Within co-operations between companies and research institutions the company usually became proprietor of the invention. Only in cases where inventive contribution of the research institute was clearly predominant and the contribution of the company

was limited to financial support or supply of equipment the situation was different. In general research institutions were interested mainly in publishing their results and did not want to procure the costs associated with patent application and enforcement of royalties themselves.

Within co-operations between companies mostly that company became patent owner whose core business was affected by the patent. An advantage of a clear assignment of patent rights was the well-defined responsibility. Further handling of patents, e. g. enforcement and licensing, did not require extensive negotiations between several parties.

d. Mergers

In mergers with an other company the intellectual property situation played an important, if not dominating role. Sometimes the existence of a patent right was the key incentive for merging.

3. Purpose of Patenting

As indicated in the introduction of this paper the patent system had been most controversial through the granting of gene sequence patents and therefore is particularly vulnerable to criticism. It is a fact that a patent may be an extensive right, however it is not admissioned without restrictive examination both, for qualifying criteria and validity

requirements. This is ensured for all types of technical and scientific innovation, and particularly true for biotechnological inventions. Major confusion and misunderstanding is provoked by the putative nature of a "monopoly" represented by a patent[12]. This is not true for the real purpose of the patent, since it does not confer the right to exploit the invention. One principal reason for patents is to be an initial filter for scientific and technological regulation, thus claiming to be the basis for contracts, rewards and incentives directing to future benefits to allow the inventors to enjoy their returns on the generation and application of knowledge.

From the perspective of some companies patenting seemed to be rather an option, to enable and secure further research by the company and to facilitate future co-operations as means of negotiation and exchange, compared to the intention to monopolize the market. This was partly due to the not promising and complex enforcement of rights.

This was especially true for research tools, since a drug possibly discovered by the use of e. g. ESTs would be a "small molecule" allowing in most cases no detection of its origin. Moreover patent infringement lawsuits often resulted only in the grant of reasonable royalties as remedy for the use of the research tools. Usually lawsuits did not result in a participation in the profits derived from selling the drug that had been developed using the research tool.

Some biotechnological companies indicated that they felt a kind of "peer group pressure" towards patenting. Companies did not want to fall behind competitors filing many patents at any rate, although the real benefit of patenting was not always recognized.

For one clinical center the purpose of patenting of genes consisted mainly of donating the commercial revenue to those patients concerned with a genetic disorder (e. g. Nijmwegen breakage syndrome).

4. Genetic Inventions and Licensing, Compulsory Licenses

As a fact, the time for licensing a patent regularly falls some years behind originating and disclosing a patented invention, therefore the momentum when a patent could be licensed

[12] Warren Jones Amanda, Patenting rDNA, human and animal biotechnology in the United Kingdom and Europe, Lawtext Publishing Ltd. 2001, p. 74.

may not be well-timed. Immense complications when dealing with patents in any licensing or collaboration proceedings are especially striking within the disputable biotechnology and drug discovery industries. Indeed, most companies that have substantial portfolios of patents do not fully understand what they have and what its value is[13]. Far-reaching potentially fatal consequences could arise for smaller companies, if they fail to handle their patent rights adequately, i.e. mining the patent portfolio for licensing opportunities in a sophisticated way. In this context the deal-makers in charge should be well aware of the technological value of a patent and also deny licensing if the conditions for rent seeking tend to be asymmetrical[14].

Governments can opt to issue, or threaten to issue compulsory licenses which provide as liability rules in a sense a potential defense to patent infringement obliging the patentee to grant a license to a potential infringer[15]. Although the patentee would lose his patent rights to some degree he could be reimbursed by license fees, which appear to offer little real benefit. Provisions for compulsory licensing are implemented as a common feature in most patent law systems, however applied very rarely, since problems of valuation and compensation seem to turn out rather complicated[16].

a. License Negotiations

There was unanimous consent that no special problems arose negotiating licenses for genetic inventions. With genetic as with other inventions the patent proprietor was usually aimed at commercializing his invention as profitable as possible. As licensing fees created income and the patentee himself possibly could not exploit all conceivable uses of his invention, the full potential of the invention could only be commercialized by licensing

[13] Robert S. Bramson, Mining the Patent Portfolio for Licensing Opportunities and Revenues, Les Nouvelles, Vol. 35, No. 3., (2000), pp. 109-115.

[14] Patrick Duxbury and Diane Mellett, License and collaboration agreements: Protecting your most valuable asset, nature biotechnology, Vol. 20, No. 1, January 2002, pp. 91-92.

[15] Trevor Cook, Catherine Doyle, David Jabbari, Pharmaceuticals Biotechnology & Law, Stockton Press 1991, pp. 322-323.

[16] Genetic Inventions, Intellectual Property Rights and Licensing Practices, Evidence and Policies, OECD, 2002.

the invention at least partially, making licensing the economically more attractive choice than denying a license. Patent owners acted rationally ("could calculate") while reaching a deal on licenses. Licensing gave the patent owner the possibility to generate revenues with minor risk than developing marketable products himself. Some licensors were too demanding and overestimated the values of their inventions. This dilated license-negotiating significantly, however the prospects of future licensing were still positive. Often there was competition among potential licensors, e. g. when various equally suitable gene expression systems existed. In such constellations alternative pathways enabled the licensee to bargain a reasonable royalty. Finally licensors depended on the commercialization of their research tools and therefore would have to renounce on revenues completely without a license contract.

b. Royalty Stacking

Despite regular license negotiations the problem of royalty stacking emerged, e. g. many licenses had to be paid to market a single monoclonal antibody.

Genuine in-house developments hardly ever occurred in the field of biotechnology. One to three licenses per marketable product could be tolerated, but increasingly often seven or more licenses were mandatory, endangering the commercialization of the final product.

It was desirable that, like in the United States, complete license packages were on offer. Besides it was feasible to include royalty-stacking clauses in license contracts, with the effect of reducing costs for each individual license if the total number of licenses to be taken exceeded 10 per cent of the turnover of the final product.

c. License Disapproval

In most of the cases where a license had been denied it was that a license had been sought from direct business competitors. Not different from other types of inventions the patent owner did not want to support his competitor's business activity.

d. Exclusive Licenses

In some fields of genetic inventions, e. g. some kinds of research tools, almost only exclusive licenses were on demand, guaranteeing the licensee for the left patent period the exclusivity of research building upon the licensed invention. This offered the licensee a better chance to recoup his invested capital.
This was why in some cases an exclusive license had been denied, i.e. if the would-be licensee was not given the confidence of realizing a commercially successful innovation.

As a consequence of that the patentee did not want to waste the exclusive license on contracting with such a license seeker.

e. Patent Pooling and Cross-licensing

Patent pooling and cross-licensing were not popular. Only three companies participated in cross-licensing or patent pooling. In their opinion such arrangements were not very effective: The fear of the participating companies of unbalanced contributions and profits from the arrangement increased the level of license fees. Nevertheless for researchers patent pools could be more attractive.

f. Compulsory Licensing

Compulsory licensing was not seen an very essential issue. Compulsory licenses were perceived as a more hypothetical alternative compared to successful license contracting, regarding the restrictive way of granting compulsory licenses by the patent offices or courts, respectively. Some wondered if there existed a kind of gentleman's agreement not to apply for compulsory licenses, as oneself did not want suffer himself from a compulsory license either.
One company discussed applying for a compulsory license twice. However it finally had not applied as essential investments could sometimes not be based on a non-exclusive

license. Likewise the consecutive existence of the compulsory license could not be relied on, since the mandatory public interest in the compulsory license could be inapplicable if the patentee began with the commercialization of a competitive product by himself.
Four companies suggested to facilitate compulsory licensing, e. g. when certain patent protected targets were integrated in the development of a medical drug. After all, the first drug to be discovered rarely was the most important one. Every one should be entitled to use an invention –especially research tools for reasonable royalties. One did not want to use the invention for free, the patentee rather should appropriately participate in the commercial success of the marketed product. Other companies stated that further facilitating compulsory licensing raised the question of the remaining value of a non-exclusive patent right. Respective to DNA-sequences they explained that the potential benefit of gene sequences was too hypothetical to establish the public interest in a compulsory license.

5. Effects of Patents on End Products on Research Activity

Functional genomics technologies is a fast-accelerating field where new products and services are developed from accumulating and complex composites of emerging *de novo* technologies. Various end-products might include DNA sequences, i.e. diagnostic tests like DNA-microarrays[17] or pharmaceuticals designed by proteins that were originated from corresponding gene expression profiles via the drug discovery value chain[18]. However, not only the end-product is eligible for patent protection, but also their use or production-methods including intermediaries[19]. These intermediary products could as well serve as end-products and thereby occupy a prominent role in the dynamic

[17] Diagnostic tests: With the recent completion of the human genome sequence and the fast-moving proliferation of the DNA-microarray-technologies, there will be a wide variety of high-quality diagnostic tests based on DNA and protein microarrays.

[18] Mark Schena, Microarray Analysis, Wiley-Liss 2003, pp. 21-25.

[19] Straus Joseph, Patenting Genes and Gene Therapy: legal and ethical aspects, in: From Genome to Therapy: Integrating new technologies with drug development, John Wiley and Sons, Ltd. 2000, p. 115.

interplay involving research activities in molecular biology, genetics and medicine as well as engineering sciences and applied bioinformatics.

a. Examination of Patents

All companies indicated that they examined patented inventions of competitors concerning novelty, disclosure and function, at least when the invention influenced their own core business. This examination was performed in view of possible opposition and invalidity procedures as well as possible license negotiations. Nonetheless these examinations could be carried out even after taking the license if an option period or cancellation opportunity had been agreed on. Competitors of the patentee were often the first to discover the lacking patentability of a patented invention.

b. Comparison of Products

Tests were performed in order to compare own products still under development to products that were already marketed by competitors. The comparison with this state of the art provided information on the patentability of own inventions. Especially when competing products proved to be superior the further investment in the development of the own end product could be re-reviewed.

c. Improvements of Inventions

Experiments serving the improvement of inventions were often conducted with own inventions. Herewith the practical applicability of the invention should be advanced or the experimental results achieved leading to dependent inventions. In this context it was reminded that the second medical indication of a drug was often more precious than the first. At the same time the companies mentioned, on principle, not to perform experiments in order to upgrade alien patents. Then only a dependent patent was available, by which the dominant patent of a competitor would have been increased in value.

Two companies admitted to work on an improvement of foreign patents only in an exceptional constellation, i. e. when the major part of the investment in an innovation had already taken place or an agreement with the proprietor of the dominant invention (patent) seemed probable. This consent could be a cross-licensing or selling of the dependent invention to the owner of the dominant patent. However an amicable settlement became the more expensive the later on in the innovation procedure one became aware of existing patents relating to the own innovation work and the more investments in the use of a dominant patent had already been made.

d. Patent Dependency

A pragmatic way of avoiding the effects of patent dependency was mentioned by one company: Buying the dominant patent. This was the way of choice if a patent obtained exclusive dominance in a field of technology that was of major value for the company's business activity.

6. Effects of Patents on Research Tools on Research Activity

In the future, the use of patented research tools by pharmaceutical or biotechnology companies is most probable within the development of novel therapeutics, since this will involve the examination of databases of gene-related biochemical substances corresponding to designated biochemical sites as well as their application to the interaction with targets. In such early-stage research activities functional genomics research tools (broad range of genes and gene functions with their expression products[20]) will be of a major interest for the scientists of the private or public sector to narrow down defined research procedures in order to reach a scientific goal. Nonetheless, currently it

[20] This could be proteins which encompass an cumulative functional diversity providing a large set of molecules including enzymes, antibodies, transcription factors, receptors, hormones or other mediators and targets.

[21] Nuffield Council on Bioethics, "The ethics of patenting DNA", Nuffield Foundation (2002), paragraph 5.38, 5.43 – 5. 47.

seems to be an open question, if the use of patented gene-related research tools by other parties with research objectives in drug discovery or diagnostics will cumulate infringement proceedings and/or damages[21].

a. Application of Research Tools

The application of research tools so far did not present a disputable issue. Firstly research tools like certain enzymes were easily available staple goods which could be bought without declaring the intended use. Purchasing the research tools leads to exhaustion of the patent right. Therefore the direction of the own research activity could remain discrete. Furthermore it was pointed out that as a rule patent infringement in making and utilization of research tools remained undetected "behind locked laboratory doors". That was why the patentee was unaware of such infringements, so that he could raise claims only against contributory infringers. The suspicion of infringement could only occur when a product was marketed that could have been developed by infringing e.g. a research tool patent. Only few of the interviewed biotech companies had reached the stage of commercialization.

b. Awareness of Legal Implications for Patented Research Tools

The research institutions complemented that their employees might not be aware of legal implications of making or using patented research tools. This was due to the fact that patent infringement law suits were not often filed against research institutions. There was little economic incentive for the patentee to file such a lawsuit, because the research institutions generated no revenues through patent infringement.
In a single case it was speculated that patent owners might fear to lose reputation when suing a publicly owned research institution. Accordingly lawsuits enforcing patents on the enzyme taq-polymerase had caused a loss of renommée.

c. Copyright Implications

One research institution believed that a kind of copyright would have sped up the sequencing of the human genome. With the legal status quo discovered gene sequences would have been kept secret temporarily. Preferably anyone should be entitled to use gene sequences given that part of the revenue to generate was passed on to the copyright proprietor.

7. Effects of Patents on Publication Activity

A significant primer for most scientific research work may be the publication of research findings for peer review. In this context however premature publication activities could create adverse effects upon subsequent endeavour to acquire patent protection for the methods and results disclosed in a paper[22]. Whereas in most European Patent Systems pre-publication collides with the objectives of the patent systems, in the United States of America patent protection is still available if a patent application is filed with the United States Patent and Trademark Office (USPTO) within one year of the publication date, so-called Grace Period[23].
Although reluctance in respect of premature publishing predominates for good reasons[24], it is not unusual to have scientists publish research details before any patent considerations have been made[25]. As the pros and cons for a Grace period are still going to be discussed

[22] Straus Joseph, Grace Period and the European and International Patent Law, Analysis of Key Legal and Socio-Economic Aspects, IIC Studies 2001, p. 77.

[23] Straus Joseph, Grace Period and the European and International Patent Law, Analysis of Key Legal and Socio-Economic Aspects, IIC Studies 2001, pp. 45.

[24] Bill Barrett, Defensive use of publications in an intellectual property strategy, nature biotechnology, Vol. 20, No. 2, February 2002, pp. 191-193.

[25] A prominent example is the publication of the results achieved by Stanley Cohen and Herbert Boyer which led to the granting of U.S. Patent 4,237.224.

the impetus within the scientific community for the continuous race to be the first appears to be unbroken. And this requires publication.

a. Companies

All the companies stated that scientific publishing of experimental results had no priority for them. On the contrary they established formalized prepublication procedures in the course of which the patent department had to agree with the intended publication. This prohibited publications precluding novelty.

b. Grace Period

The interviewed companies opposed the introduction of a grace period into German and European patent law. The legal certainty that existed without a grace period was perceived as more important than the incentive to early publication. At least the grace period of one year provided by U.S.-law was considered too long. On the opposite side the research institutions favoured the introduction of a grace-period. They were unable to establish pre-publication procedures like the companies as the individual researchers were rarely willing to consult the patent department (if one existed) before each and any speech or conference. On the whole scientific researchers were not sensitive for the fact that those talks and conferences could constitute prior art. Publications in scientific magazines were not regarded as that problematic since a patent application could still be filed during the time-consuming peer-review process, i. e. prior to the actual publication.

8. Lawsuits Dealing with Genetic Inventions

One main issue for reasonably policing an invention also true for genetic inventions concentrates on the value of a patent which on the other hand depends itself on the capability to anticipate others from applying the claimed invention without prior licensing. The reasons that patent protected inventions are infringed by using them without

authorization are multiple, however, due to such a diversity of products or processes in certain fields of biotechnology the predominant motivation to do so is the belief of potential infringers that the patent owner would never become aware of their illegal use[26]. But when occurring infringement has become evident to the patent proprietor, it is possible for him to terminate the illegal use through legal proceedings. Since litigation could be a financial high-risk[27], this approach should be kept in mind as *ultima ratio*. Furthermore, during a litigation the validity of a patent might be jeopardized by the alleged infringer in the sense that the patent could be revoked or the economically decisive claims could be narrowed to insignificance through the appealed court. Besides alternative dispute resolutions[28], the parties could agree to resolve the problem by licensing the invention under reasonable contractual terms.

a. Pharmaceutical Companies

The well established pharmaceutical companies emphasized that lawsuits dealing with genetic inventions had not occurred to any larger extent than in other fields of technology. Most biotechnological companies were too ambitious to co-operate with pharmaceutical companies to sue the pharmaceutical companies.

Some uttered the opinion that mainly in the United States lawsuits accumulated, despite the doubtful validity and scope of certain patent claims.

This was due to the heavy competition among biotechnological companies with the intention to reach a dispute settlement leading to an opportunity of licensing the own invention to the sued company. In this respect the doubtful validity and scope of certain patent claims propagated lawsuits.

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[26] Saliwanchik Roman, Protecting Biotechnology Inventions, A Guide for Scientists, Brock/Springer Series in Contemporary Bioscience (1988), pp. 61 following.

[27] James D. Myers and Robert Glatz, Procedural Aspects of Patent Litigation, in: The Law and Strategy of Biotechnology Patents edited by Kennth D. Sibley, Butterworth-Heinemann (1994), pp. 231-232.

[28] As a result of the long delays and the high costs associated with resolving disputes by traditional trial mechanisms, there is an increasing emphasis on negotiating settlement or applying alternative methods of dispute resolution like arbitration or mediation.

b. Biotechnological Companies

All but one biotechnological companies testified they never had been involved in a patent lawsuit. This could result from the fact that a great proportion of them did not market any products yet, so that any proprietor of a possibly infringed patent had difficulties in realizing that his patent could have been infringed and had little economic incentive to file a lawsuit.

Possible motivation for nevertheless filing a lawsuit preceding marketing by the alleged infringer were urgent financial need as well as the intention to arrange a licensing agreement or to advance competition from the level of marketing to the level of research and development. The latter could lead to a preventive suppression competition.

In general, the concern to be sued appeared greater than the inclination to file a lawsuit. In other words, especially the smaller companies made use of a defensive strategy for enforcing patent rights. This was justified on the one hand by high expense of manpower and financial resources, on the other hand by uncertain outcome of a patent infringement or invalidity trial. The economic incentive was also diminished by reasonable royalties, that were granted as maximum remedy in most patent infringement cases. An inhibition for filing lawsuits was also very often the vagueness of law concerning validity and reach of claims in gene-related patents, e. g. microarrays. Above all few precedents existed that would make the outcome of a patent infringement lawsuit more predictable. For this reason only written reminders were exchanged that might lead to a dispute settlement. Furthermore possible plaintiffs and defendants of patent infringement trials were potential licensors and licensees who did not intend to negatively affect their business relationship. This was why the opinion was expressed that the tendency to file a lawsuit was more obvious between biotechnological companies than between biotechnological companies and pharmaceutical companies. One was more likely to sue a direct competitor from whom a license would be difficult to obtain.

c. Lawsuits

In one case lawsuits by a direct competitor from a foreign country had been filed. The sued company wondered whether such lawsuits served the legitimate interests of the plaintiff or constituted an abuse of a patent right on order to expel a competitor from a market of common interest. E. g., in one case a lawsuit was not only filed the day after the patent grant. Also it was sued because of a claim describing more the technology of the defendant than of the plaintiff. In this case the broadest claims had been "hidden" in the last parts of the patent.

d. Trial Duration

There were complaints as to the long duration of trials, especially in the United States. The persisting legal uncertainty and the uncertainty of further business action as well as the impact on potential investors burdened especially the small companies. A trial duration of several years exceeded the average life expectancy of biotech start-ups.

9. Patenting and Secrecy

Heavy financial efforts are underway in the public and private biotechnology sector to determine research information and restrict access to its use by patenting or secrecy, e.g. depending on the degree of implemented confidentiality during the research and development stage. Other considerations refer to the prior art to which the subject matter of the invention relates or to the requirements of patentability[29]. Patenting provides a strategy for protecting inventions without secrecy. Within the sector of industrial research, the patent system promotes more disclosure than would occur if secrecy were the only means of excluding competitors. In some sectors patenting is relatively inefficient when it

[29] Margreth Barrett, Intellectual Property, Cases and Materials, Second Edition 2001, American Case-book Series, West Group, p. 337.

comes to secure the rents due to an invention therefore secrecy is favoured as a non-legal protective mechanism within a competitive environment[30].

a. Research Tools

Because of the difficult protection and enforcement of research tool inventions one company wondered whether to keep research tool discoveries secret in the future.

b. Secrecy vs. Patent Protection

Other companies advocated the view that at least for process patents, that are difficult to enforce, secrecy could be more effective than patent protection. Recently patent protection was encouraged by sophisticated analyzing tools which allow more and more deductions from an end product to the complete production process, e. g. by identifying catalytic converter remains. To protect the owner of process patents it would be desirable to provide for a regimen in which potential infringers would have to provide for more information on the actually used methods.

c. Secrecy for Important Inventions

In one case secrecy was mandatory as important discoveries were excluded from patenting. Secrecy would have been successful because it would have taken a great amount of effort to discover the secret knowledge, even from the marketed end product. The classified knowledge could have been licensed similar to a patented invention.

[30] Carine Peeters and Bruno van Pottelsberghe de la Potterie, Strategic Management of Innovation and Patenting Performances, September 2003, p. 7, http://www.iir.hitu.ac.jp-/file/WP03-17bru-no.pdf.

10. Importance of Legal Knowledge and Business Strategies

For initial securing the protection of inventions as well as exploiting them legal professionalism is the key factor for successful competition. The type of patent professional with whom the inventor is likely to get into contact might depend on whether the inventor is independent or is employed by a large or a small company or an university[31]. However, a high degree of sensitivity of the scientists concerning legal knowledge to determine the patentability of an invention seems to be the first step in patenting an invention. The next step should be a close cooperation between the patent agent, in-house or not, even before a research development is at the stage of a formal invention report[32], otherwise creating a defining strategy for obtaining strong global patent rights might be too difficult.

Besides, after patenting and licensing, the commercialization of know how and technology could only be successful, if institutions were exposed to the dynamics of business competition.

a. Large Companies

While large companies maintained in-house patent departments, smaller companies at least co-operated with external lawyers on a permanent basis. This was partly due to the emphasis venture capital firms put on the protection of intellectual property. The co-operation between companies and patent lawyers often extended to patent search, which was then demanded as an external service. The great advantage the internet provided for patent search was stressed.

[31] Larger companies, which may file multiple patents applications a year, will normally have established a working relationship with a particular law firm, and often with the own patent attorney employed in the firm. Smaller companies will regularly deal directly with a patent attorney in private practice. Technology transfer agencies handle the technology transfer for research institutes such as universities.

[32] Grubb Philip W. Patents for Chemicals, Pharmaceuticals and Biotechnology, Fundamentals of Global Law, Practice and Strategy, Clarendon Press, Oxford (1999), pp.273 – 287.

The interviewed institutions pointed out the fact that not all of their employees were completely sensitive in respect of the implications of patent law. As early as in their university classes natural scientists should be confronted with the basics of patent law. Even established scientists should be given more opportunities to undergo special legal training in patent law. In so far the United States set a good example.

b. Smaller Companies

One smaller company's representative outlined the impression that patent attorneys showed only minor interest in solving legal problems of their clients, as they made a living by exactly those problems. A possible countermeasure would be standardized fees for classes of cases.

c. Public Academic Institutions

The representatives of public academic institutions emphasized that contrary to some statements that they lanced too few patent applications the opposite was true. A multitude of patent applications, especially for genetic inventions, was filed. Yet they partially had been filed not in the name of the academic institutions but in the name of co-operating companies. The academic institutions did not file the patent applications themselves because they lacked managerial staff qualified in dealing with patent applications, licensing and enforcing patents.

11. Patent Document and Patent Scrutiny

In an ideal fashion, the patent claim language is so clear and unambiguous that its meaning is out of dispute. Nevertheless, this goal is difficult to accomplish and fairly often due to the fact that claims are written by people providing just a very incomplete understanding of the precise nature of the subject matter of an invention. As a result, the significance of words implemented in a patent is often the focus of patent litigation

referring to validity or infringement unless such language was sorted out by the patent examiner[33]. Resulting from such a high research activity in the field of biotechnology in recent years still large numbers of biotechnology patent applications were filed. Therefore, waiting time from the date of filing to the initial examination of the application could be up to several years interfering negatively with the long-term planning of a biotech company, otherwise, in certain circumstances companies might regard this aspect as an advantage[34].

a. Language Barrier

Criticized was the language barrier between natural scientists and lawyers. Scientific publications were easy to read and understand, patent documents were not. On the contrary patents had been successfully challenged because of their alleged ambiguity, although their meaning was easy to understand for a person skilled in the art.
In some instances the impression had arisen that patent attorneys had tried to hide the broadest claims in patent applications, e. g. as "patent claim number 48". In other cases unusual word spelling of biological terms had been applied on purpose to hide the gist of inventions.

b. Patent Documents

Some complained that patent documents were not very substantial compared to scientific publications. To master the scientific peer-review process a scientific paper had to be consolidated by sophisticated experimental data. Patent examination seemed to be comparatively superficial, making many granted patents appear speculative or emerging

[33] Chisum Donald S., Craig Allen Nard, Herbert F. Schwartz, Pauline Newman, F. Scott Kieff, Principles of Patent Law, Cases and Materials, Second Edition 2001, University Case Book Series, Foundation Press, pp. 836 – 839.

[34] For the pharmaceutical industry in particular, where the registration of a new drug is a long-lasting and costly procedure, deferred examination is a practiced standard to lower the financial risks for the case that a pharmaceutical is abandoned during clinical trials.

from a mere "educated guess". The generous way of examining patents by German or European Patent Office derived presumably from understaffing.
In addition, on the one hand the patent offices employed more chemists than biologists, on the other hand the staff had ended their scientific education years ago so that they could not always appropriately judge recent discoveries in the field of biotechnology. It was suggested to establish a peer-review program for patent examinations resembling the one for scientific publications with a high impact factor. However secrecy could become a problem if patent examiners sought external advice from publicly appointed experts. Meanwhile the whole branch suffered from doubtful validity and scope of certain patent claims, e. g. risky lawsuits, or with whom to negotiate a license if several rivalling patents existed?

c. Extended Granting Period

Criticism was voiced concerning the extended duration until the grant of a patent. Having several years of limited protection until the granting of a patent a claimed DNA-sequence could already have been used by others at the time of granting. The long waiting period exceeded the planning frame of biotech start-up-companies.

d. Patent Search

Patent search for patent examiners as well as inventors became increasingly intricate, time-consuming and costly by patents covering multiple members of a sequence family in a single patent and by claiming molecules described as "hybridizing with" the claimed ones. This way easily 1,000 - 2,000 patent applications could become relevant, exceeding the capacity of present patent search tools.

12. Statutory Clarity with Genetic Inventions

Although there is much greater statutory clarity with gene patents, e.g. through the Revised Guidelines on the Examination of Patent Applications[35] in the United States of America including also gene patents that must disclose specific, substantial and credible utility or in Europe through the EU Directive 98/44/EC[36] claiming a specified function for DNA sequences within a patent, there is still evident concern about associating property rights with human biological materials regarding the genome as common human heritage or opposing the inventive element when identifying the utility of genes. Others pronounced practical implications of gene patents that include impediments to research information, to the creation of other innovative products or to clinical information in a clinical setting, so-called "access issues"[37]. For those reasons some propose special laws for genetic inventions also codifying against absolute protection of gene sequences.

a. Special Regulations for Genetic Inventions

All of those interviewed did not support an idea for special regulations for genetic inventions. In particular a discrimination of genetic and chemical inventions was denied. Even the European Directive on the legal protection of biotechnological inventions (EU Directive 98/44/EC) could prove outdated shortly, as science in the field of biotechnology progressed dynamically. It was unsatisfactory that naturally occurring substances could be patented without disclosure of utility, gene sequences, however, not.
In any case the specificities of genetic inventions could diminish in future the importance of patents in this field, bearing in mind, e. g., that even analyzing the function of a gene could be performed automatically. Under such conditions the requirement of an inventive

[35] Introduced by the USPTO in 2001.

[36] EU Directive 98/44/EC of the European Parliament and of the Council of the European Union of July 6, 1998 on the legal protection of biotechnological inventions.

[37] Genetic Inventions, Intellectual Property Rights and Licensing Practices, Evidence and Policies, OECD 2002, pp. 10 following.

step could be met only by downstream technologies for which protection would be available along the lines applied for conventional inventions such as medical drugs.

b. Absolute Product Protection of Genetic Inventions

Pharmaceutical companies stressed that absolute protection of substances had proven successful. This kind of protection was essential in order to pay tribute to the fact that e. g. with the development of a medical drug about 40 % of engineering expenses were caused by the proof of non-toxicity, metabolization and non-allergic characteristics. These costs were related to providing an active substance, not to the discovery of a certain medical indication.

Competitors could be prevented from building upon these results only by the absolute protection of the provided substance. In addition, only the provision of the substance put a competitor in a position to search for new medical indications.

The biotechnological companies characterized the value of absolute protection not as essential. Absolute protection was not advocated *per se*, but a discrimination of genetic and chemical inventions was denied. Above that absolute protection of DNA-sequences was regarded as a facilitating means of enforcing patents disclosing certain utilities of genetic information. On the contrary others criticized absolute protection of inventions including single DNA-sequences since all claims should be restricted to the inventor's contribution to the state of the art.

The discussion on absolute protection of genetic information was neutralized by the fact that genetic information generated by the Humane Genome Project (HGP) was publicly available, depicting only the protection of newly found functions.

13. Reach-through Claims

As a recent phenomenon in biotechnology an increasing number of patent applicants aim at patent protection for future downstream inventions by means of "reach-through-claims"[38] providing the patentee a dominant control over future inventions by obtaining exclusive rights to the first in line patent owner by way of legal enforcements rather than as the outcome of negotiating reach-through rights[39]. While some remain sceptical about further existence of reach-through claims other practitioners are startled by the negative economic implications[40] of protecting prospective inventions by this mode d'emploi. Since this technique of creating broad biotech patents is a global phenomenon, the Trilateral Project B3b[41] has been performed as a comparative study on "reach-through claims" to analyse the factual impact of reach-through claims. Though the economic arguments on both sides have theoretical merit, the empirical evidence by the project would presume that prior generations of gene patents have not significantly hindered progress in the genomics domain.

Among our interview partners the problem of reach-through claims was discussed controversially: Some asserted that worries about such claims were unjustified, because reach-through claims did not exist or were invalid. Others replied to have been confronted with such claims and that it was unresolved until the decision of an Opposition Division of the European Patent Office (EPO) if reach-through claims were valid or not.

Reach-through claims as intended parts of license contracts, e. g. for microarrays, could sometimes be defeated, but in any way the license negotiations became more cumbersome by the demand of reach-through royalties.

[38] For example, in genomics research the identification of gene expression patterns of a new drug target that controls metabolic events in the human body may lead to the use of that target (receptor) within different drug discovery value chains.

[39] Stephan G. Kunin, Mark Nagumo, Brian Stanton, Linda S. Therkorn, Stephan Walsh, Reach-Through Claims in the Age of Biotechnology, American, University Law Review 2002, Vol. 51, pp. 616-619.

[40] Concerns evoked about reach-through royalties that increase royalty stacking, thus making project management more complex and the cooperations more delicate when costly negotiations become necessary.

[41] Trilateral Project B3b, Mutual understanding in Search and Examination, Report on Comparative Study on Biotechnological Patent Practices, performed by the USPTO, EPO, JPO 2001: http://www.uspto.gov/web/tws/B3b_reachthrough.pdf.

14. Comparison of Laws, Harmonization of Laws

Through the introduction of some of the provisions of the European Biodirective into the EPC, the requirements for obtaining patents for genetic inventions in Europe have been clarified and recent case law has supplied guidelines for interpreting these provisions[42]. However, the situation in Europe has not yet been harmonized as several member states, whose national courts might set different standards with regard to what can and cannot be patented in biotechnology, have failed to implement the European Directive. At the moment there seems to be considerable political pressure to install an EU patent ("Community Patent")[43] to secure patent protection with same effects throughout the single market, i.e. the territory of the entire European Union. An international central body facilitating applicants' filing applications in 123 States is the regulatory framework of the Patent Cooperation Treaty (PCT), which is administered by the International Bureau of the World Intellectual Property Organization (WIPO)[44]. Even if a number of international patent agreements with harmonized patentability criteria were achieved, further harmonization activities should be performed to facilitate the enforcement of patent rights.

a. International Harmonization

The necessity of international harmonization of law became apparent. The impression persisted that the guidelines for patent examiners of different countries as regard to genetic inventions varied in detail. That constituted a drawback since important key inventions were applied for a patent and enforced in several countries in any case. Divergence existed e. g. concerning the requirements of proving genetic functionality. Differences existed as well relating to the possibility of including multiple members of a sequence family in single patent application.

[42] Gerald Kamstra, Marc Döring, Nick Scott-Ram, Andrew Sheard, Henry Wixon, Patents on Biotechnological Inventions: The E.C. Directive, Special Report, Sweet & Maxwell 2002, pp. 1-8.

[43] Commission of the European Communities, Proposal for a Council Regulation on the Community Patent, Brussels August 2000, http://europa.eu.int/comm/internal_market/en-/indprop/patent/412en.pdf.

[44] Patent Cooperation Treaty: http://www.wipo.org/treaties/registration/pct/

b. National Patents

Disapproved was also that in Europe after uniform decision to grant patents by the EPO, these patents split up in various national patents each treated according to national legislation. Undesirable was the hypothetical situation where a patent on a DNA-sequence was first granted by the EPO, but then was in some countries protected as a substance independent of a certain use, in others only in connection with a specific use.

c. National Applicants

Few of the interviewed deplored, that national patent offices tended to prefer national applicants or that the general patenting policy was directed the way that suited mostly the national industries.

d. Submarine Patents

As a delicate question two companies stressed that under the former American Inventors Protection Act (AIPA)[45] inventions were published only at the time of grant of a patent, not within a certain period of time after application (so-called submarine patents).
At the time of a grant of a patent already considerable investment could have been made that then proved not to be usable without infringing the patent. European firms did not profit from any delayed publications as they applied their inventions for patent protection in Europe where patent applications had been published after eighteen months from application or priority date.

[45] American Inventors Protection Act AIPA, November 1999, http://www.uspto.gov/web-/offices/dcom/olia/aipa/

15. Genetic Inventions and Ethics

As mentioned above in the introductory lines genetic inventions are subjects of controversy, challenged by the lack of public acceptance and strong pressure from public interest groups. In many instances the situation is shaped due to distorted individual and social features of risk perception and how risk perception is linked to the open debate of concern. Thus, the amplification of the ethical discourse might have significant consequences on how genomics research and medical applications of modern biotechnology might be processed in the future. Some biotechnological companies noted that they suffered from the ethical debate on dealing with genetic inventions and the distorted perception of the impact of patenting genetic inventions. Not commonly known was that patent rights did not confer any license to practice the invention. However it was observed that the political environment had improved since the introduction of special legislation on genetic engineering in Germany (Gentechnikgesetz), making public protests negligible. The general clauses of patent law, e. g. the exclusion of inventions from patenting that could only be practiced in contradiction to ordre public or morality were sufficient to enable using genetic inventions in a responsible way.

IV. Summary

The essence of this investigational project was to assess how the interrelationship of patent law and research on the one hand as well as in the interplay between patent law and licensing practices (business strategies) on the other hand influence developments in science and technology in the area of genomics.

The most important conclusions, at least for Germany, were that so far companies do not count so much on filing law suits rather than to come to terms on reasonable royalty rates or equivalent co-operations. This as a fact that infringement events are hard to identify due to that patent thicket in the field of biotechnology. The other aspect is that so far not very many end-products have reached the market which could be potential targets of legal actions.

One high ranking issue mentioned was the lack of sensitivity in respect of legal knowledge and expertise on business strategies among scientists, especially at universities. There, much is still left to be done to install a coherent IP strategy and infrastructure consisting of educational approaches towards the researchers as well as the instalment of university technology transfer organizations (UTTOs).

None of the interviewees were in favour of special regulations for gene-related inventions as from the practical point of view this would not be desirable since biotechnology is not as far apart from other technologies that are well patentable. Moreover from a technological standpoint, the coincidence of genetics and technology within a gene patent does not influence the technique of the patenting procedure and the bottleneck of patent examination that special laws for genetic inventions are justified. Concerning ethical considerations the existing patent system proves sufficient legal clarity and legally binding towards universal human rights. However, the need for harmonized international laws was given unanimous emphasis.

Most of the other difficulties and challenges discussed with the specialists *in praxi* were found to be solvable under the individual circumstances between the parties not demanding any external intervention.

Appendix 1: The Questionnaire

1. Profile of company

a) Marketed product
b) Company established when
Since when active in the market
c) Turnover/year world-wide
Development since establishment of company
d) Number of employees world-wide
Thereof in R & D
Source of recruitment
e) Size of company in relation to direct competitors
f) Origin of financial sources, participation in the stock-market
Financial dependency on potential patent rights
g) Mergers with other companies
Significance of patents for merging
h) Co-operation with other companies
Purpose of Co-operation
Significance of patents for merging

2. Patents

a) Number of filed patents
Thereof with claims on gene sequences
Development since establishment of company
b) Number of granted patents
Thereof with claims on gene sequences
Development since establishment of company
c) Company exclusive owner of patents
d) Participation in patent pools
Attitude towards patent pools
e) Significance of own patents for the company's business
Thereof with claims on gene sequences
f) Significance of competitor's patents for the company's business
Thereof with claims on gene sequences

3. Licences

a) Number of granted licences
Thereof with claims on gene sequences
Development since establishment of company
b) Licensees
c) Number of used licences
Thereof with claims on gene sequences
Development since establishment of company
d) Have licences been refused in the past
Reasons
Applied for compulsory licence
e) Cross licensing

4. Patents and R & D

a) Annual investment in R & D
b) R & D continued, when only dependent patent was available
R & D continued, when no patent was available
c) Significance of competitor's patents for own R & D
Field with competitor's patents excluded
Significance of research tools for own R & D
d) Significance of data bases for R & D
Satisfied with access to data bases
e) Subject of competitor's patents tested
f) Public funding of R & D
Significance of patents
g) Scientific publications
Impact of patent law on time, quality and quantity of publication
Attitude towards grace period
h) Spin-offs of genomic R & D

5. Patents and patent litigation

a) Lawsuits because of alleged patent infringement
   Success
   Costs
b) Consequences of lawsuits for R & D
c) In-depth knowledge of patent law
   External legal advice taken
d) Special qualities of genetic patents, that should be dealt with by patent law
e) Significance of dependency of a patent
f) Justification of absolute protection of a substance, independent of disclosed use
g) Comparison of legal framework for R & D in the field of biotechnology in Germany and other countries

Appendix 2: Statistics

1. The Sample Group (n=25)

– 4 large pharmaceutical companies
– 9 small and medium sized biotechnological companies
– 7 research institutes
– 5 clinical institutions

2. Specialization of the Interviewed

interview partner	specialization
1. pharmaceutical companies	development and marketing of medical drugs
2. biotechnological companies	development of medical drugs (no marketing yet); partially services like purification, sequencing, target identification, screening, expression analysis, development of expression systems
3. research institutions; scientific administration	tumor immunology, molecular biochemistry; administration of research institutions
4. clinical institutions	genetic consulting, basic research in anti-retroviral therapy, molecular cytogenetics, gene therapy

3. Age of the Interviewed

Interview partner	foundation year
1. pharmaceutical companies	prior to 1900
2. biotechnological companies	2001: 1 2000 - 1998: 2 1997 - 1994: 3 1992; 1988; 1985
3. research institutions, scientific administration	1964 (genome research since 1987); 1970; 1970; 1975; 1990
4. clinical institutions	1970; 1970; 1972; 1976; 1985 genome research since mid-80's

4. Turnover/Year Worldwide

Interview partner	turnover/budget per annum
1. pharmaceutical companies	€ 3,000 - 6,900 million
2. biotechnological companies	no marketing of drugs yet partially turnover in services of € 1.75 - 60 million
3. research institutions, scientific administration	€ 0.75 - 105 million
4. clinical institutions	€ 1.1 – 7.5 million

5. Number of Employees Worldwide

Interview partner	Employees
1. pharmaceutical companies	24,000 - 117,300
2. biotechnological companies	4.5 - 1,600
3. research institutions, scientific administration	40 – 620
4. clinical institutions	60 – 120

6. Number of Applications for Genetic Inventions

Interview partner	patent applications
1. pharmaceutical companies	about 100*
2. biotechnological companies	25 – 180**
3. research institutions, scientific administration	50 – 100**
4. clinical institutions	1 – 20**

* per annum

** total number

7. Number of Granted Genetic Patents

Interview partner	granted patents
1. pharmaceutical companies	500 - 1,100
2. biotechnological companies	0 – 55
3. research institutions, scientific administration	30 – 110
4. clinical institutions	1 – 6

8. Number of Granted and Obtained Licenses

Interview partner	granted licenses	obtained licenses
1. pharmaceutical companies	n. a.	
2. biotechnological companies	0 - 28	1 - multiple
3. research institutions, scientific administration	0 - 83	0 - 10
4. clinical institutions	0 - 3	0

9. Number of Lawsuits on Genetic Inventions

Inter view partner	lawsuits
1. pharmaceutical companies	0 - 2
2. biotechnological companies	0 - multiple
3. research institutions, scientific administration	0 - 4
4. clinical institutions	0 - 1

10. Number of Co-operations

Interview partner	co-operations
1. pharmaceutical companies	many
2. biotechnological companies	0 - many
3. research institutions, scientific administration	2 - 91
4. clinical institutions	0 - 5

11. Spin-offs

Interview partner	spin-offs
1. pharmaceutical companies	-
2. biotechnological companies	-
3. research institutions, scientific administration	3
4. clinical institutions	1 - 3

Appendix 3: The Sample Group

Pharmaceutical Companies

1. Bayer AG
51368 Leverkusen

2. Merck KG aA
Postfach
64271 Darmstadt

3. Schering AG
13342 Berlin

4. Boehringer Ingelheim GmbH
55216 Ingelheim am Rhein

Biotechnological Companies

5. Atugen AG
Robert-Rössle-Str. 10
13125 Berlin

6. Epigenomics AG
Kastanienallee 24
10435 Berlin

7. GeneScan Europe AG
Engesserstr. 4b
79108 Freiburg/Breisgau

8. GPC Biotech AG
Fraunhoferstr. 20
82152 Martinsried/München

9. MediGene AG
Lochhamer Str. 11
82152 Planegg/Martinsried

10. metaGen Pharmaceuticals GmbH
Oudenarder Str. 16
13347 Berlin

11. MorphoSys AG
Lena-Christ-Str. 48
82152 Martinsried/Planegg

12. Rhein Biotech GmbH
Eichsfelder Str. 11
40595 Düsseldorf

13. Qiagen GmbH
Max-Volmer-Str. 4
40724 Hilden

Research Institutions, Scientific Administration

14. Ascenion GmbH
85764 München/Neuherberg

15. BioM AG
Am Klopferspitz 19
82152 Martinsried/München

16. Deutsches Krebsforschungszentrum
Im Neuenheimer Feld 280
69120 Heidelberg

17. Garching Innovation GmbH
Hofgartenstr. 8
80539 München

18. Max-Delbrück-Centrum für Molekulare Medizin
Robert-Rössle-Str. 10
13125 Berlin

19. Max-Planck-Institut für Molekulargenetik
Ihnestr. 73
14195 Berlin

20. Max-Planck-Institut für Biochemie
Am Klopferspitz 18a
85152 Martinsried

Clinical Institutions

21. Klinikum Grosshadern
Ludwig-Maximilians-Universität München
Marchioninistr. 15
81377 München

22. Institut für Humangenetik
Charité – Humboldt-Universität
Augustenburger Platz 1
13353 Berlin

23. Institut für Humangenetik
Universität Heidelberg
Im Neuenheimer Feld 328
69120 Heidelberg

24. Institut für Humangenetik
Ludwig-Maximilians-Universität München
Goethestr. 29
80336 München

25. Institut für klinische und molekulare Virologie
Universität Erlangen
Schlossgarten 4
91054 Erlangen

EXHIBIT I

POLICY FORUM

SCIENCE AND LAW

View from the Bench: Patents and Material Transfers

John P. Walsh,[1,2]* Charlene Cho,[1] Wesley M. Cohen[3]

Scholars have argued that the growing number of patents on research inputs may now impede upstream, noncommercial research by creating an "anticommons" in which rights holders may impose excessive transaction costs or make the acquisition of licenses and other rights too burdensome to permit the pursuit of scientifically and socially worthwhile research (*1*, *2*). Alternatively, owners of the rights over key upstream discoveries may restrict follow-on research through the exercise of exclusivity (*3*, *4*). The prospect of financial gain from upstream research has raised the further concern that academics are becoming more reluctant to share information, findings, or research materials (*5*, *6*). In 2003, a small-sample interview study suggested that, despite numerous patents on upstream discoveries, academic researchers have accessed knowledge without the anticipated frictions (*7*). Receiving material requested from other researchers could, however, prove problematic (*8*, *9*).

The *Madey* v. *Duke* decision of 2002 raised anew the question of the impact of research tool patents on biomedical research by clarifying that there was no general research exemption shielding academic researchers from infringement liability (*10*). This very visible decision and continuing concerns over the impact of research tool patents on academic science prompted our current study.

We report findings from a survey of 414 biomedical researchers in universities, government, and nonprofit institutions (*11*). In this group of academic, biomedical researchers, 19% currently receive industry funding for their research (representing 4% of their research budget); 22% applied for a patent in the past two years, with an average of 0.19 patent applications per year per respondent; 35% have some business activity [i.e., have participated in negotiations over rights to their inventions, have begun developing a business plan, had a startup, had a process or product in the market, or had licensing income].

LOGISTIC REGRESSION PREDICTING RECEIVING REQUESTED MATERIAL

Variable	Estimate
Scientific competition	–0.058 ± 0.029*
Academic supplier	0.007 ± 0.005
MTA	0.012 ± 0.004**
Patented	0.005 ± 0.007
Patent status unknown	–0.004 ± 0.004
Drug	–2.217 ± 0.683**

Values ± SEM. *$P < 0.05$; **$P < 0.01$.

Although common, patents in this field are not typically used to restrict access to the knowledge that biomedical scientists require. To begin with, few academic bench scientists currently pay much attention to others' patents. Only 5% (18 out of 379) regularly check for patents on knowledge inputs related to their research. Only 2% (i.e., 8) have begun checking for patents in the 2 years since *Madey* v. *Duke*, which suggests little impact of the decision. Five percent had been made aware of intellectual property (IP) relevant to their research through a notification letter sent either to them or their institution, which differs little from the 3% who reported having received such notification 5 years ago (prior to the *Madey* v. *Duke* decision). Furthermore, although 22% of respondents report being notified by their institutions to respect patent rights (versus 15%, 5 years ago), such notification did not appreciably affect the likelihood of checking for patents—5.9% of those receiving such instruction checked for patents versus 4.5% of those not receiving instruction.

Only 32 out of 381 respondents (8%) believed they conducted research in the prior 2 years using information or knowledge covered by someone else's patent. However, even for the few who were aware of others' patents, those third-party patents did not have a large impact on their research. Of the 32 respondents who were aware of relevant IP, four reported changing their research approach and five delayed completion of an experiment by more than 1 month. No one reported abandoning a line of research. Thus, of 381 academic scientists, even including the 10% who claimed to be doing drug development or related downstream work, none were stopped by the existence of third-party patents, and even modifications or delays were rare, each affecting around 1% of our sample. In addition, 22 of the 23 respondents to our question about costs reported that there was no fee for the patented technology, and the 23rd respondent said the fee was in the range of $1 to $100. Thus, for the time being, access to patents on knowledge inputs rarely imposes a significant burden on academic biomedical research.

Our research thus suggests that "law on the books" need not be the same as "law in action" if the law on the books contravenes a community's norms and interests (*9*, *12*). Although the new survey did not explicitly ask respondents their opinions about a research exemption, our results suggest that infringement remains of only slight concern. In contrast, research on clinical diagnostic testing (*13*, *14*) suggests that when the research is itself also a commercial activity, patent holders are more likely to assert and clinical researchers more likely to abandon infringing activities.

In addition to examining access to others' intellectual property, we consider the extent to which scientists can access the tangible research materials and data created by other labs, highlighted as another source of friction that may be impeding biomedical innovation (*5*, *8*, *15*). Indeed, concerns about increasing noncompliance with material transfer requests have prompted the National Institutes of Health to issue guidelines designed to encourage the exchange of materials created with federal funding (*16*).

About 75% of our academic respondents made at least one request for a material in the past 2 years. On average, academics made about seven requests for materials to other academics and two requests to industry labs in the past 2 years. However, 19% of our respondents report that their most recent request for a material was denied (*17*). Moreover, noncompliance with such requests appears to be growing (see supporting online text). Campbell and colleagues (*5*) reported that, among genomics researchers, about 10% of requests were denied in the 3 years, 1997–99. For the

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genomics researchers in our sample, the denial rate for 2003–04 was 18% (95% confidence interval, ±3.7%).

Over a 1-year period, an average of one in six respondents reported that delays in receiving materials from other academics caused at least one project they were working on to suffer a greater than 1-month delay, a substantial delay in a fast-moving research field. Noncompliance by other academics with research input requests resulted in about 1 in 14 scientists abandoning at least one of their projects each year.

We conducted two regression analyses to probe the reasons for noncompliance (see supporting online text). The first examined whether the respondent's most recent request was satisfied (see table, p. 2002). Statistically significant predictors of noncompliance included a measure of scientific competition (i.e., the number of competing labs) and whether the requested material was itself a drug. The patent status of the requested material had no significant effect on noncompliance. A second analysis with other variables—particularly characteristics of the prospective supplier—examined predictors of the number of times the respondent failed to comply with requests (see table, this page). Here, the burden of compliance (i.e., number of requests per dollar of funding); scientific competition; and commercial orientation (i.e., whether the respondent has engaged in any of the business activities listed above) increase the likelihood of noncompliance. Finally, the number of respondent publications, indicative of respondent eminence or the opportunity cost of responding, also increases the likelihood of noncompliance.

In addition to these regressions, we also asked respondents directly why they denied requests. The major self-reported reasons for noncompliance included the cost and/or effort involved and protecting the ability to publish, with commercial incentives much less prominent (*5*, *18*). We find, however, the multivariate regression analysis to be more credible than the self-reported relationships for the following reasons: (i) it uses a more objective measure of commercial orientation, while controlling for the effects of other variables and (ii) it is less likely to be influenced by a "socially desirable response bias" that leads academics to subordinate less socially desirable incentives (e.g., commerce) compared with more desirable ones (e.g., intellectual challenge) (*19*).

We also considered costs and burdens associated with material transfer agreements (MTAs). Only 42% of requests required an MTA, and only 11% of requests for research inputs led to an MTA negotiation lasting more than 1 month. Moreover, in almost all cases, there was no immediate fee for the requested material. However, for 8% of research input requests, negotiating the MTA stopped the research for more than 1 month. Although MTAs do not commonly entail delays or impose fees, they frequently come with conditions. MTAs, especially from industry suppliers, often include demands for reach-through rights of some form. Of executed MTAs, 29% had reach-through claims, and 16% provided for royalties. Twenty-six percent of MTAs imposed publication restrictions. Requests for drugs were the most likely to yield such a restriction, with 70% of such agreements including some restriction on publication of the research results using the transferred drug.

As a case study, we also collected data from an additional 93 academic scientists who are conducting research on one of three signaling proteins (CTLA-4, EGF, and NF-κB) that are patent-intensive research areas with enormous commercial interest, involving large pharmaceutical firms, small biotechnology firms, and universities. These are the very conditions where issues of access to IP should be evident. Although the incidence of adverse consequences due to restricted access to IP was more manifest here than in the random sample, it was still infrequent (only 3% of respondents reported stopping a project in the past 2 years because of a patent). On the other hand, access to materials was even more problematic in these areas than in the random sample (*18*). For example, 30% of researchers in these fields did not receive their last requested material.

Our results offer little empirical basis for claims that restricted access to IP is currently impeding biomedical research, but there is evidence that access to material research inputs is restricted more often, and individual research projects can suffer as a consequence. To the extent that any redirection of a scientist's research effort or reallocation across investigators because of denied access impedes scientific progress, this is cause for concern. In contrast, if such redirection reduces duplicative research or increases the variety of projects pursued, social welfare may even increase (*20*, *21*). In addition, it is not clear whether patent policy contributes to restricted access to materials, although the commercial activities fostered by patent policy do seem to restrict sharing, as do the burden of producing the materials and scientific competition.

Scientific progress in biomedicine may be well served by a study of the welfare impacts of restrictions on material transfers, and, if warranted, greater diligence in the monitoring and enforcement of the applicable NIH guidelines.

NEGATIVE BINOMIAL REGRESSION PREDICTING NUMBER OF REFUSALS TO SEND REQUESTED MATERIAL

Variable	Estimate
Commercial orientation	0.010 ± 0.004*
Scientific competition	0.078 ± 0.040*
Publications	0.075 ± 0.037*
Request burden	0.038 ± 0.019*
Budget	0.008 ± 0.042
Industry funding	0.006 ± 0.005
Drug discovery	0.000 ± 0.007
Male	–0.008 ± 0.004†

Values ± SEM. *$P < 0.05$; †$P < 0.10$.

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