Chicago-Kent Law Review

Volume 75
Issue 1 *Symposium on Legal Disputes Over Body Tissue*

Article 12

December 1999

Owning Genes: Disputes Involving DNA Sequence Patents

John Murry

OWNING GENES: DISPUTES INVOLVING DNA SEQUENCE PATENTS

JOHN MURRAY*

INTRODUCTION

The growth of the biotechnology industry and the advent of the Human Genome Project (the "HGP") have been accompanied by an increasing number of patent applications claiming deoxyribonucleic acid ("DNA") compounds[1] on the basis of a novel base sequence ("DNA sequence claims").[2] Between 1980 and 1997, inventors filed about 5000 applications claiming complete gene sequences in the United States, resulting in more than 1500 patents.[3] In addition, 350 applications, covering 500,000 partial gene sequences, were pending. At the end of 1998, Incyte Pharmaceuticals, Inc. of Palo Alto, California, reported that it had filed applications covering 1.2 million partial gene fragments.[4]

DNA molecules are complex chemical compounds. Although novel chemical compounds have been traditionally considered patentable, DNA sequence patents have raised much controversy.[5] Proponents of DNA patenting claim that such protection is essential if innovative research is to be converted into new drugs, vaccines and

* J.D. Candidate, Chicago-Kent College of Law, 1999. I wish to thank Professor Lori Andrews and Professor Dorothy Nelkin for their guidance throughout the writing and editing process.

1. The "single-stranded" DNA molecule consists of a chain of alternating sugar residues and phosphate groups with one of four nitrogenous bases bound to each sugar residue: adenine (A), cytosine (C), guanine (G) or thymine (T). *See* ROBERT SCHLEIF, GENETICS AND MOLECULAR BIOLOGY 22 (Johns Hopkins Univ. Press 1993) (1986). "Double-stranded" DNA is formed by the non-covalent linking of the bases of two "complementary" DNA strands to form a spiral ladder. *See id.* The pairing of bases is always such that A pairs only with T, and C only with G. *See id.*

2. *See* S.M. Thomas et al., *Ownership of the Human Genome*, 380 NATURE 387, 387-88 (1996). Between 1981 and 1995, a total of 1175 patents for human DNA sequences alone have been granted worldwide. *See id.* at 387.

3. *See* Eliot Marshall, *Companies Rush to Patent DNA*, 275 SCIENCE 780, 780-81 (1997).

4. *See* Incyte Pharmaceuticals, Inc., *Incyte Issued First EST Gene Patent* (visited June 29, 1999) <http://www.incyte.com/news/1998/PR9829-estpatent.html>.

5. *See, e.g.*, Leslie Roberts, *NIH Gene Patents, Round Two*, 255 SCIENCE 912, 912-13 (1992).

diagnostic tests.[6] However, those who oppose such protection claim that the patenting of DNA sequences will destroy research collaboration and slow down the development of future products.[7] Others object to the patenting of "life," including DNA sequences, upon moral grounds,[8] or claim that such patent protection may violate a property right of the individuals donating the original DNA samples.[9] In addition, some object to the patenting of plant and animal genes found in Third World countries in the absence of a mechanism to share the wealth generated by such patents.[10]

This Note examines the controversies surrounding the patenting of the breast cancer susceptibility genes, BRCA1 and BRCA2, as well as Expressed Sequence Tags ("ESTs"). In doing so, it discusses how patenting standards apply to DNA and how the patent system has dealt with the particular issues raised by attempts to patent partial and whole genes.

I. GENE PATENTING CONTROVERSIES

The availability of automated sequencing technology[11] has resulted in efforts to sequence the DNA of both the human genome[12] and the genomes of various nonhuman species.[13] In addition, the discovery of genetic links to diseases such as breast cancer,[14] colon cancer[15] and Huntington's disease,[16] has led to efforts to identify the

6. *See* George Poste, *The Case for Genomic Patenting*, 378 NATURE 534, 534-36 (1995).

7. *See* Leslie Roberts, *Scientists Voice Their Opposition*, 256 SCIENCE 1273, 1273 (1992).

8. *See* Ronald Cole-Turner, *Religion and Gene Patenting*, 270 SCIENCE 52, 52 (1995) (discussing a statement issued at a press conference by a group of religious leaders that "humans and animals are creations of God, not humans, and as such should not be patented as human inventions").

9. *See* David Dickson, *Whose Genes Are They Anyway?*, 381 NATURE 11, 11, 13-14 (1996) (discussing plans by the Human Genome Diversity Project to collect DNA samples from 500 linguistically distinct groups throughout the world to determine the extent of genetic variation in the human race).

10. *See* Neil Gross & John Carey, *Who Owns the Tree of Life?*, BUS. WK., Nov. 4, 1996, at 194, 194.

11. *See generally* AUTOMATED DNA SEQUENCING AND ANALYSIS (Mark D. Adams et al. eds., 1994) (reviewing the state of the art of DNA sequence analysis).

12. *See, e.g.*, W.R. McCombie et al., *Expressed Genes, Alu Repeats and Polymorphisms in Cosmids Sequenced from Chromosome 4p16.3*, 1 NATURE GENETICS 348, 348 (1992) (describing the sequencing of part of the Huntington's disease region in chromosome four).

13. *See, e.g.*, Claire O'Brien, *Entire E. Coli Genome Sequenced—at Last*, 385 NATURE 472, 472 (1997) (discussing the completion of sequencing of the bacterium *Escherichia coli*).

14. *See* Jeff M. Hall et al., *Linkage of Early-Onset Familial Breast Cancer to Chromosome 17q21*, 250 SCIENCE 1684, 1684 (1990).

15. *See* Gloria M. Peterson et al., *Presymptomatic Direct Detection of Adenomatous Polyposis Coli (APC) Gene Mutations in Familial Adenomatous Polyposis*, 91 HUM. GENETICS

particular genes that cause this susceptibility. The identification of such genes has often been followed by attempts to patent these discoveries. Many object to such patents for a variety of reasons, illustrated by two controversies. The legal and technical arguments surrounding attempts to patent BRCA1, BRCA2 and ESTs encompass the viewpoints of both those who support and oppose attempts to patent newly discovered DNA sequences.

A. Gene Hunting—The Search for the Breast Cancer Gene

Although genetic factors contribute to about only five percent of all breast cancer cases, they are a factor in approximately twenty-five percent of all cases diagnosed where patients are under the age of thirty.[17] Because of this linkage, researchers have tried to isolate the gene responsible and develop tests to allow the early identification of those at high risk of inheriting this form of cancer. In late 1994, these efforts culminated in the isolation of BRCA1, mutations of which may increase susceptibility to breast and ovarian cancer.[18] In 1996, researchers located BRCA2, a second breast cancer susceptibility gene, on chromosome 13q.[19] A large number of mutations to the BRCA1 gene were soon described by an international group of investigators.[20] The groups making these discoveries patented both the BRCA1 and BRCA2 genes as well as many of the mutations causing susceptibility to breast and ovarian cancer. The events occurring during the hunt for the BRCA1 gene, and its eventual patenting, provide a useful insight into the position of those who object to the way that DNA patenting is currently progressing.

Researchers, using genetic linkage techniques, first located a breast cancer susceptibility gene in 1990.[21] This involved a study of the inheritance of polymorphisms[22] through many generations of

307, 307 (1993).

16. *See* Huntington Disease Collaborative Research Group, *A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes*, 72 CELL 971, 971 (1993).

17. *See* Yoshio Miki et al., *A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene BRCA1*, 266 SCIENCE 66, 66 (1994).

18. *See* Donna Shattuck-Eidens et al., *A Collaborative Survey of 80 Mutations in the BRCA1 Breast and Ovarian Cancer Susceptibility Gene*, 273 JAMA 535, 535 (1995) (describing the structure of the BRCA1 gene).

19. *See* S.V. Tavtigian et al., *The Complete BRCA2 Gene and Mutations in Chromosome 13q-linked Kindreds*, 12 NATURE GENETICS 333, 333 (1996).

20. *See* Shattuck-Eidens et al., *supra* note 18, at 535-36.

21. *See* Hall et al., *supra* note 14, at 1684.

22. *See* NATIONAL RESEARCH COUNCIL, MAPPING AND SEQUENCING THE HUMAN

families and the correlation of these polymorphisms with the incidence of breast cancer in these families.[23] The initial location placed the gene on chromosome 17q. However, it was not until 1993 that the gene was located to a region of one to two million bases of DNA on this chromosome.[24] The availability of improved markers eventually allowed the gene to be isolated to a region of 600,000 bases.[25] The isolation of the BRCA1 gene involved an international collaboration of most of the groups involved in breast cancer linkage analysis.[26] A 1993 report by these groups summarized the results of linkage studies performed on 214 families. These linkage studies involved the use of a common set of markers and population genealogies that were obtained from either cancer registries or collaborating physicians.[27]

In late 1994, a team of scientists from Myriad Genetics, working with groups at the University of Utah and the National Institutes of Health (the "NIH"), succeeded in identifying and sequencing the BRCA1 gene.[28] Later, in 1996, Myriad scientists announced the discovery of the BRCA2 gene, a second breast cancer susceptibility gene, located on chromosome 13q.[29] Myriad filed a patent application covering the discovery of the BRCA1 sequences and eventually obtained two DNA sequence patents, one claiming the sequence of the BRCA1 gene itself, and the other claiming a number of harmful mutations of this gene.[30]

However, Myriad soon found itself involved in a legal battle with OncorMed, Inc. over the rights to the BRCA1 gene. OncorMed had been granted a patent covering a BRCA1 allele representing the most likely BRCA1 sequence to be found in the majority of the normal population.[31] Although this sequence is very similar to the previously disclosed Myriad sequence, it differs slightly because of the natural

GENOME 40-41 (1988) (describing a restriction fragment length polymorphism and its use in linkage studies in mapping and sequencing the human genome).

23. *See* D.F. Easton et al., *Genetic Linkage Analysis in Familial Breast and Ovarian Cancer: Results from 214 Families*, 52 AM. J. HUM. GENETICS 678, 678 (1993).

24. *See* Miki et al., *supra* note 17, at 66 (describing the isolation of BRCA1).

25. *See id.*

26. *See* Easton et al., *supra* note 23, at 678.

27. *See, e.g., id.* at 678-81.

28. *See* Miki et al., *supra* note 17, at 66.

29. *See* Tavtigian et al., *supra* note 19, at 333.

30. *See* United States Patent 5,747,282, dated May 5, 1998 (claiming the DNA sequence of the BRCA1 gene); United States Patent 5,693,473, dated December 2, 1997 (claiming a number of harmful mutations of the BRCA1 gene).

31. *See* United States Patent 5,654,155, dated August 7, 1997.

occurrence of different polymorphisms of the normal BRCA1 gene. Myriad and OncorMed sued each other, both parties claiming infringement of their respective patents.[32] In May 1998, the parties settled this dispute.[33] Myriad gained exclusive rights to OncorMed's patents for BRCA1 and BRCA2 for breast and ovarian cancer genetic testing. OncorMed also agreed to cease offering BRCA1 and BRCA2 genetic services. However, both parties retained diagnostic and therapeutic rights to their respective patents.

Natural differences occurring between the DNA of individuals result in many minor differences in the DNA sequence of a given gene.[34] Hence, some criticized the granting of two such similar patents.[35] One researcher in the field complained that the whole point of patent protection would be negated if every new variation of a gene were allowed patent protection. Instead, the first discoverer of a new gene should be given broad rights to ensure adequate compensation for that discovery.[36] This is especially important for a gene such as BRCA1. Researchers have identified at least eighty different cancer susceptibility mutations to the BRCA1 gene.[37] In theory, a different group could have patented each of these mutations. If normal noncancer susceptibility mutations of the gene may also be patented, then a great number of patents could be granted, each covering a slightly different version of the same gene. Such a situation could either make the individual patents worthless or, alternatively, cause a situation where multiple royalties significantly increase the cost of any medical products produced using the patented sequences.

A dispute concerning who should be named as inventors on the BRCA1 patent arose when contributing scientists, working at the NIH, were omitted from the original patent application covering the BRCA1 gene sequence.[38] This dispute was eventually resolved with

32. *See* Eliot Marshall, *The Battle over BRCA1 Goes to Court; BRCA2 May Be Next*, 278 SCIENCE 1874, 1874 (1997).

33. *See* Myriad Genetics, Inc., *Myriad Genetics Obtains OncorMed's BRCA1/BRCA2 Genetic Testing Program in Patent Settlement* (visited June 29, 1999) <http://www.myriad.com/pr/19980518.html>.

34. *See* SCHLEIF, *supra* note 1, at 227-31.

35. *See* Marshall, *supra* note 32, at 1847.

36. *See id.*

37. *See* Shattuck-Eidens et al., *supra* note 18, at 535.

38. *See* Helen Gavaghan, *NIH Resolves Dispute on Cancer Gene Patent*, 373 NATURE 649, 649 (1995).

the inclusion of the NIH scientists as inventors.[39] Myriad and its licensee Eli Lilly & Co. retained exclusive worldwide rights to the commercialization of the BRCA1 gene, although the NIH shares in any revenue. But others involved in the search of the BRCA2 gene objected to Myriad's BRCA2 sequence patent on the grounds that other groups, which had contributed to the basic research necessary to the isolation of the gene, were excluded.[40] The patenting of the gene also raised objections based on the fear that such patents make diagnostic tests more expensive and discourage other scientists from working in the area.[41]

Myriad countered such arguments by claiming that DNA patents are essential if biotechnology companies are to attract money for risky development projects.[42] The company pointed out that it had invested millions of dollars in the development of a comprehensive test for breast cancer susceptibility.[43]

B. Private and Public Genes—The Patentability of Expressed Sequence Tags

Although the precise biological mechanism of action of the BRCA1 and BRCA2 genes was not known when the Myriad patent applications were filed, these applications did involve DNA coding sequences for proteins of known biological effect. For example, mutations in the BRCA1 gene were known to account for roughly forty-five percent of inherited breast cancer and eighty to ninety percent of families with increased risk of early onset breast and ovarian cancer.[44]

However, it is possible to obtain and sequence expressed DNA gene fragments without knowing the complete structure of the gene from which they are derived or the biological function of the proteins

39. *See id.*

40. *See* Clive Cookson, *Research into Breast Cancer Has Highlighted Concerns About the Use of Information*, FIN. TIMES, June 27, 1996, at 12, 12. The Director of the Cancer Research Campaign, a United Kingdom charity, complained that, while the charity had contributed to Myriad's efforts to determine the structure of BRCA1, its scientists were "suddenly shunned." *Id.*

41. *See* Eliot Marshall, *Rifkin's Latest Target: Genetic Testing*, 272 SCIENCE 1094, 1094 (1996) (describing efforts by antibiotechnology activist Jeremy Rifkin to challenge the Myriad BRCA1 patents). Some also complained that genes, like BRCA1 and BRCA2, are products of nature and should not be patented. *See id.* For a discussion of Rifkin's concerns regarding the biotechnology industry, see generally JEREMY RIFKIN, THE BIOTECH CENTURY (1998).

42. *See* Marshall, *supra* note 41, at 1094.

43. *See id.*

44. *See* Easton et al., *supra* note 23, at 678.

coded by these sequences.[45] One method of DNA sequencing, the cDNA technique, uses messenger ribonucleic acids ("mRNAs"), transcribed from DNA coding sequences, to produce complimentary DNA ("cDNA"). These cDNAs, termed ESTs, are fragments containing about 400 bases, corresponding to only part of an expressed gene.[46] However, some point out that ESTs may be used as probes, allowing expressed gene sequences to be identified without searching the entire genome.[47]

Research scientist J. Craig Venter, while working at the NIH, developed an automated DNA sequencing method based on ESTs.[48] Venter claimed that his technique would allow expressed genes to be sequenced quickly and at low cost. However, the publicly funded HGP rejected this approach in favor of a genomic sequencing method where the entire genome is sequenced, not just the approximately five percent of DNA corresponding to expressed genes.[49] Nevertheless, in 1992, the NIH filed patent applications for more than 2000 partial gene sequences, which were determined using Venter's technique.[50] This action caused much criticism from researchers involved with the HGP.[51] Some criticized the applications on the grounds that the ESTs did not meet the technical requirements for patentability.[52] Others argued that, even if the ESTs did meet these requirements, patents on ESTs would impede the open exchange of information on which the HGP depended.[53]

The NIH later withdrew its EST applications,[54] leaving the

45. *See generally* Mark D. Adams et al., *Complementary DNA Sequencing: Expressed Sequence Tags and Human Genome Project*, 252 SCIENCE 1651, 1651-56 (1991).

46. *See, e.g.*, Tim Beardsley, *Piecemeal Patents: The U.S. Reconsiders Patents on DNA Fragments*, 267 SCI. AM. 107, 107 (1992).

47. *See* Glenn A. Friedrich, *Moving Beyond the Genome Projects*, 14 NATURE BIOTECHNOLOGY 1234, 1234 (1996) (describing the relations between DNA sequencing companies and their pharmaceutical company partners); *see also* Poste, *supra* note 6, at 534. It is claimed that ESTs also have commercial value in diagnostic tests for altered gene expression and as structural templates for oligonucleotide-based therapeutic agents. *See id.*

48. *See* Mark D. Adams et al., *Sequence Identification of 2,375 Human Brain Genes*, 355 NATURE 632, 632 (1992).

49. *See* NATIONAL RESEARCH COUNCIL, *supra* note 22, at 56-74.

50. *See* Bernadine Healy, *Special Report on Gene Patenting*, 327 NEW ENG. J. MED. 664, 665 (1992) (describing the reasons behind the NIH's decision to file the patent applications).

51. *See* Leslie Roberts, *Genome Patent Fight Erupts*, 254 SCIENCE 184, 184-86 (1991) (describing attempts by the NIH to obtain patents on a large number of ESTs without knowing the function of the gene fragments).

52. *See id.*

53. *See id.*

54. *See* Christopher Anderson, *NIH Drops Bid for Gene Patents*, 263 SCIENCE 909, 909 (1994).

technical questions regarding their patentability unresolved. However, the controversy surrounding the patentability of ESTs did not disappear. While the HGP concentrated its efforts on the sequencing of the entire human genome, privately funded corporations put a higher priority on sequencing expressed genes.[55] In 1992, Venter quit the NIH to head The Institute of Genome Research ("TIGR"), a not for profit DNA sequencing center. TIGR received its financial backing from Human Genome Sciences, Inc. ("HGS"), a privately funded, for profit corporation. By sequencing ESTs, companies such as HGS were in a position to sequence entire genes much faster than those using the conventional approach. A consortium of HGS and TIGR, with $125 million in financial backing from the pharmaceutical company SmithKline Beecham, amassed a database containing a large number of ESTs.[56] Concerns were expressed regarding possible attempts by HGS to patent EST sequences. In 1996, reports claimed that the consortium filed about 200 of the 450 applications for human gene patents.[57]

The issue of EST patenting became the focus of arguments regarding the release of DNA sequence data. Some accused TIGR and HGS of locking up their EST sequences and placing restrictions on academic researchers in return for access to the HGS database.[58] In addition, some researchers believed that restrictions placed upon the release of sequence data from the TIGR database would slow down research on pathogenic organisms.[59] The movement supporting the immediate release of sequence data culminated in a requirement that laboratories receiving grants from the NIH release preliminary human DNA sequence data quickly and without legal limitations.[60] The pharmaceutical company Merck & Co., SmithKline Beecham's

55. *See* Eliot Marshall, *A Showdown over Gene Fragments*, 266 SCIENCE 208, 208 (1994).

56. *See id*; Eliot Marshall, *The Company That Genome Researchers Love to Hate*, 266 SCIENCE 1800, 1800-01 (1994).

57. *See* Arthur L. Caplan & Jon Merz, *Patenting Gene Sequences: Not in the Best Interests of Science or Society*, 312 BRIT. MED. J. 926, 926 (1996).

58. *See* Eliot Marshall, *Is Data-Hoarding Slowing the Assault on Pathogens?*, 275 SCIENCE 777, 777, 779 (1997).

59. *See id.*

60. *See* National Human Genome Research Institute, *NHGRI Policy on Release of Human Genomic Sequence Data* (visited March 7, 1997) <http://www.nhgri.nih.gov/Grant_inf. . .g/ Statements/RFA/data_release.html>; *see also* Eliot Marshall, *Genome Researchers Take the Pledge: Data Sharing*, 272 SCIENCE 477, 477 (1996). The NIH also required that grantees notify them as soon as they inform their own institutions that a discovery may be patentable. *See id.* This policy has been extended to cover microbial genome sequences. *See* National Institutes of Health, *Data Release Policy: Microbial Genome Sequencing Projects* (visited March 17, 1999) <http://www.nih.gov/grants/guide/notice-files/ not99-040.html>.

main competitor, also announced that it would finance a duplication of the work already completed by HGS and TIGR, and that this data would be available without restriction. In 1997, TIGR announced that it had terminated its agreement with HGS and released its database of over 600,000 ESTs.[61] However, private corporations continued to compile EST sequences. For example, Incyte claims that it has an EST database consisting of three million EST sequences, 2.3 million of which are of priority to Incyte itself.[62] Incyte also claims to have the ability to process 28,000 ESTs per day.[63]

EST patentability issues resurfaced in early 1997 with an announcement by the United States Patent and Trademark Office (the "USPTO") that it would allow claims on ESTs based on their utility as probes.[64] At that time, reports claimed that at least 350 EST patent applications, covering more than 500,000 sequences, were pending at the USPTO.[65] However, the USPTO also acted to limit the number of sequences that could be claimed in any one application to ten. Hence, applicants wishing to patent a large number of ESTs would be required to file thousands of new applications. This greatly increased the transaction costs involved in obtaining DNA sequence patents.

Concerns remained about the possible impact of EST patents. Some of the filed applications claimed not only the EST sequences themselves, but also the complete sequences of the genes from which the ESTs were derived as well as the proteins coded from these genes.[66] Even where this was not so, some believed that the rush to make partial sequences public would undermine attempts to patent the complete gene sequences when these were determined. The USPTO added to these concerns by issuing a statement in 1998 stating that broad patent claims might be allowed for some ESTs.[67] Hence, claims for ESTs could, in some cases, give patent rights over a later discovered complete gene sequence.

61. *See* Emma Dorey et al., *TIGR Releases EST Data Publicly*, 15 NATURE BIOTECHNOLOGY 397, 397 (1997).

62. *See* Incyte Pharmaceuticals, Inc., *LifeSeq* (visited June 29, 1999) <http://www.incyte.com/products/lifeseq/lifeseq.html>.

63. *See* Incyte Pharmaceuticals, Inc., *Databases* (visited June 29, 1999) <http://www.incyte.com/products/databases.html>.

64. *See Gene Fragments Patentable, Official Says*, 275 SCIENCE 1055, 1055 (1997).

65. *See* Eliot Marshall, *Companies Rush to Patent DNA*, 275 SCIENCE 780, 781 (1997).

66. *See* Roberts, *supra* note 5, at 912-13.

67. *See* Dorothy R. Auth, *Are ESTs Patentable?*, 15 NATURE BIOTECHNOLOGY 911, 911 (1997); *see also* Ken Chahine, *Patent Office Resurrects EST Debate*, 16 NATURE BIOTECHNOLOGY 711, 711 (1998).

Such a situation has caused great concern that those who finally isolate a gene sequence would be required to pay royalties to the patentee of any EST sequence contained in that gene. This situation could slow the development of biotechnology, and it has caused many to call for the limitation of EST claims.[68] In late 1998, Incyte claimed to have received the first U.S. patent for an EST.[69] This patent claims polynucleotides and a full-length gene that encodes for protein kinases. However, the ESTs covered are unlike those in the original NIH application in that they are highly characterized. The full-length gene from which they are derived is identified, and its function is known. Nevertheless, the granting of this patent again renewed fears that overly broad proprietary rights would be granted to EST sequences.[70]

In May 1998, the debate over privately funded sequencing was renewed when Venter announced that he planned to form a new company, Celera Genomics, for the purpose of "substantially" sequencing the human genome in three years, at a cost of as little as $300 million.[71] The HGP's sequencing efforts are expected to cost ten times more. Venter's efforts are backed by $200 million in funding from Perkin-Elmer Corporation, the world's largest manufacturer of automated sequencing instruments.[72] He plans to use a technique, whole-genome "shotgun" sequencing, which TIGR has used to sequence several bacteria. The entire human genome will be broken up into segments of no more than 5000 bases. These segments will then be sequenced and assembled into the complete genome. The HGP groups work with much smaller sequences. They first break the genome up into sequences of 150,000 bases and then break each of these sequences into smaller fragments for sequencing.

Venter's approach has its critics. Shotgun sequencing has been

68. *See, e.g.*, Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation?: The Anticommons in Biomedical Research*, 280 SCIENCE 698, 698 (1998) (arguing for coherent boundaries of upstream patents to minimize restrictive licensing practices that interfere with product development).

69. *See* Tony Relchhardt, *Patent on Gene Fragment Sends Researchers a Mixed Message*, 396 NATURE 499, 499 (1998).

70. *See id.*

71. *See* Eliot Marshall & Elizabeth Pennisi, *Hubris and the Human Genome*, 280 SCIENCE 994, 994 (1998).

72. *See* Vicki Glaser, *PE/TIGR Provokes Genome Sequencing Skeptics*, 16 NATURE BIOTECHNOLOGY 610, 610 (1998); *see also* James C. Mullikin & Amanda A. McMurray, *Sequencing the Genome, Fast*, 283 SCIENCE 1867, 1867-68 (1999) (describing Perkin-Elmer's ABI Prism 3700 DNA analyzer, which is to be used by Venter's company in the sequencing efforts).

considered before and rejected for a variety of reasons.[73] Some claim that assembly of the genome will present considerable difficulties. Others complain that Venter's approach will leave more gaps in the genome than will conventional sequencing methods. In addition, others fear that Venter's group will attempt to patent their sequences. Venter rejected this objection. He says that his company will only patent 100 to 300 pharmacologically interesting genes, and thereafter genes will be patented only when clear uses have been identified. Partly to safeguard its claims, Celera intends to release sequence information quarterly instead of on a daily basis, as many publicly funded laboratories do. This approach has generated considerable criticism.

Venter's entry into the race to sequence the human genome, along with that of Incyte, has caused the HGP to reassess its goals and plan for a "working draft" of the human genome, constructed using shotgun sequencing, to be completed by 2001.[74] This deadline was later advanced by eighteen months.[75] In addition, Celera and a HGP group will join forces to sequence the genome of the fruit fly *Drosophila melanogaster*, and discussions are underway of a joint effort to sequence the human genome using whole-genome shotgun sequencing.[76]

The debate concerning the release of newly sequenced data shows no sign of coming to an end. The patentability of Single Nucleotide Polymorphisms ("SNPs") is considered by some to be likely to cause similar debate as was raised by ESTs.[77] SNPs are small variations in the genetic code that occur approximately once every 1000 DNA bases along the three billion, DNA base human genome.[78]

73. *See* Philip Green, *Against a Whole-Genome Shotgun*, 7 GENOME RES. 410, 410-16 (1997) (rejecting the use of whole-genome shotgun sequencing to sequence the human genome). *But see* James L. Weber & Eugene W. Myers, *Human Whole-Genome Shotgun Sequencing*, 7 GENOME RES. 401, 401-06 (1997) (supporting the use of whole-genome shotgun sequencing to sequence the human genome).

74. *See* Vicki Brower, *Genome II: The Next Frontier*, 16 NATURE BIOTECHNOLOGY 1004, 1004 (1998).

75. *See* Elizabeth Pennisi, *Academic Sequencers Challenge Celera in a Sprint to the Finish*, 283 SCIENCE 1822, 1822 (1999).

76. *See* Elizabeth Pennisi, *Fruit Fly Researchers Sign Pact with Celera*, 283 SCIENCE 767, 767 (1999).

77. *See, e.g.*, *"SNPs" Are Next Focus of Intellectual Property Debate Among Researchers*, 60 "The Pink Sheet" (F-D-C REP.) 23 (May 18, 1998) [hereinafter Pink Sheet] (reporting that NIH Director Harold Varmus considers that the patentability of SNPs is likely to be the next topic in the debate regarding the patentability of research tools).

78. *See* Elizabeth Pennisi, *A Closer Look at SNPs Suggests Difficulties*, 281 SCIENCE 1787, 1787 (1998).

A number of pharmaceutical companies are already reported to have taken steps to obtain databases containing SNP information.[79] Calls have been made for the immediate release of information in SNP databases with unconditional access. However, many consider it likely that at least some SNPs will be patented.[80]

SNPs offer researchers a valuable method for identifying genes associated with a given disease. They may be used in the same way as genetic markers were used during the isolation of the BRCA genes. Fears that SNPs could be patented have led to calls that a new repository of SNP information be set up and that this information should be freely available to the public.[81] Recently, a partnership, which was set up by large pharmaceutical companies, has announced that it will spend $45 million to archive SNPs and make this information freely available.[82]

II. THE PATENTABILITY OF DNA

The debate regarding the patentability of the BRCA genes and ESTs has centered on two questions. Firstly, does the DNA involved meet the statutory requirements for patentability? Secondly, even if this is so, are there other ethical or policy reasons that should prevent a patent from being granted?

A. The Statutory Requirements for Patentability

The first of these questions can be answered only after reviewing the statutory requirements for patentability and discussing how these standards have been applied. A U.S. patent confers a twenty-year exclusive right[83] to prevent others from making, using, selling, offering

79. *See* Sylvia Davidson, *Incyte SNPs Up Hexagen for New Firm*, 16 NATURE BIOTECHNOLOGY 895, 895 (1998) (discussing efforts by a consortium of companies to develop SNP databases at a cost of $150 to $200 million); Eliot Marshall, *Snipping Away at Genome Patenting*, 277 SCIENCE 1752, 1752 (1997) (discussing an agreement between Abbott Laboratories and the genomics company Genset, where Abbott would gain rights to markets of potential use in pinpointing genes involved in multi-gene diseases).

80. *See* Pink Sheet, *supra* note 77, at 23.

81. *See* Marshall, *supra* note 79, at 1752.

82. *See* Eliot Marshall, *Drug Firms to Create Public Database of Genetic Mutations*, 284 SCIENCE 406, 406 (1999).

83. Revisions in international trade laws in the General Agreement on Tariffs and Trade have resulted in the term of a U.S. patent being changed to 20 years, measured from the date the patent application is filed, rather than 17 years, measured from the date the patent is issued by the United States Patent Office. *See* Uruguay Round Agreements Act, Pub. L. No. 103-465, 108 Stat. 4809 (codified as amended at 19 U.S.C. § 3501 (1994)).

for sale, or importing the invention.[84] A patent may be obtained for certain classes of invention,[85] including chemical compounds like DNA molecules,[86] only when particular statutory requirements are met.

An invention must also have a known utility.[87] It must achieve some desired result and have at least some minimum social benefit. Traditionally, the potential role of a chemical compound for drug testing is not sufficient to meet the utility requirement.[88] Nor is the fact that it can be used to make another compound sufficient to meet the utility requirements unless some utility is shown for the final compound.[89] The BRCA genes would meet this requirement because of their potential use in the diagnosis of breast cancer. However, the utility of an EST is more questionable, especially if nothing is known about the genes from which it is derived.

An invention must also be novel to be patentable.[90] The prior art must not contain all the elements of the invention in a single reference.[91] In the case of a chemical compound, a chemical is not novel if it is present in nature.[92] However, purified preparations of naturally occurring biological products meet the novelty requirement if the compound was not previously available in an isolated or purified state and the purified product may be used in a way the impure product could not.[93] Purified partial and complete genes meet this requirement because isolation and purification of the DNA allows for uses that are not possible when the DNA is in its natural state.

In addition, patent protection cannot be obtained for an obvious

84. *See* 35 U.S.C. § 154 (1997).

85. Patents are given to the inventor of "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101 (1994).

86. *See* Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991) (stating that "[a] gene is a chemical compound, albeit a complex one"), *cert. denied*, 502 U.S. 856 (1991).

87. To be patentable, an invention must be "new and useful." 35 U.S.C. § 101.

88. *See* Brenner v. Manson, 383 U.S. 519, 534-35 (1966) (disallowing patent protection for a novel process of manufacture of certain known steroids, which had no known utility).

89. *See In re* Application of Joly, 376 F.2d 906, 908 (C.C.P.A. 1967) (rejecting product and process claims related to esters of 2-enols of steroids and the methods of their preparation on the basis of insufficient disclosure of utility).

90. *See* 35 U.S.C. § 102 (1994).

91. *See* Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 677 (Fed. Cir. 1988).

92. *See* Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 132 (1948).

93. *See In re* Application of Bergstrom, 427 F.2d 1394, 1400-02 (C.C.P.A. 1970) (allowing a patent for purified prostaglandin although structurally identical impure compounds existed in nature).

invention.[94] To determine whether an invention is obvious, the scope and content of the prior art, the differences between the prior art and the invention, and the level of ordinary skill in the pertinent art are considered.[95] Because of problems unique to chemicals, detailed subrules have developed to determine the non-obviousness of chemical inventions.[96] In particular, structural similarity between a claimed compound and prior art compounds may create a showing of prima facie obviousness.[97] If this is established, the burden of showing non-obviousness then shifts to the patent applicant,[98] and the burden may be met by showing that the claimed compound has unexpectedly improved properties over the prior art.[99] Hence, prima facie non-obviousness for a DNA molecule depends on a lack of similarity between the claimed molecule and DNA molecules previously disclosed. If this is not present, the inventor must show that the claimed DNA has unexpected properties.

Finally, the patent applicant must enable and supply a written description of the invention. Historically, the written description informed the public of what the inventor claimed as the invention.[100] This function was distinct from enablement, which required that those skilled in the art could use the invention without undue experimentation.[101] However, more recently, the written description requirement has been applied to require that the original patent

94. *See* 35 U.S.C. § 103 (1997). A patent will not be granted if the "differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." *Id.* § 103(a).

95. *See* Graham v. John Deere Co., 383 U.S. 1, 17 (1966) (developing the four-part obviousness test). The *Graham* court also suggested that secondary indications of obviousness, such as commercial success, long felt but unsolved needs, or failure of others might be used to "give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id.* at 17-18.

96. *See, e.g.*, Chris P. Konkol, *The "Problem Solved" In Re Wright and In Re Dillon*, 31 IDEA 131, 131-32 (1990); Helmuth A. Wegner, *Prima Facie Obviousness of Chemical Compounds*, 6 AM. PAT. L. ASS'N Q. J. 271, 271 (1978).

97. *See In re* Dillon, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc), *cert. denied*, 500 U.S. 904 (1991). Closely related homologs, analogs, and isomers may create prima facie obviousness. *See id.* at 696.

98. *See id.* at 692.

99. *See id.*

100. *See generally* Janice M. Mueller, *The Evolving Application of the Written Description Requirement to Biotechnological Inventions*, 13 BERKLEY TECH. L. J. 615 (1998) (describing the historical development of the written description requirement).

101. *See id.* at 616-17; *see also In re* Application of Fisher, 427 F.2d 833, 836 (C.C.P.A. 1970). Whereas compliance with the enablement standard is a matter of law, compliance with the written description requirement is a matter of fact. *See* Fiers v. Revel, 984 F.2d 1164, 1170 (Fed. Cir. 1993).

claims are supported by sufficient detail so that new claims or modifications to the original claims can be determined to be encompassed by the original invention.[102]

The written description requirement[103] is not met unless the specification describes the invention in sufficient detail so that one skilled in the art would reasonably consider that the inventor was in possession of the claimed subject matter.[104] In the case of a chemical compound, the written description requirement may not be met even though sufficient information is disclosed to enable one skilled in the art to produce and use a claimed compound.[105] The specification must convey clearly to those skilled in the art that the inventor invented that specific compound.[106] Hence, the written description requirement may be met by setting forth the chemical structure of a compound.[107] Alternatively, the requirement may be met by describing sufficient properties of the compound that allow predictability of the chemical structure by one skilled in the art.[108]

B. The Application of Patentability Standards to DNA

The task of applying the statutory requirements to DNA has fallen to the Court of Appeals for the Federal Circuit (the "Federal Circuit"). So far, the Federal Circuit has applied the obviousness and written description requirements to DNA in a way that allows those who determine the complete structure of a gene to obtain patent protection despite the previous disclosure of partial DNA sequences from the gene. The court has also limited the scope of sequence claims by placing requirements on the ways in which a DNA sequence must be adequately described in the patent specification.

102. *See In re* Application of Ruschig, 379 F.2d 990, 994-95 (C.C.P.A. 1967).

103. The specification of a U.S. patent must contain "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same." 35 U.S.C. § 112 (1994).

104. *See Fiers*, 984 F.2d at 1170.

105. *See In re* Application of Ahlbrecht, 435 F.2d 908, 911 (C.C.P.A. 1971).

106. *See Ruschig*, 379 F.2d at 996.

107. *See* Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572 (Fed. Cir. 1997).

108. *See* Kennecott Corp. v. Kyocera Int'l, Inc., 835 F.2d 1419, 1421 (Fed. Cir. 1987). In *Kennecott*, a patent applicant originally disclosed "ceramic bodies" without disclosing their later claimed "equiaxed microstructure" property. *Id.* at 1423. The Federal Circuit held that the "equiaxed microstructure" property was supported by the original specification because such a structure was an inherent property of the "ceramic bodies" originally disclosed. *See id.*

1. Obviousness

The Federal Circuit has treated DNA as a chemical composition and applied chemical case law based on structural similarity when determining the non-obviousness of a DNA molecule.[109] However, because of the degeneracy of the genetic code,[110] where more than one DNA sequence may code for a given protein, the court has held that the prior art disclosure of a full or partial amino acid sequence does not necessarily render the DNA sequence coding for that amino acid sequence obvious.

In *Deuel*, the court found the existence of a general method of isolating DNA molecules to be "essentially irrelevant" as to whether the specific DNA molecules would have been obvious without other prior art suggesting the claimed DNA molecules.[111] The court stated that a case for obviousness is normally based on structural similarity between the claimed compound and a prior art compound.[112] Thus, the combination of a reference disclosing a partial amino acid sequence for a protein together with a reference teaching a general method of DNA cloning did not render DNA molecules coding for the protein obvious.[113] The redundancy of the genetic code meant that a great number of possible DNA molecules could have coded for the protein.[114] Hence, there was no motivation to prepare the specific DNA claimed.[115]

Deuel has been criticized extensively for taking a standard of obviousness suited to chemical compounds and mistakenly applying that standard to the protein/DNA relationship.[116] According to this rationale, it is wrong to treat DNA as a simple polymer of nucleic

109. *See Amgen*, 927 F.2d at 1207-09.

110. *See* SCHLEIF, *supra* note 1, at 183-218 (describing the process of protein synthesis). Proteins comprise a chain of amino acids, 20 of which exist in nature. *See id.* at 150-51. Each amino acid is coded for by a series of three DNA bases, called a "codon." *See id.* at 188-90. More than one codon may code for a particular amino acid. *See id.* at 189.

111. *In re* Deuel, 51 F.3d 1552, 1559 (Fed. Cir. 1995).

112. *See id.* at 1558.

113. *See id.* at 1557.

114. *See id.* at 1158.

115. *See id.* at 1559. However, the court noted that for simple proteins of small size or proteins lacking in redundancy each possible DNA may be obvious over the protein sequence. *See id.* For example, a prior art genus of 20 compounds rendered every species within the genus unpatentable. *See id.*

116. *See, e.g.*, Anita Varma & David Abraham, *DNA Is Different: Legal Obviousness and the Balance Between Biotech Inventors and the Market*, 9 HARV. J.L. & TECH. 53, 78-79 (1996). Some argue that a "suggestion" test be applied to establish the elements of a prima facie case of obviousness where less emphasis is given to the protein/DNA structural relationship. *See id.* at 78-84.

acids because, unlike traditional polymers, minor changes in the base structure of DNA can produce major changes in function.[117] *Deuel* has also been criticized for effectively ignoring the non-obviousness standard and awarding patent protection where the methods available to determine the structure of the DNAs were "obvious to try" and were performed with a "reasonable expectation of success."[118]

However, the criticism of the *Deuel* decision has not been universal. Many in the biotechnology industry support the decision as giving necessary protection to new biotechnology inventions.[119] Even some that are critical of the *Deuel* outcome have recognized that the court had little alternative if it wanted to protect new products and prevent damage to the growth of the industry.[120] They claim that *Deuel* allows those who isolate DNA sequences using "routine" methods to obtain patents for their inventions; this encourages further research. The holding also allows those who determine the complete structure of a gene to obtain patent protection although the DNA sequence of a small part of the gene was present in the prior art.

2. Written Description

In *Fiers v. Revel*, when determining whether an inventor had conceived[121] a DNA sequence, the Federal Circuit held that the conception of DNA, like the conception of any other chemical, required a definition of the molecule other than by its functional utility.[122] Conception does not occur until the inventor has "a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it."[123] Definition of the compound by its principal biological property is not sufficient.[124]

117. *See id.* at 67-68.

118. Philippe Ducor, *The Federal Circuit and In Re Deuel: Does § 103 Apply to Naturally Occurring DNA?*, 77 J. PAT. & TRADEMARK OFF. SOC'Y 871, 889-890 (1995).

119. *See, e.g.*, D.D., *U.S. Court Rules Discovery of Gene Sequence "Not Obvious,"* 375 NATURE 94, 94 (1995) (reporting on the response of the Biotechnology Industry Association to the *Deuel* decision).

120. *See* Ducor, *supra* note 118, at 898.

121. Conception of an invention requires the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1376 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987).

122. *See Fiers*, 984 F.2d at 1169.

123. *Id.* (quoting *Amgen*, 927 F.2d at 1206).

124. *See id.* at 1168-69.

If conception of a DNA molecule requires a precise definition, then the written description also requires such specificity.[125] The court also rejected a requirement that conception of a DNA molecule requires knowledge of the DNA sequence only where isolation of the DNA is difficult.[126] The sequence must be disclosed irrespective of the difficulty of the method of isolation of the DNA.

In *Regents of the University of California v. Eli Lilly & Co.*, the court again addressed the issue of the written description required to support claims directed at cDNA sequences.[127] A claim for an organism containing cDNA coding for human insulin was held invalid for lack of an adequate written description.[128] Although the specification contained a general method for obtaining human cDNA along with the amino acid sequences for human insulin, no information regarding the cDNA's structural or physical features was present.[129] Because the cDNA was not described in the patent disclosure, the written description was inadequate.[130]

Some criticize the decision in *Eli Lilly* as involving a significant deviation from the status quo and a heightening of the patentability requirements for biotechnological inventions.[131] In addition, the requirement that the DNA structure be disclosed is criticized as placing an unnecessary restriction on the manner in which the compound may be described.[132] Some also consider that, while the decision will not affect recently filed patents, many patent rights secured by early pioneers in the field may be ruled as invalid.[133] However, *Eli Lilly* does limit the breadth of DNA sequence claims. In doing so, the decision prevents inventors from overreaching by claiming more than they have disclosed. This is especially important in the case of ESTs because disclosure of an EST sequence may be

125. *See id.* at 1171.

126. *See id.* at 1168. The defendant in *Fiers* argued that the examiner had incorrectly interpreted *Amgen* as requiring that conception required knowledge of the DNA in all cases. *See id.* In particular, the defendant claimed that *Amgen* was distinguishable because of the great difficulty in determining the DNA sequence in that particular situation. *See id.* In contrast, the defendant claimed that his method of determining DNA sequences could have been easily carried out by one of ordinary skill in the art. *See id.*

127. Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1562 (Fed. Cir. 1997).

128. *See id.* at 1567.

129. *See id.*

130. *See id.*

131. *See, e.g.*, Mueller, *supra* note 100, at 615.

132. *See id.* at 633.

133. *See* Harris A. Pitlick, *The Mutation on the Description Requirement Gene*, 80 J. PAT. & TRADEMARK OFF. SOC'Y 209, 222-23 (1998).

followed by an attempt to claim the full gene from which the EST is derived. The decision also limits the breadth of claims for full gene sequences. In the case of a gene such as BRCA1, the disclosure of a particular sequence will not allow the inventor to claim mutations of the gene.

III. THE PRESENT STATUS OF DNA PATENTABILITY

The establishment of standards for the written description and non-obviousness of DNA sequences has resulted in greater predictability in the requirements that must be met before these sequences may be patented. For example, when the full DNA sequence for a protein of known utility is known, patent protection may be obtained if the other statutory requirements are met. Although many other issues remain to be resolved regarding attempts to patent DNA sequences, the present standards do provide a basis to examine the concerns surrounding the BRCA and EST issues.

A. BRCA Mutations—Multiple Patents on a Single Gene

The issues surrounding the patenting of the BRCA genes center on two questions. The first concerns at what stage of the development process should patent protection be given. The second issue involves the breadth of patent protection given. Should a mutation of a gene that is already in the public domain be patentable?

Myriad obtained a patent on the BRCA1 sequence because it was the first to describe the complete DNA sequence of the gene. Such an outcome is clearly in line with *Eli Lilly*, but is criticized because no reward is available for those who contributed at an earlier stage on the isolation of the gene. Such contributions may range from genetic linkage studies that allowed the initial location of the gene to a specific region of a particular chromosome to the development of SNPs or ESTs used in the final isolation of the gene. However, if patent protection is available for an EST corresponding to a fragment of the BRCA1 gene, or a SNP that is shown to be correlated to the incidence of breast cancer, this would not be so. In addition, claims limited to the sequence disclosed, as required by *Eli Lilly*, would allow for patent protection for the later disclosed complete gene sequence.

In view of the holding in *Deuel*, it is unlikely that a full-length gene sequence would be considered obvious on the basis of its

structural similarity to a single EST sequence that was not previously identified with that specific gene. It would be impossible to predict the entire gene structure from such a sequence. However, when multiple ESTs belonging to the same gene have been previously disclosed, there may come a point when the full gene sequence is considered as being obvious in light of the EST sequences.[134] This is even more likely to be the case where there is some suggestion in the prior art that one or more ESTs were associated with the complete gene.

Despite the holding in *Deuel*, the previous disclosure of a complete gene sequence may make a mutation of the gene prima facie obvious. However, even if this is so, non-obviousness can be demonstrated by showing unexpected properties of the mutated gene, such as a correlation to disease susceptibility. Hence, patent protection for a mutation is supported when the mutation is related to a disease state. In the case of harmful BRCA mutations, which are shown to be correlated to the incidence of breast cancer, non-obviousness is clearly supported.

Patent protection for nonharmful mutations that are present in the "normal" population is more difficult to support. However, the OncorMed patent covering a "consensus normal DNA sequence" stated that, by allowing naturally occurring nonharmful mutations to be identified, this sequence offered greater accuracy and reliability for genetic testing than did the previously disclosed Myriad BRCA1 sequence. Here, the advantages offered by the OncorMed sequence clearly overcame any presumption of obviousness due to structural similarity between the two sequences.

The case law developed by the Federal Circuit in its application of the statutory requirements for patentability clearly allow for multiple patents to be granted on a single gene. As has occurred with the BRCA1 gene, different inventors may obtain patents on sequences differing only slightly. Such a situation is likely to lead to more litigation like that which occurred between Myriad and OncorMed. However, these situations may be resolved by cross-licensing agreements between the holders of the patents, as occurred here. The alternative is to grant broad patent protection to the inventor who first isolates a gene and then hold all mutations to this gene obvious. This would be an unacceptable alternative because it

134. This could be so independently of whether patents were obtained for the EST sequences.

would not provide incentives for inventors to pursue further research.

B. *The Patentability of Expressed Sequence Tags*

As stated previously, many consider ESTs to have great commercial value because they may be used to help isolate the full gene sequence.[135] However, objections to the patentability of ESTs have centered on claims that they lack utility.[136] Recently, as a result of the decisions in *Eli Lilly* and *Fiers*, the USPTO has announced that patents directed at ESTs will be examined.[137] If such patent applications are granted, it is possible that the Federal Circuit will eventually have the opportunity to resolve long-standing differences regarding whether ESTs meet the utility requirement.[138]

Claimed utilities for an EST include its use as a diagnostic marker for the gene of which it is a part.[139] However, until this gene is identified and shown to have a practical utility, patent protection for such ESTs may not be allowed.[140] But an EST may also be used to isolate a complete gene, and this function may provide the utility necessary for patentability of an EST derived from an unidentified gene. Thus, the question of EST utility depends on the particular facts of the application in question. If, as in the case of the Incyte "EST" patent, the full sequence of the corresponding gene is known as well as the function of the protein coding from this gene, the utility

135. *See, e.g.*, Marshall, *supra* note 55, at 208 (discussing databases of DNA fragments compiled by private concerns with the hope that these sequences will be useful in identifying disease genes and mapping active sites on the human genome).

136. *See, e.g.*, Leslie Roberts, *Top HHS Lawyer Seeks to Block NIH*, 258 SCIENCE 209, 209 (1992).

137. *See* John J. Doll, *The Patenting of DNA*, 280 SCIENCE, 689, 690 (1998) (stating that the USPTO views the examination of patent applications for ESTs and SNPs as analogous to any other invention); *see also* Vincent Kiernan, *Furore in U.S. over Patents for "Bit Part" DNA*, NEW SCIENTIST, Feb. 22, 1997, at 11, 11.

138. *See* Thomas D. Kiley, *Patents on Random Complementary DNA Fragments?*, 257 SCIENCE 915, 915-17 (1992). Kiley argues that the NIH's EST patent application was an attempt to obtain control over the "raw material of scientific experimentation before research has determined the practical value of such material." *Id.* at 915. Similarly, Poste argues that "[o]pposition to the patenting of genomic inventions threatens to erode the foundation of intellectual property rights needed to convert innovative research into new drugs, vaccines and diagnostic tests." Poste, *supra* note 6, at 534.

139. For a detailed discussion of the NIH's EST patent application and an opinion regarding the patentability of the disclosed DNA fragments, see Rebecca S. Eisenberg & Robert P. Merges, *Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences*, 23 AIPLA Q. J. 1, 13-14 (1995).

140. *See Brenner*, 383 U.S. at 535 (stating that a compound does not meet the utility requirement by being used in research concerning another compound unless the later compound has a known utility).

requirement will almost certainly be found to be met. However, if no information regarding the nature of the complete gene is available, an EST could be considered as being a chemical intermediate for a compound with no known function. In such a situation, precedent would suggest that the EST is not patentable. Nevertheless, supporters of gene patenting have argued that, because such ESTs are sold commercially as tools for the identification of complete genes,[141] they have an immediate benefit and should be subject to patent protection even if the function of these genes is unknown.[142] However, even accepting that a library of ESTs has commercial value, some sequences in the library are likely to be valuable as markers and some are not. If no indication of the proven utility of a particular sequence is disclosed, a significant amount of experimentation is still required to determine the ultimate utility of that sequence. This may preclude the granting of patent rights and provide a mechanism to protect against premature claims.

If patent protection is granted to particular EST sequences, the scope of this protection must be determined. The USPTO's view is that broad sequence claims for ESTs may be supported.[143] Given the Federal Circuit's reluctance to uphold broad DNA patent claims in *Eli Lilly*, it is likely that the court will reject such broad EST claims.[144] However, such a decision is likely to be years away; until then, much uncertainty will remain as to the proper scope of EST patent protection. Although those involved in testing for mutations of a gene may prevent infringement by avoiding a patented EST sequence or by altering the sequence in the EST region, the risk of multiple damages may have a chilling effect on future biotechnology product development.

The patentability of SNPs[145] is likely to cause similar debate as was raised by ESTs.[146] A number of pharmaceutical companies are already reported to have taken steps to obtain databases containing

141. *See, e.g.*, Jon Cohen, *The Genomics Gamble*, 275 SCIENCE 767, 771 (1997). For a report on the $125 million agreement between SmithKline Beecham and HGS, which will allow SmithKline Beecham access to HGS's database of DNA sequences, see *id.* at 768.

142. *See, e.g.*, Poste, *supra* note 6, at 534-36 (arguing that ESTs have commercial value in diagnostic tests for altered gene expression in disease states).

143. *See* Chahine, *supra* note 67, at 711.

144. *See id.*

145. SNPs are single base variations in the genetic code that occur approximately once every 1000 bases along the three-billion-base human genome. *See* Elizabeth Pennisi, *A Closer Look at SNPs Suggests Difficulties*, 281 SCIENCE 1787, 1787 (1998).

146. *See* Pink Sheet, *supra* note 77, at 23-24.

SNP information.[147] Such information may provide a means of locating genes causing disease susceptibility in the same way that the BRCA genes were isolated. Calls have been made for the immediate release of information in SNP databases with unconditional access; however, many consider it likely that at least some SNPs will be patented.[148]

Although some SNPs may be of great value because they represent important mutations that may be used to identify either those persons susceptible to particular diseases, or those who will best respond to a given therapy, others are likely to be useless.[149] Hence, attempts to patent SNP sequences raise the same problems of utility as do attempts to patent ESTs. Unless a particular SNP is shown to have a definite utility, the sequence does not meet the requirements for patentability. Such utility may be shown if the sequence is linked to a specific disease or is shown to be expressed in such a proportion of the general population to make it useful in some other way.

In addition to questions of utility, a claim for a SNP sequence may be rejected if the sequence is obvious in view of a prior art sequence. For example, if the DNA sequence coding for a particular protein is in the prior art, a sequence corresponding to a similar protein with one amino acid different may be considered as being prima facie obvious.[150] However, such a finding may be rebutted if it is shown that the claimed sequence shows "unexpected results" by the establishment—that differences in properties are of some practical advantage.[151] Although the presence of the sequence at a high frequency in the general population may not be sufficient to establish non-obviousness, the identification of a specific disease or susceptibility of a particular form of therapy with the mutation is more likely to rebut the initial showing of obviousness.[152]

147. *See* Davidson, *supra* note 79, at 895; Marshall, *supra* note 79, at 1752-53.

148. *See* Pink Sheet, *supra* note 77, at 23.

149. *See id.*

150. The U.S. Patent and Trademark Office Board of Patent Appeals and Interference has rejected a DNA coding for h-Interleukin-3 as obvious in view of a prior art DNA having a single amino acid substitution at a single position. *See Ex parte* Anderson, 30 U.S.P.Q.2d 1866, 1869-70 (1993). The board's decision specifically noted that the substitution did not produce a significant change in the chemical composition of the molecule. *See id.* at 1869. In addition, the board rejected the claim that the chemical properties of the invention differed from the prior art simply because it was present at a high frequency in the general population. *See id.* at 1870.

151. *See id.* at 1869.

152. *See id.* at 1969-70.

IV. DO DNA SEQUENCE PATENTS PROMOTE NEW PRODUCT DEVELOPMENT?

Even if DNA meets the statutory requirements for patentability, some argue that, at least for some forms of DNA, patent protection should not be granted. Such objections have taken a variety of forms. Many raise the concern that, particularly in the biotechnology area, the granting of patents with broad claims and the "stacking" of patent royalties will inhibit research and slow the development of new products.[153] These objections are not specific to the patenting of DNA sequences, but have been raised in many other areas of biotechnology.[154] Others limit objections to the patenting of specific forms of DNA, like ESTs and SNPs, on the basis that such patents will inhibit scientific progress by limiting cooperation between researchers. Finally, some researchers claim that, because of the unique nature of the international cooperation involved in the HGP, patent protection should not be granted for human DNA sequences.

In their widest form, objections to the patenting of the results of "basic" research raise the concern that these patents may have a stifling effect on the downstream development of products based upon this research.[155] Such concerns are said to be particularly relevant when the research leads to multiple owners of patent rights, resulting in overlapping patent claims. Alternatively, the existence of multiple patents, each covering a different aspect of a biotechnology product, may result in the stacking of patent licenses, leading to significant increases in the cost of the final product. These concerns are relevant to DNA patents in a number of areas. For example, conflicting rights and the stacking of royalties may occur if patents are granted for multiple ESTs present in the same gene. This is especially true if broad EST patents allow those who patent an EST to obtain patent rights over the full gene. In addition, even if a complete gene is patented, others may obtain patents for slightly different forms of the same gene, as happened with the BRCA1 gene.

However, assuming that the patent concept does contribute to scientific innovation and offers benefits to society, patent protection

153. *See* Richard Stone, *Sweeping Patents Put Biotech Companies on the Warpath*, 268 SCIENCE 656, 657 (1995) (discussing the response to the granting of a patent covering all forms of genetically engineered cotton).

154. *See* Melvin Blecher, *Dominating Patents: A View from the Bridge*, 34 CLINICAL CHEMISTRY 1705, 1705-08 (1988) (reviewing the response of the immunodiagnostics industry to broad patents).

155. *See* Heller & Eisenberg, *supra* note 68, at 698.

must start at some stage. With the BRCA genes, the identification of the gene sequence was the chosen boundary. Here, upstream property rights were limited. The final reward went to Myriad because of the isolation of the BRCA genes. The objections raised here went to the lack of reward to those who were involved in the early stages of the search for the genes. Neither those who contributed the DNA samples necessary for the initial linkage studies nor those who performed the initial work on isolating the gene were rewarded with property rights in the final test.

Two alternative solutions are available in a situation such as that which occurred with BRCA1. First, patent rights could be withheld. This could perhaps be justified on the grounds that the public provided the samples that made the isolation of the gene possible. Also, because significant public funding was provided to those involved in the linkage studies, the withholding of patent rights is justified because the public has already "paid" for the invention. However, this viewpoint ignores the reality that Myriad succeeded partly because of its superior funding. This funding was provided based on the availability of patent protection for the products developed. If such protection is not available, small biotechnology companies such as Myriad are unlikely to be successful when competing against larger players with superior production, distribution and marketing resources.

The other alternative is to reward those who contributed earlier in the race to isolate the BRCA genes. From the point of view of fairness, this is an attractive option. However, the arguments raised by the patenting of research tools would apply in this situation. This approach also ignores the fact that many groups were engaged in a race to identify the gene. Some, including Myriad, were motivated by the prospect of obtaining intellectual property rights. To give rights to all involved negates the purpose of the patent system. Those objecting to the granting of similar DNA sequence patents to Myriad and OncorMed raise this argument. If sequence patents are narrow and easy to circumvent, they are probably not worth much. Narrow property rights are unlikely to result in the funding necessary to provide new biotechnology products.

Such arguments have additional force when applied to the patentability of ESTs. Here, even if one assumes that publicly funded sequencing efforts should not apply for patent protection, private efforts by companies such as TIGR and Incyte have contributed

significantly to advances in sequencing technology. These efforts have caused the HGP to refocus its efforts, leading to plans for a more efficient and faster sequencing of the human genome. Without the private funding, obtained on the promise of future patent protection, those innovations would not have been possible. This factor strongly supports a claim that for DNA sequences the patent system is achieving its primary aim of promoting new innovation.

Questions remain about the stage at which patent protection should be given and to the appropriate breadth of that protection. Clearly, a patent application like the NIH's EST application raises many concerns. However, this application is by no means typical. Although a final determination as to the patentability of the sequences was not made, serious doubts exist because of a lack of utility. In addition, because of restriction requirements placed on the number of sequences from different genes that may be claimed in one application, future applications claiming such a great number of sequences could be split into numerous applications, greatly increasing the cost to the applicant. This factor by itself is likely to significantly reduce applications containing many unrelated sequences of uncertain utility. Hence, as applied to ESTs, the present patentability requirements offer an adequate solution to the problem of promoting invention by creating incentive without offering patent protection at too early a stage.

The rules developed by the Federal Circuit also provide a suitable framework for determining the appropriate breadth of patent protection. In the case of ESTs, application of the written description requirement will likely result in claims being limited to the EST sequence itself when the full gene structure is not disclosed. In addition, under *Deuel*, incentive remains for those who go on to discover the structure of the complete gene. When a complete gene, such as BRCA1, is patented, protection against trivial sequence changes should be given. Also, subsequently discovered mutations that provide the basis for improved diagnostic or therapeutic products should be protected.

CONCLUSIONS

Attempts to fit DNA sequence claims into the conventional patentability framework developed for chemicals have raised questions as to whether these criteria are applicable to DNA. Despite this, over the past ten years, no new patentability rules have

been developed for application to DNA sequences. Instead, DNA patentability issues, such as those raised surrounding the BRCA genes and ESTs, are in the process of being resolved using conventional patentability criteria.

Many issues remain, particularly regarding ESTs, but questions regarding utility look likely to be resolved on a case-by-case basis. The questions to be answered involve the breadth of claims allowed for ESTs rather than whether protection should be given. Private funding, attracted by the prospect of profitable new products, has played an important part in the success of sequencing efforts, and there are strong indications that this will be even more so in the future. Such funding probably would not be available without a strong patent system.

A strong argument can be made for the immediate release of sequence data generated by publicly funded organizations. These organizations have often taken this approach and, in many cases, not applied for patent protection. However, such requirements should not be imposed upon the private sector. A strong patent system is essential for the development of biotechnology. Nothing suggests that the situation is any different in regard to the specific issue of DNA sequence patents.