Research in the Shadow of DNA Patents

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I. INTRODUCTION

To many observers, the past twenty-five years of intellectual property jurisprudence appear to have installed the *en masse* patenting of DNA molecules as a fixture on the biotechnology landscape. Since the U.S. Supreme Court's 1980 *Diamond v. Chakrabarty* decision,[1] in which the Court ruled that a genetically-altered bacterium is a "nonnaturally occurring manufacture or composition of matter" eligible for a U.S. patent,[2] the issuance of patents on genetic material has become commonplace. Decisions of the Federal Circuit, established in 1982, have consistently held that "isolated and purified" DNA molecules excised from genes are patentable if they are useful, novel, nonobvious and adequately disclosed.[3] Accordingly, in recent years the burgeoning biotechnology industry has filed thousands of patent applications, and the Patent Office has issued thousands of patents, claiming millions of DNA molecules.[4] By 2001, with DNA patenting already in high gear, the Patent Office issued detailed guidelines for the examination of DNA patent applications that restated the legal doctrines governing patentability and characterized the law as essentially settled.[5]

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[1] 447 U.S. 303 (1980).

[2] Id. at 309-310.

[3] *See, e.g.*, In re Deuel, 51 F.3d 1552 (Fed. Cir. 1995); In re Bell, 991 F.2d 781 (Fed. Cir. 1993). Dissents from the Federal Circuit doctrines discussed in this Article have been limited to a small minority of the court. *See infra* note 200.

[4] *See* Derwent GENESEQ <http://www.derwent.com/geneseq/> (visited September 15, 2002).

[5] United States Patent & Trademark Office, Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001) [hereinafter Utility Guidelines].

Specifically, the Patent Office has concluded that the constitutional purpose of "promot[ing] the Progress of . . . useful Arts"[6] is advanced by the awarding of a patent to one who discloses the structural formula for a DNA molecule with a specific, substantial and credible utility, "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."[7]

Many observers of the patent system have warned of the public costs of DNA patenting, citing serious consequences ranging from the obstruction of downstream pharmacological research to the commodification of human bodies and identities. These commentators have provided valid and important insights into the tensions between the patenting of DNA molecules and principles of ethics, political economy, and natural law. To date, however, they have generally been unable to engage the patent system on the legal question of DNA patentability,[8] because they have failed to challenge the critical factual assumption that DNA patents promote the discovery and disclosure of structural formulae for new, nonobvious and useful DNA molecules.[9]

The aim of this Article is to call this assumption into question and thereby to renew the debate over DNA patenting. The critical points of engagement for this renewed debate will most likely be patent claims directed to very short single strands of DNA, otherwise known as *oligonucleotides*.[10] An oligonucleotide can be used to *probe* for the presence of DNA molecules containing a complementary subsequence. This probing capability can be used in many ways, for example, to test for the presence of DNA sequences that are known to be associated with certain biological functions, and to target chemical reactions to specific DNA molecules.[11] These procedures can lead to the discovery of other new and useful oligonucleotides.[12] Because oligonucleotide patent

[6] U.S. CONST., art. I, § 8, cl. 8.

[7] Utility Guidelines, *supra* note 5, at 1094 cmt. 5; *see generally* section III.A (surveying legal justifications and critiques of the patent bargain).

[8] *See infra* section III.E; *cf.* Donna M. Gitter, *International Conflicts Over Patenting Human DNA Sequences in the United States and the European Union: An Argument for Compulsory Licensing and a Fair-Use Exemption*, 76 N.Y.U. L. REV. 1623, 1651 (2001) (concluding that "arguments against the patentability of human DNA sequences, per se, are a dead letter under U.S. law"); *but see infra* note 200 (noting that the Federal Circuit remains divided on the doctrinal distinction between structural and methodological disclosure of DNA molecules).

[9] *See infra* text accompanying notes 191-196.

[10] For simplicity, throughout this Article we will use the term "oligonucleotides" in place of the more specific term "oligodeoxynucleotides."

[11] *See infra* text accompanying notes 216-227.

[12] *See infra* section IV.B.

claims are typically drafted in open-ended terms, they usually also cover all of the longer DNA molecules that include the recited oligonucleotides. Accordingly, oligonucleotide claims are among the broadest and most preclusive claims that frequently appear in DNA patents.

Specifically, this Article applies theoretical and empirical results from bioinformatics to establish nontrivial upper bounds on the efficacy of research procedures in the case where scientists are precluded from using certain oligonucleotides. Today's oligonucleotide patents may impair these procedures, thereby delaying or preventing the discovery of additional patentable oligonucleotides tomorrow. Oligonucleotide patents therefore present policy tradeoffs not only between private research incentives and the public domain, but also between current and future innovation within the same field of research. To the extent that the granting of DNA patents is said to promote "Progress" in the field of oligonucleotide research, this Article provides initial quantitative evidence that any such "Progress" will be inherently self-defeating. As the first systematic effort to quantify the preclusive effects of DNA patenting on specific laboratory procedures in genetic research, this Article serves to initiate the necessary task of identifying and mapping the technological fault lines on which current DNA patent doctrine uneasily stands.

The remainder of this Article is organized as follows. Part II introduces relevant concepts from genetics and biotechnology. Part III reviews critical commentary on the patenting of DNA molecules and the patent system's response to this controversy. Part IV surveys several specific laboratory procedures that utilize oligonucleotides and examines the extent to which the performance of two such procedures, sequencing by hybridization and cluster analysis of gene expression data, may be degraded as a result of DNA patenting. Part V concludes by identifying some directions for future research.

II. Some Principles and Applications of Biotechnology

A. The Structure and Function of DNA Molecules

The entire collection of genetic material of a particular organism is known as its "genome." Each cell in an organism contains a copy of the same genome, in the form of a set of structures called "chromosomes," which are made up of DNA. A DNA molecule consists of two long chains, or "strands," each made up of smaller molecules called "nucleotides." Each nucleotide consists of a sugar ("deoxyribose"), a phosphate, and a base. There are four kinds of bases: adenine ("A"), thymine ("T"), cytosine ("C") and guanine ("G"). Each base has a

unique complement: in a DNA molecule, an A on one strand is always paired with a T on the other, and a C on one strand is always paired with a G on the other (and vice versa).[13] The order of bases occurring along one strand of a DNA molecule is referred to as the molecule's "structural formula," "nucleotide sequence" or "DNA sequence."[14] The last term is also sometimes used to refer to the DNA molecule itself.[15]

Numerous variations, or "polymorphisms," exist among the genomes of different individuals of the same species. Some of these variations occur in the form of "single nucleotide polymorphisms" (SNPs), regions in the genome where there is a difference of only one nucleotide in a longer sequence of nucleotides.[16] As recognizable markers of individuality in the human genome, SNPs can serve as the basis for the study of statistical associations between DNA sequences and the prevalence of disease among different individuals.[17]

The two ends of each strand of a DNA molecule are distinguishable in that the sugar at one end (the "5' end") has a free fifth carbon atom and the sugar at the other end (the "3' end") has a free third carbon atom.[18] The sequence of each strand is the order of bases in the strand, reading from the 5' end to the 3' end. Two strands can join, or "hybridize," to form a DNA molecule (the familiar "double helix") if, when the 5' end of each strand is aligned with the 3' end of the other, there is a correspondence of complementary base pairs between their two sequences. Since the sequence of each strand can be inferred from the other by reversing the sequence and replacing each base with its complementary base, such sequences are called "reverse complements."

Closely related to DNA molecules are ribonucleic acid ("RNA") molecules. Although RNA and DNA encode essentially the same genetic sequence information, RNA molecules differ chemically from DNA molecules in that their nucleotides use a different base, uracil ("U") instead of thymine ("T"), as the complement of adenine ("A"). RNA molecules also use a different sugar, ribose instead of deoxyribose.

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[13] *See generally* J.D. WATSON ET AL., MOLECULAR BIOLOGY OF THE GENE (1987).

[14] *See* Oak Ridge National Laboratory, *Genome Glossary* <http://www.ornl.gov/TechResources/Human_Genome/glossary/> (visited June 17, 2002) (defining DNA sequence as "The relative order of base pairs, whether in a DNA fragment, gene, chromosome, or an entire genome.").

[15] *See, e.g.*, U.S. Patent No. 5,935,837, claim 13 (issued Aug. 10, 1999) (using the language "[a]n isolated and purified DNA sequence" to claim an isolated and purified DNA molecule).

[16] *See* DESMOND S.T. NICHOLL, AN INTRODUCTION TO GENETIC ENGINEERING 175 (2002).

[17] *See id.*

[18] *See* JOAO SETUBAL & JOAO MEIDANIS, INTRODUCTION TO COMPUTATIONAL MOLECULAR BIOLOGY 5-6 (1997).

Genetic sequence information is inherited through processes of reproduction. Certain contiguous segments of chromosomal DNA, known as "genes," constitute the basic units of inheritance. Within each gene typically are segments of DNA that encode protein chains ("polypeptides") to be synthesized by the cell interspersed with non-coding segments of DNA. The coding regions of a gene are called "exons" and the non-coding regions are called "introns."

Genes provide the original blueprints for protein synthesis, but do not participate directly in the building of polypeptides. Instead, a working copy of the DNA sequence information from each of a gene's exons is "transcribed" from one strand (the "antisense" strand) of the gene to a complementary single-stranded messenger RNA ("mRNA") molecule. Ribosomes in the cell then use the sequence information in the mRNA molecule to arrange amino acids into a polypeptide. This process may be repeated, with thousands of mRNA molecules and polypeptides being derived from a single DNA molecule.[19] Genes and exons that serve in this way as the source of sequence information for protein synthesis in this way are said to be "expressed."

Each group of three consecutive bases in the mRNA strand (a "codon") corresponds to a specific amino acid, according to a scheme generally known as the "genetic code." For example, the mRNA sequence 5'-AUGCAGACA-3' corresponds to the amino acid sequence Methionine-Glutamine-Threonine. While there are 64 possible sequences of three bases that can be derived from the four RNA bases A, C, G and U, only 20 kinds of amino acids are used in the building of polypeptides. Some of the 64 codons encode the same amino acids, while others do not encode amino acids at all, but signal the end of the polypeptide chain ("stop codons"). The resulting redundancy in the encoding scheme is known as the "degeneracy" of the genetic code. The degeneracy of the genetic code implies that many different DNA molecules may encode the same amino acid sequence.

. . . In cloning and other genetic engineering procedures, it is often useful to have a DNA molecule that is reverse-complementary to a particular mRNA molecule. Such a DNA molecule may be synthesized from the mRNA molecule by using a special enzyme known as "reverse transcriptase" to create a reaction called "reverse transcription." The resulting product is referred to as a complementary DNA molecule, or "cDNA" for short.[20] A cDNA may be single-stranded or double-stranded.

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[19] *See* Elisa Izaurralde, *RNA Export*, 81 CELL 153 (1995).

[20] DESMOND S.T. NICHOLL, AN INTRODUCTION TO GENETIC ENGINEERING 90-92 (2002).

Two DNA molecules are said to be "homologous" if their sequences are similar. There are various quantitative measures of sequence similarity, or "homology." The most common measure is the percentage of bases that appear at the same locations in both base sequences. For example, two DNA molecules 60 base pairs in length that differ in three base locations are said to have 95% base homology (or simply "95% homology"). Homology may also be measured by the percentage of amino acids that match at corresponding locations in the encoded polypeptide chains. For example, if two DNA molecules encoding polypeptide chains 20 amino acids in length that differ in three amino acid locations, the molecules are said to have 85% amino acid homology.

B. OLIGONUCLEOTIDES

An "oligonucleotide" is a relatively short single strand of a DNA molecule, typically 2 to 50 bases in length. The suffix "mer" may be used to create a shorthand term for an oligonucleotide of a given length. For example, a "10-mer" refers to an oligonucleotide 10 bases in length.

Oligonucleotides bearing a particular DNA sequence can hybridize at locations on other single-stranded DNA molecules where the reverse-complementary sequence occurs. This sequence-specific hybridization property makes oligonucleotides useful for detecting DNA molecules that contain a particular subsequence, and for causing chemical interactions to occur at a particular location on a DNA molecule.

Oligonucleotides having a given nucleotide sequence can be synthesized from scratch in the laboratory through an iterative sequence of chemical reactions whereby each DNA molecule is built up one nucleotide at a time in reverse order (from the 3' end to the 5' end).[21] The process is often performed by an automated instrument, known as a "DNA synthesizer,"[22] capable of creating trillions of oligonucleotides in a single run.[23] Typically the procedure produces a mixture of both full-length oligonucleotides and shorter, incomplete molecules. A

[21] JOSEPH SAMBROOK & DAVID W. RUSSELL, MOLECULAR CLONING: A LABORATORY MANUAL 10.42 (2001).

[22] *See, e.g.*, Applied Biosystems, *ABI 3900 High-Throughput DNA Synthesizer* (available at http://docs.appliedbiosystems.com/pebiodocs/00104042.pdf) (sales brochure).

[23] *See* SAMBROOK, *supra* note 21, at 10.46 (estimating the minimum amount of an oligonucleotide synthesized by an automatic machine as 5 to 50 nanomoles). DNA synthesizers have recently been used to replicate the entire genome of the polio virus. *See* Jeronimo Cello et al., *Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of Natural Template*, 297 SCIENCE 1016 (August 9, 2002).

variety of methods, including gel electrophoresis and reversed-phase chromatography,[24] are available to remove the shorter molecules from the mixture, thereby leaving the oligonucleotides in isolated and purified form.

Miniaturization technologies have made it possible to fabricate small chips, known as "microarrays" (or, colloquially, as "DNA chips"), that can hold thousands of isolated, purified, single-stranded DNA molecules ("probes") in separate, identified locations. When a solution containing an unknown sample of DNA molecules is washed against a microarray under conditions favorable for hybridization, the microarray probes are able to hybridize with DNA molecules in the sample that contain their reverse-complementary sequences. In this way, a single microarray can be used to test a sample for the presence of thousands of DNA sequences simultaneously.

Oligonucleotides produced by a DNA synthesizer and cDNAs produced by reverse transcription[25] are both suitable for use as probes on a microarray. Some manufacturers fabricate microarrays by preparing the probes first and then depositing them into the appropriate locations on the chip. Other firms synthesize the probes directly on the chip, using technologies such as photolithography, ink jet printing, and electrochemistry to regulate the locations where chemical reactions are to occur.

One manufacturer in particular, Affymetrix, Inc., has marketed microarrays called GeneChips that can hold up to 400,000 different oligonucleotide probes.[26] Affymetrix holds broad patents covering photolithography methods for controlling chemical synthesis[27] and the fabrication of high-density microarrays that can be achieved using such methods.[28] Because of the scalability of photolithography technology, the number of oligonucleotide probes that can fit on a microarray has

[24] *See id.* at 10.48-.49.

[25] *See supra* text accompanying note 20.

[26] *See* Randall Osborne, *Affymetrix Venture Raises $100M to Exploit Wafers for Genomics*, BIOWORLD TODAY, April 4, 2001.

[27] See U.S. Patent No. 5,753,788 (issued May 19, 1998) ("Photolabile Nucleoside Protecting Groups").

[28] See U.S. Patent No. 5,744,305, claim 1 (issued April 28, 1998) (claiming "[a]n array of oligonucleotides, the array comprising: a planar, non-porous solid support having at least a first surface; and a plurality of different oligonucleotides attached to the first surface of the solid support at a density exceeding 400 different oligonucleotides/cm^2, wherein each of the different oligonucleotides is attached to the surface of the solid support in a different predefined region, has a different determinable sequence, and is at least 4 nucleotides in length").

been increasing exponentially,[29] creating unprecedented opportunities for genetic research.[30]

Noting the potential benefits from such massive parallelism in clinical experimentation, leading scientists[31] and a former U.S. president[32] have singled out microarrays as a technology that may eventually unlock the secrets of human genetic variation. In practical terms, this means that physicians will someday use microarrays to determine the diseases a newborn infant will be prone to later in life,[33] tailor medications to patients' individual genomes,[34] or, less ambitiously, to decide whether a sore throat is treatable with antibiotics.[35] Although clinical medicine has yet to embrace predictive gene testing as a diagnostic approach,[36] microarrays are already being used to test for drug-resistant mutations in the HIV virus,[37] cancer-related mutations in breast tumors,[38] and polymorphisms related to the ability to metabolize various drugs.[39] The microarray market is expected to grow to $10 billion within the next five to ten years.[40]

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[29] *See Gene Expression: New Analysis Product Line Launched*, GENOMICS & GENETICS WKLY., May 12, 2000, at 23 (quoting Affymetrix's Stephen Fodor's comment that photolithographic technology has allowed for the shrinkage of "feature sizes" according to Moore's Law); Julia Boguslavsky, *Chip Market is Evolving*, RESEARCH & DEVELOPMENT, March 1, 2002, at 20 (quoting Affymetrix's Thane Kreiner's statement that GeneChip customers "are benefiting from the principles of Moore's Law"); Osborne, *supra* note 26 (reporting that an Affymetrix venture has been developing microarrays that can hold up to 60 million probes); Alexandra Stikeman, Biochips Go Big Time, MIT's Tech. Rev., March 2001, ("In the last few years, the biotech industry has set out to establish its own version of Moore's Law.").

[30] *See generally* Section IV.B; *see also* Eric S. Lander, *The Scientific Foundations and Medical and Social Prospects of the Human Genome Project*, J. L. MED. & ETHICS 184, 187 (1998) (predicting future uses of microarrays to "tease apart the genetic factors contributing to heart disease, cancer risk, schizophrenia, manic depression, and attention deficit disorder"); David Stipp, *Gene Chip Breakthrough*, FORTUNE, March 31, 1997, at 56 (describing ongoing advances in genetic research attributable to microarrays). For surveys of oligonucleotide microarray applications, *see, e.g.*, MARK SCHENA, ED., MICROARRAY BIOCHIP TECHNOLOGY (2000); Todd R. Nelson, *Chip, Chip, Array! An Analysis of DNA Chip Technology* (2000) (available at http://www.tamirfishman.com/download/NELSON_DNA_Technology.pdf).

[31] *See, e.g.*, Eric S. Lander, *Scientific Commentary: The Scientific Foundations and Medical and Social Prospects of the Human Genome Project*, 26 J.L. MED. & ETHICS 184, 187 (1998).

[32] *See Report on the State of the Union: Message from the President*, 144 CONG. REC. S20-02 (1998) (text of President William J. Clinton's 1998 State of the Union address) ("Within a decade, 'gene chips' will offer a roadmap for prevention of illness throughout a lifetime.").

[33] David Stipp, *Gene Chip Breakthrough*, FORTUNE, Mar. 31, 1997, at 56; Tim Studt, *Gene Chip Technologies Transform Biological Research*, RES. & DEV., Feb. 1, 1998, at 38.

[34] See Robert F. Service, *Microchip Arrays Put DNA on the Spot*, 282 SCIENCE 396, 396 (Oct. 16, 1998).

[35] *See* Stipp, supra note 33 ("That's 40 gazillion sore throats a year times, say, $5 a chip – zounds, this is enough to make Andy Grove feel deja vu all over again!").

[36] *See* Michael J. Malinowski, *Separating Predictive Genetic Testing from Snake Oil: Regulation, Liabilities and Lost Opportunities*, 41 JURIMETRICS J. 23, 33-41 (2000).

[37] Tom Foremski, *Biological and Man-Made Designs Converge to Create DNA Chips*, ELECTRONICS WKLY., Jan. 11, 1995, at 20; Jon Mainwaring, *Gene-ius*, ELECTRONICS WKLY., May 28, 1997, at 18.

[38] *See* Stipp, *supra* note 33.

[39] *See* Tam Harbert, *A Chip Off the Old Block?*, ELECTRONIC BUS. TODAY, Apr. 1, 2000, at 60.

[40] *See* Alexandra Stikeman, *Biochips Go Big Time*, MIT'S TECH. REV., March 2001, at 31.

III. THE CONTROVERSY TO DATE

Arguments against DNA patents to date have generally fallen into three groups. The first group protests that the private value of the right to exclude the public from using a claimed DNA molecule far exceeds the public benefit of encouraging the molecule's discovery and disclosure. The second group focuses on the concern that DNA patents confer private exclusionary rights to some of the most fundamental attributes of the human organism, such as entire genes, genomic sequence information, or the four-letter "genetic alphabet." The third group contends that DNA molecules do not fall within any of the statutory categories of inventions that are eligible for a patent. In general, I find these objections meritorious and relevant in the context of the continuing public policy debate over DNA patenting. As I will now explain, however, they appear to have little purchase on a legal system that has already interpreted the Patent Act to permit the issuance of patents claiming millions of DNA molecules as compositions of matter.[41]

A. DNA PATENTS AND THE PATENT "BARGAIN"

Federal authority to issue patents is derived from Congress's enumerated constitutional power "[t]o promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."[42] By its own terms, this grant does not include the authority to create "patent monopolies of unlimited duration"[43] or to issue "'patents whose effects are to remove existent knowledge from the public domain, or to restrict free access to materials already available.'"[44] Accordingly, in addition to establishing a limited patent term,[45] the federal patent statutes establish various conditions of eligibility for a patent. The invention must be useful,[46] novel,[47] and nonobvious,[48] and the applicant must supply an enabling written description of the invention,[49] including the best mode

[41] *See, e.g.*, Derwent GENESEQ <http://www.derwent.com/geneseq/> (visited July 15, 2004) (describing a commercial database of more than 3 million sequences cited in DNA patents).

[42] U.S. CONST., art. I, § 8, cl. 8. This provision "is really two grants of power rolled into one; first, to establish a copyright system and, second, to establish a patent system." See In re Bergy, 596 F.2d 952, 958 (C.C.P.A. 1979). The terms "Science," "Authors" and "Writings" refer to the objects of copyright law, while the terms "useful Arts," "Inventors" and "Discoveries" refer to the objects of patent law. Id.

[43] Bonito Boats Inc. v. Thunder Craft Boats Inc., 489 U.S. 141, 146 (1989).

[44] *Id.* (quoting Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 6 (1966)).

[45] *See supra* note 66

[46] 35 U.S.C. § 101

[47] 35 U.S.C. § 102.

[48] 35 U.S.C. § 103..

[49] 35 U.S.C. § 112, ¶ 1.

for carrying out the invention.[50] The Patent Office publishes the applicant's disclosures, ordinarily eighteen months after the application[51] and, in any event, simultaneously with the issuance of a patent.[52]

The federal patent system thereby effects "a carefully crafted bargain"[53] or a "quid pro quo"[54] whereby the public gains knowledge of how to practice a useful, new, and nonobvious invention (which it is free to do upon expiration of the patent term), and the inventor receives the right to exclude the public from practicing the invention during the patent term. The efficacy of the patent bargain in promoting the "Progress of . . . Useful Arts" inheres in the patent system's maintenance of a rough parity between the social value of an invention disclosure and the private value of the exclusionary rights granted to the inventor who makes the disclosure.[55]

The patent system attempts to maintain this balance by regulating the issuance and enforcement of patents in accordance with the statutory

[50] *See id.*

[51] *See* 35 U.S.C. § 122(b) (providing that patent applications shall be published 18 months after filing unless subject to a secrecy order or the applicant requests earlier publication or nonpublication).

[52] See 35 U.S.C. § 154(a)(4).

[53] *See* Bonito Boats Inc. v. Thunder Craft Boats Inc., 489 U.S. 141, 150-51 (1989) ("The federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years.") In *Bonito Boats*, the Supreme Court found that the care with which the U.S. Congress crafted the patent system as an innovation policy constitutes a "pervasive" scheme of federal regulation, and as such serves to preempt state regulation in the area of industrial design. Id. at 167.

[54] *See* Brenner v. Manson, 383 U.S. 519, 534-35 (1966) ("The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly [to an inventor] is the benefit derived by the public from an invention with substantial utility.").

[55] *See, e.g.*, JOHN W. SCHLICHER, PATENT LAW: LEGAL AND ECONOMIC PRINCIPLES § 1.04[1], at 1-18 (2001) ("The so-called 'private value' of any invention to its producer will be less than its 'social value' to consumers, if the [producer] is unable to prevent others from using it without permission. . . . The patent law reduces the gap between private and social value by giving the first person to create an invention the right for a time to exclude others from using it."); Ian Ayres & Paul Klemperer, *Limiting Patentees' Market Power Without Reducing Innovation Incentives: The Perverse Benefits of Uncertainty and Non-Injunctive Remedies*, 97 MICH. L. REV. 985, 1008 (1999) ("[T]he current patent system . . . allows the patentee to capture a rough and limited proxy of consumer value and then lets the potential innovator decide whether the benefits of innovation justify the costs."); William F. Baxter, *Legal Restrictions on Exploitation of the Patent Monopoly: An Economic Analysis*, 76 YALE L.J. 267, 268-71 (1966) (noting that an optimum innovation policy would equalize social and private valuations of innovative outputs, but arguing that subsidies and patent monopolies are incapable of achieving an exact balance); Howard F. Chang, *Patent Scope, Antitrust Policy, and Cumulative Innovation*, 26 RAND J. ECON. 34, 49 (1995) (arguing that research will be underproduced if its social value exceeds its appropriable private value); Mark F. Grady & Jay I. Alexander, *Patent Law and Rent Dissipation*, 78 VA. L. REV. 305, 308 (1992) (describing optimal patent grant as an award to the inventor of rent equal to "[t]he difference between what society would pay for an innovation and its actual cost of development"); Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265, 266 (1977) (citing A.C. PIGOU, THE ECONOMICS OF WELFARE 183-85 (4th ed. 1960)) (noting that insofar as a patent functions as a reward, it "tends to make the amount of private investment in invention closer to the value of its social product").

conditions for patentability.[56] The utility requirement of § 101 and § 112, ¶ 1 provides that only inventions capable of providing some benefit to society are entitled to a patent.[57] The novelty requirement of § 102 makes sure that a patent issues only when knowledge of the invention is not already available to the public.[58] The nonobviousness requirement of § 103 further restricts patentability to inventions that represent advances beyond the application of ordinary skill to publicly available knowledge.[59] The written description and enablement requirements of § 112, ¶ 1 ensure that knowledge of the patented invention is transmitted in a form that can be used immediately by the public.[60] Finally, the best mode requirement of § 112, ¶ 1 compels the public disclosure of the most valuable form of the patented invention known to the inventor as of the application date.[61] By requiring utility, novelty, nonobviousness, and adequate disclosure, the Patent Act provides that a private party may receive a patent (and the right to obtain federal injunctions to enforce it[62]) only when the public has received all knowledge necessary to practice an invention that is of significant independent social value. Patent scope also tends to correlate the social importance of a patented invention with the private value of the patent.[63] Other things equal, a pioneering invention that has no close prior art and introduces a widely applicable technology is entitled to broader patent claims than an invention that contributes little to public knowledge.[64] The scope of the claims in turn largely determines the market value of the patent.[65]

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[56] *See supra* text accompanying notes 55-62.

[57] *See, e.g.*, Brenner, 383 U.S. at 534-35.

[58] *See, e.g.*, Bonito Boats, 489 U.S. at 148.

[59] *See, e.g.*, Bonito Boats, 489 U.S. at 150.

[60] *See, e.g.*, Joan E. Schaffner, *Patent Preemption Unlocked*, 1995 WIS. L. REV. 1081, 1093-94.

[61] *See* SCHLICHER, supra note 55, at § 7.02.

[62] *See* 35 U.S.C. §§ 281, 283; *see also* Smith Int'l, Inc. v. Hughes Tool Co., 718 F.2d 1573, 1577-78 (Fed. Cir. 1983) (characterizing the "injunctive power of the courts" as the principal source of value in the patent grant).

[63] *See, e.g.*, In re Sus, 306 F.2d 494, 497 (C.C.P.A. 1962) ("The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed.").[64] *See* Westinghouse v. Boyden Power Brake Co., 170 U.S. 537, 561-62 (1898) (defining a pioneer patent as "a patent covering a function never before performed, a wholly novel device, or one of such novelty and importance as to mark a distinct step in the progress of the art"); Perkin-Elmer Corp. v. Westinghouse Elec. Corp., 822 F.2d 1528, 1532 (Fed. Cir. 1987) (stating that pioneer patent claims are entitled to broad construction under doctrine of equivalents); Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 845-52 (reviewing relationship between enablement and claim breadth); Samson Vermont, *A New Way to Determine Obviousness: Applying the Pioneer Doctrine to 35 U.S.C. § 103(a)*, 29 AIPLA Q.J. 375, 395-96 (2001) ("If an invention is truly a major invention, the scope of its claims will almost necessarily be broad.").

[65] *See, e.g.*, Tim Baumann, *Evaluating the Value of a Patent Portfolio*, CORP. COUNS., July 2001, at 1 ("Ascertaining the 'value' of any patent begins by determining what is covered by the claims. . . ."). The private value of a patent need not coincide with its market value, because a patent owner is under no obligation to license or otherwise commercialize the patented invention. *See, e.g.*, Special Equip. v. Coe, 324 U.S. 370, 378-79 (1945).

Various commentators have disputed this balance in the case of DNA patents, arguing that their preclusive effects on genetic research and health care far exceed any public benefits from the discovery and disclosure of the claimed DNA molecules. On the one hand, the owner of a valid DNA patent has a right in the United States, for a term of twenty years from the application date,[66] to exclude others from making, using, offering for sale, selling, or importing any of the claimed DNA molecules.[67] On the other hand, a patent disclosure that describes a previously unknown statistical association between a DNA molecule and a particular disease may nevertheless fail to yield meaningful insight into disease prevention and treatment.[68] Accordingly, many critics are concerned that the issuance of DNA patents provides the public with only preliminary characterizations of DNA sequences that provide few public health benefits, while allowing the patentee to impede research on how patented DNA molecules actually function in the disease process and development of diagnostic and therapeutic services for patients.[69]

The balance between social and private values is made more salient by the fact that many DNA patents are due at least in part to publicly funded research.[70] Some critics of DNA patents contend that the public is entitled to the full benefit of the research it has sponsored, and are

[66] See 35 U.S.C. § 154(a)(2) (providing for patent term of 20 years from date of application); 35 U.S.C. § 154(b) (providing for adjustments to patent term to compensate for delays caused by Patent Office inaction, interferences, secrecy orders, and appeals).

[67] 35 U.S.C. § 154(a)(1).

[68] *See* GARY ZWEIGER, TRANSDUCING THE GENOME 125-34 (2001).

[69] *See* Utility Guidelines, *supra* note 163, at 1094 cmt. 7; Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCIENCE 698, 699 (1998) ("gathering the necessary licenses [for preclinical testing of pharmaceutical products] may be difficult or impossible"); Martin Bobrow & Sandy Thomas, *Patents in a Genetic Age*, 409 NATURE 763 (2001) ("The patenting system should help people channel their energy towards inventions of genuine therapeutic or diagnostic value and discourage frenetic cataloguing DNA sequences that are a long way from being a final useful product."); Thomas Kiley, *Patents on Random Complementary DNA Fragments*, 257 SCIENCE 915 (1992) ("These patents cluster around the earliest imaginable observations on the long road toward practical benefit, while seeking to control what lies at the end of it."); Bartha Maria Knoppers, *Status, Sale and Patenting of Human Genetic Material: An International Survey*, 22 NATURE GENETICS 22, 23-26 (1999); Jon F. Merz et al., *Disease Gene Patenting is a Bad Innovation*, 2 MOLECULAR DIAGNOSIS 299, 301 (1997); John F. Merz et al., *Diagnostic Testing Fails the Test*, 415 NATURE 577 (2002); Kate Murashige, *U.S. Perspective, Patenting and Ownership of Genes and Life Forms*, INT'L BUS. LAW., March 2000, at 100 ("Patents on materials that are essential research tools . . . e.g., receptors needed to screen drug candidates . . . [and] the stacking of royalties required greatly escalates research costs."); C. Thomas Caskey et al., *HUGO Statement on Patenting of DNA Sequences*, GENOME DIGEST, April 1995, at 6; American College of Medical Genetics, Position Statement on Gene Patents and Accessibility of Gene Testing (visited June 6, 2002) <http://www.faseb.org/genetics/acmg/pol-34.htm> ("[R]estricting the availability of gene testing . . . retards the usually very rapid improvement of a test that occurs through the addition of new mutations or the use of new techniques by numerous laboratories that have accumulated samples from affected individuals over many years."); *cf.* Utility Guidelines at 1095 n. 13 (noting comment that because techniques for DNA sequencing have become so routine, all DNA molecules should be considered obvious as a matter of law).

[70] See Merz, *supra* note 69, at 301.

concerned that patent owners will be unable or disinclined to use patented technology to advance public health objectives.[71] For example, patent owners may prohibit physicians from providing state-of-the-art genetic tests and therapies to their patients.[72] Some commentators argue that patent rights should not be permitted to override medical ethics by interfering with the development and provision of patient care.[73] Others are concerned that gene patents will engender a "new eugenics" by encouraging the commercialization of genetic testing and thereby bringing market forces to bear on genetic choices.[74]

Modern patent doctrine accommodates a wide disparity between the private and social valuations of a claimed invention.[75] As far as the Patent Office and the courts are concerned, every valid patent issued under the Patent Act promotes the "Progress of . . . Useful Arts,"[76] even though its publication is unlikely to produce a public benefit commensurate with the private value of the patent grant.[77] Since a patent

[71] *See* Howard Markel, *Patents Could Block the Way to a Cure*, N.Y. TIMES, Aug. 24, 2001, at __; Merz, *supra* note 69, at 301-03; Blanton, supra note 72 (reporting cancer geneticist Dominque Stoppa-Lyonnet's statement that "Monopoly is not good for genetic testing because the commercial interests are stronger than the quality interests.").

[72] *See* Kimberly Blanton, *Corporate Takeover: Exploiting the U.S. Patent System*, BOSTON GLOBE, Feb. 24, 2002, at 10 (reporting patent notification letters received by Dr. Debra Leonard); *Kurt Eichenwald, Push for Royalties Threatens Use of Down Syndrome Test*, N.Y. TIMES, May 23, 1997, at A1 (reporting abandonment of prenatal testing in response to fears of patent litigation); Margaret Graham Tebo, *The Big Gene Profit Machine*, ABA JOURNAL, April 2001, at 51 (reporting concerns by Lori Andrews and Jeremy Rifkin that DNA patents will prevent some patients from obtaining needed medical procedures); American College of Medical Genetics, supra note 69 ("[Patent enforcement efforts] limit the accessibility of competitively priced genetic testing services and hinder test-specific development of national programs for quality assurance. They also limit the number of knowledgeable individuals who can assist physicians, laboratory geneticists and counselors in the diagnosis, management and care of at-risk patients.").

[73] *See* Merz, *supra* note 69, at 302-03 (discussing the tension between patent policies and medical ethics).

[74] *See* James Donahue, Note, *Patenting of Human DNA Sequences: Implications for Prenatal Genetic Testing*, 36 BRANDEIS J. FAM. L. 267 (1998).

[75] *See infra* text accompanying notes 167-170; *cf.* Timothy Caulfield et al., *Patenting Human Genetic Material: Refocusing the Debate*, 1 NATURE REV. GENETICS 227, 228-29 (2000) (explaining that in the United States, Canada and Japan, "intellectual property law is not structured to handle social policy considerations").

[76] *See* 35 U.S.C. § 131 (requiring the issuance of a patent upon every application that satisfies the Patent Act's conditions for patentability).

[77] *See e.g.*, Baxter, *supra* note 55, at 269 ("[T]he resources presently being devoted to innovation probably are somewhat too large or too small."); Jack Hirschleifer, *The Private and Social Value of Information and the Reward to Inventive Activity*, 61 AM. ECON. REV. 561, 571 (1971) (arguing that resources presently being devoted to innovation may be excessive); Richard R. Nelson, *The Simple Economics of Basic Scientific Research*, 67 J. POLIT. ECON. 297 (1959) (arguing that resources presently being devoted to innovation are insufficient).

The most significant variable in U.S. patent policy, the length of the patent term itself, does not appear to have been determined with the aim of equalizing social and private valuations of innovative outputs. *See, e.g.*, Baxter, *supra* note 55, at 272-74.

application may be filed several years before the invention is commercialized, a patent disclosure does not necessarily teach the public how to use the invention in an economically beneficial way.[78] The public must also bear the costs of administering the patent system and handling litigation.[79] In contrast, inventors enjoy discretion as to whether or not to seek a patent, and have an incentive to do so only when they perceive the private value of the patent to be greater than the social value of any required invention disclosures.[80] Moreover, a patent owner may enjoy valuable private benefits over and above the acquisition of exclusionary rights. For example, a firm can often use the size and technical content of its patent portfolio as signals to convey information about the firm's condition credibly and efficiently to market observers.[81]

Economic theories of the patent system provide various explanations of and justifications for this apparent imbalance in the patent bargain. While the function of a patent has traditionally been described as a reward to encourage both the creation and the disclosure of useful inventions,[82] the latter purpose is sometimes characterized as subordinate[83] to account for the observation that the public benefit from disclosure alone is often insufficient to justify the patent grant.[84] The

[78] *See* Kitch, *supra* note 55, at 287-88; DONALD S. CHISUM, 1 CHISUM ON PATENTS § 4.02[2], at 4-12 (2001) ("The basic quid pro quo of the patent system is monopoly by the government in exchange for disclosure of a new and useful product or process, not for disclosure of all the uses to which the product or process can be put."). One commentator has even suggested that a patent disclosure may mislead the public as to the economic value of the invention. *See* Phanesh Koneru, *To Promote the Progress of Useful Art[icle]s?: An Analysis of the Current Utility Standards of Pharmaceutical Products and Biotechnological Research Tools*, 38 IDEA: J.L. & TECH. 625, 644 (1998) (suggesting that competitors of the patentee "might erroneously assume that the patentee would normally disclose (and thus has disclosed) the best use and would not invest further in the invention to find other uses").

[79] *See* Donald F. Turner, *The Patent System and Competitive Policy*, 44 N.Y.U. L. REV. 450, 454-55 (1969).

[80] SCHLICHER, *supra* note 55, § 1.04[2], at 1-25.

[81] *See* Clarisa Long, *Patent Signals*, 69 U. CHI. L. REV. 625, 627 (2002).

[82] *See, e.g.*, Bonito Boats, Inc. v. Thunder Craft Boats, Inc., 489 U.S. 141, 151 (1989) ("The federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years."); Kewanee Oil Co. v. Bicron Corp., 416 U.S. 470, 480-81 (1974) (describing patent laws as fostering productive efforts by inventors and insuring adequate and full disclosures of inventions); Grant v. Raymond, 31 U.S. 218, 241-42 (1832) ("[The patent grant] is the reward stipulated for the advantages derived by the public for the exertions of the individual, and is intended as a stimulus to those exertions."); ALFRED E. KAHN, THE ROLE OF PATENTS, IN COMPETITION, CARTELS AND THEIR REGULATION 308, 311 (John P. Miller ed., 1962); A. Samuel Oddi, *Beyond Obviousness: Invention Protection in the Twenty-First Century*, 38 AM. U. L. REV. 1097, 1101 (1989).

[83] *See, e.g.*, SCHLICHER, *supra* note 55, § 1.04[5] at 1-30 (noting that most court decisions indicate that the dominant goal of the Patent Act is to encourage the creation of inventions).

[84] *See id.* § 1.04[3], at 1-26 (concluding that the quid pro quo theory is a "conceptual error" that "predisposes the court to try to reward the act of disclosure rather than the act of inventing").

observed tendency of inventors to seek patents long before beginning commercialization efforts[85] has suggested the alternative theory that the patent system provides incentives for patent owners to improve and commercialize their inventions by preventing any resulting rents from being dissipated due to the redundant efforts of competitors.[86] Other commentators have disregarded any inequities by taking a narrower view of the patent bargain, defining the social value of an invention as the total rent the public is willing to pay for the invention when it has been patented and offered in the market,[87] and the private value of a patent as the total rent that a profit-maximizing inventor can obtain in the market from the users of the patented invention;[88] in a free, efficient market, the

[85] *See* Kitch, *supra* note 55, at 271 (citing JOHN JEWKES ET AL., THE SOURCES OF INVENTION 263-410 (1959)).

[86] *See* Grady & Alexander, *supra* note 55, at 316-21; *see also* Kitch, *supra* note 55, at 275-80 (analogizing the patent grant to prospecting rights in undeveloped land); *but see* Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 871-78 (1990) (arguing that the public generally benefits from vigorous competition in the race to develop improvements to patented inventions). To the extent that overbroad patents covering basic technologies might encourage rent-dissipating competitions to obtain patents in the first place, *see* Donald G. McFetridge & Douglas A. Smith, *Patents, Prospects, and Economic Surplus: A Comment*, 23 J.L. & ECON. 197 (1980), theorists contend that the courts have generally interpreted the patent statutes to avoid such a result. *See* Grady & Alexander, *supra* note 55, at 322-50; *but see* Robert P. Merges, *Rent Control in the Patent Districts: Observations on the Grady-Alexander Thesis*, 78 VA. L. REV. 359, 366-69 (1992) (arguing that patent doctrine, not the objective of minimizing rent dissipation, better explains the outcomes of cases studied by Grady and Alexander).

[87] *See* Carvalho, *supra* note 117, at 52-53.

[88] *See id.* at 36. According to this view, the primary function of the patent system is to provide a legal mechanism whereby one who has developed a valuable piece of information (i.e., an invention) can disclose it to the market while retaining the right to appropriate its value. *See id.* at 52 ("[T]he patent system exists because it is the only known legal institution that allows inventors to put a price on technology and at the same time permits society to measure, through the competitive interplay of market forces, the adequacy of such a price with relative efficiency."); *cf.* SCHLICHER, *supra* note 55, § 1.04[3], at 1-25 to 1-26 (arguing that invention disclosures serve primarily to notify the public of the scope of the patentee's property rights).

To persuade a buyer that a piece of information is valuable, it may be necessary for the seller to disclose the information itself. This pricing problem, known as Arrow's information paradox, may preclude transactions in such information. *See* Kenneth J. Arrow, *Economic Welfare and the Allocation of Resources for Invention*, *in* THE RATE AND DIRECTION OF INVENTIVE ACTIVITY: ECONOMIC AND SOCIAL FACTORS 609, 614-16 (1962); *but see* Oded Goldreich et al., *Proofs That Yield Nothing But Their Validity or All Languages in NP Have Zero-Knowledge Proof Systems*, 38 J. ASSOC. COMPUTING MACHINERY 691 (1991) (proving essentially that where a buyer's valuations of information products can be efficiently verified by computers, it is possible for the seller to prove the value of an information product to such a buyer without disclosing the information itself). The patent system overcomes this problem by creating a legal distinction between disclosing the invention and conferring ownership of it. *Cf.* Mark Lemley, *Romantic Authorship and the Rhetoric of Property*, 75 TEX. L. REV. 892 (1997) ("[I]ntellectual property actually offers a way out of [Arrow's information] paradox."); Robert P. Merges, *Intellectual Property and Digital Content: Notes on a Scorecard*, CYBERSPACE LAW., June 1996, at 15, 16 ("Sellers will be willing to disclose some or even all of the information in their possession when that information is protected by a property right").

two are necessarily the same.[89] In sum, regardless of whether the patent system is seen as promoting "Progress" by rewarding inventors, by reducing rent dissipation by competitors, or by facilitating transactions in information goods, such "Progress" does not require the patent system to engage in an explicit comparison between the public benefit and the private value of each patent.

This relaxed approach to the patent bargain is ultimately reflected in the administration of the patent system. The Patent Office and the courts are charged with interpreting and applying the statutes through which Congress has implemented the system's constitutional purpose to promote "Progress."[90] The Patent Act does not call for any direct comparison between the private value of a patent grant and the benefit the public will receive from the invention disclosure, because the primary concern of the patent system is "Progress," not the size of the inventor's reward.[91] Without more, objections to the apparent imbalance between the private and social valuations of claimed DNA molecules do not provide a basis for a legal challenge to the validity or enforceability of any DNA patent.

[89] *See id.* at 51; *cf.* Application of Kirk, 376 F.2d 936, 964 (C.C.P.A. 1967) ("[I]f the inventor has given nothing, the government has given nothing. The right to exclude others from the use of something no one wishes to use is worthless — economically."); Lowell v. Lewis, 15 F. Cas. 1018, 1019 (No. 8568) (C.C. Mass. 1817) (Story, J.) ("[W]hether [the invention] be more or less useful is a circumstance very material to the interests of the patentee but of no importance to the public. If it be not extensively useful, it will silently sink into contempt and disregard."). This recharacterization of the patent bargain does not reconcile the disparity between the social and private valuations of a patented invention, because it fails to account for the public opportunity cost of the activities excluded during the patent term and the public benefit from the invention's disclosure.

[90] *See* Graham v. John Deere, 383 U.S. 1, 6 (1966) ("Within the limits of the constitutional grant, the Congress may, of course, implement the stated purpose of the Framers by selecting the policy which in its judgment best effectuates the constitutional aim. . . . It is the duty of the Commissioner of Patents and of the courts in the administration of the patent system to give effect to the constitutional standard by appropriate application, in each case, of the statutory scheme of the Congress.").

[91] *See, e.g.*, Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 330-31 (1945) ("The primary purpose of our patent system is not reward of the individual but the advancement of the arts and sciences."); United States v. Masonite Corp., 316 U.S. 258, 278 (1942) (citation omitted) ("[T]he promotion of the progress of science and the useful arts is the 'main object'; reward of inventors is secondary and merely a means to that end."); Motion Picture Patents Co. v. Universal Film Mfg. Co., 243 U.S. 502, 511 (1917) ("[T]his court has consistently held that the primary purpose of our patent laws is not the creation of private fortunes for the owners of patents but is 'to promote the progress of science and useful arts.'").

B. DNA PATENTS AND THE HUMAN ORGANISM

Many commentators have viewed DNA patenting with alarm as a project to confer exclusionary property rights in life itself, including human life. They have described DNA patents in such expansive terms as "patents on life,"[92] "patents on the human genome,"[93] and patents on the genetic alphabet,[94] and have warned that DNA patents will result in the creation of "patent monopolies."[95] Some critics contend that DNA patenting has the effect of commodifying parts of the human body that, while microscopic in scale, are intimately connected to personal

[92] *See, e.g.*, Ned Hettinger, *Patenting Life: Biotechnology, Intellectual Property, and Environmental Ethics*, 22 B.C. ENVTL. AFF. L. REV. 267 (1995); Merrill Goozner, *Patenting Life*, AM. PROSPECT, Dec. 18, 2000.

[93] *See, e.g.*, Rebecca S. Eisenberg, *Patenting the Human Genome*, 39 EMORY L.J. 721 (1990); Laurie L. Hill, *The Race to Patent the Genome: Free Riders, Hold Ups, and the Future of Medical Breakthroughs*, 11 TEX. INTELL. PROP. L.J. 221 (2003).

[94] *See, e.g.*, Elizabeth L. Mitchell, Book Note, 10 HARV. J.L. & TECH. 377, 378-79 (reviewing JAMES BOYLE, SHAMANS, SOFTWARE AND SPLEENS: LAW AND THE CONSTRUCTION OF THE INFORMATION SOCIETY (1996)) (comparing patenting of genetic sequences to monopolization of the alphabet); Linda Maher, *The Environment and the Domestic Regulatory Framework for Biotechnology*, 8 J. ENVTL. L. & LITIG. 133, 191-92 (1993) (same); Charles Leroux, *Biotech's Traffic Cop: Chicago Attorney Lori Andrews Stands Where Science and the Law Intersect*, CHI. TRIB., Oct. 7, 2001, at 12 (reporting Lori Andrews's comment that "It's like some greedy company came along and patented the alphabet, and then charged each of us every time we spoke or wrote."); Peter G. Gosselin & Paul Jacobs, *Patent Office Now at Heart of Gene Debate*, L.A. TIMES, Feb. 7, 2000, at A1 (quoting American College of Medical Genetics Executive Director Michael S. Watson's statement that "It's as if somebody just discovered English and allowed the alphabet to be patented.").

[95] *See, e.g.*, Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1024-46 *passim* (1989); Melissa E. Horn, Note, *DNA Patenting and Access to Healthcare: Achieving the Balance Among Competing Interests*, 50 CLEV. ST. L. REV. 253, 268-69 (2002) (stating that "[t]he granting of patents creates legalized monopolies designed to encourage innovation" but that this "is having an undesirable and contradictory effect"); Bruce Ramsey, *Living Assets: Patenting of Human Cell Lines, Genes by Biotech Companies Creates an Ethical Firestorm*, SEATTLE POST-INTELLIGENCER, June 19, 1995, at B4 (reporting Council for Responsible Genetics's objection to the "conversion" of DNA molecules into "corporate property through patent monopolies").

identity.[96] Women's organizations have protested that patents on breast cancer genes represent an "assault on women" which "denies them control over the most intimate aspect of their being, their bodies' genetic blueprint."[97] Religious leaders have condemned the patenting of genes as an illegitimate effort to claim that which can only be owned by God.[98]

The project of sequencing an entire human genome, completed in 2001 in separate efforts by a government-funded international consortium[99] and by Celera Corporation,[100] has focused public attention on the role of genomic sequence information in genetic research. This focus has induced some critics of DNA patents to frame their arguments as an appeal to an emerging public concern that rights in the human genome sequence itself are being parceled out to the private sector. In 2002, for example, bipartisan House legislation was proposed to amend the Patent Act to permit public access to certain noninfringing uses of patented "genetic sequence information."[101] Co-sponsor Rep. Lynn N. Rivers described the proposed amendment as a response to "the popular

[96] *See, e.g.*, Utility Guidelines, *supra* note 163, at 1093 cmt. 4; Baruch Brody, *Protecting Human Dignity and the Patenting of Human Genes*, in A. Chapman, ed., PERSPECTIVES ON GENE PATENTING 111-26 (1999) ("[I]t is wrong to commercialize something with which individuality and personhood is intertwined"); *see also* Mark J. Hanson, *Biotechnology and Commodification Within Health Care*, 24 J. MED. & PHIL. 267 (1999) ("If the rhetoric regarding our genes becomes increasingly commodified at a time when media reports continue to strengthen the link between genes and human traits that centrally define us both as a species and as individuals, a subtle but not insignificant offense to notions of personhood and concomitant self-perception may occur."); *cf.* Margaret Jane Radin, *Market-Inalienability*, 100 HARV. L. REV. 1849, 1881 ("Systematically conceiving of personal attributes as fungible objects is threatening to personhood, because it detaches from the person that which is integral to the person."); *but see* David B. Resnik, *DNA Patents and Human Dignity*, 29 J.L. MED. & ETHICS 152 (2001) (arguing that DNA patents do not violate human dignity because they do not constitute complete commodification of human beings).

Similar concerns have arisen over the sale of human tissues containing specimens of DNA molecules, such as cell lines and tissue samples. *See, e.g.*, Moore v. Regents of the University of California, 793 P.2d 479, 506-23 (Cal. 1990) (Mosk, J., dissenting) (objecting to denial of patient's demand for recovery of proceeds from sale of cell line developed from patient's tissues); Doug Hanchett & Michael Lasalandra, *Friends Outraged at Plan to Freeze Ted's Body*, BOSTON HERALD, July 7, 2002, at 1 (reporting reactions to son's plan to preserve baseball player Ted Williams's corpse in order to sell DNA specimens).

[97] *U.S. Coalition Counters Breast Gene Patents*, 381 NATURE 265 (1996).

[98] *See* Richard D. Land & C. Ben Mitchell, *Patenting Life: No*, 63 FIRST THINGS 20, 20-22 (1996).

[99] *See* International Human Genome Sequencing Consortium, *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860 (2001).

[100] *See* J.C. Venter et al., *The Sequence of the Human Genome*, 291 SCIENCE 1304 (2001).

[101] *See Introduction of the "Genomic Research and Diagnostic Accessibility Act of 2002" H.R. 3967 and the "Genomic Science and Technology Innovation Act of 2002" H.R. 3966*, 148 CONG. REC. E353-03 (daily ed. March 14, 2002) (statement of Rep. Lynn N. Rivers) [hereinafter "Rivers statement"].

Although the patenting of other biotechnological inventions have raised interesting issues of patent law, the scope of this article is limited to patents claiming one or more DNA molecules. For a comprehensive survey of biotechnology patent law in the United States, *see* KENNETH J. BURCHFIEL, BIOTECHNOLOGY AND THE FEDERAL CIRCUIT (1995). Throughout this Article, the term "patent" refers to a utility patent and the term "DNA patent" refers to a patent claiming one or more DNA molecules as a composition of matter.

view in this country that owning the rights to a part of the human body is inappropriate and even immoral."[102]

Other commentators have argued that the issuance of DNA patents in the United States is contrary to an emerging international consensus that the human genome should be treated as a common heritage of humankind.[103] According to this view, the human genome is not a proper subject for the exercise of national sovereignty because it is a part of every human body and a manifestation of the evolution of the entire human species.[104] In these respects, the human genome is analogous to geographic areas such as seabeds,[105] Antarctica,[106] and the Moon,[107] that international treaties have identified as unique and irreplaceable resources to be shared and preserved for the benefit of all humanity.[108]

While these criticisms of DNA patents may be grounded in genuine public concerns, they do not constitute a legal objection to the validity or enforceability of any DNA patent. First, DNA patents do not preclude the use of genetic sequence information.[109] In fact, an application for a patent must include a disclosure of "words, structures, figures, diagrams, formulas, etc. that fully set forth the claimed invention,"[110] a requirement

[102] Rivers statement, supra note 101.

[103] *See* Utility Guidelines, supra note 163, at 1094 cmt. 6; Melissa L. Sturges, Note & Comment, *Who Should Hold Property Rights to the Human Genome? An Application of the Common Heritage of Humankind*, 13 AM. U. INT'L L. REV. 219, 245-47 (1997); Ned Hettinger, *Patenting Life: Biotechnology, Intellectual Property, and Environmental Ethics*, 22 B.C. ENVTL. AFF. L. REV. 267, 286-87 (1995); *cf.* Barton Beebe, Note, *Law's Empire and the Final Frontier: Legalizing the Future in the Early Corpus Juris Spatialis*, 108 YALE L.J. 1737 (1999) (predicting that the vision of the human genome as the common heritage of humankind will serve an important cultural purpose regardless of its ultimate effect on legal doctrine).

[104] See Sturges, *supra* note, at 249-50.

[105] *See* United Nations Convention on the Law of the Sea, Dec. 10, 1982, U.N. Doc. A/CONF.62/122 (1982), reprinted in 21 I.L.M. 1261(providing that no country shall unilaterally exploit seabed resources); Lt. Martin A. Harry, *The Deep Seabed: The Common Heritage of Mankind or Arena for Unilateral Exploration?*, 40 NAVAL L. REV. 207, 208 (1992) (describing position taken by the Group of 77, a coalition of developing countries); *cf.* J.M. Spectar, *The Fruit of the Human Genome Tree: Cautionary Tales About Technology, Investment, and the Heritage of Humankind*, 23 LOY. L.A. INT'L & COMP. L. REV. 1, 22-26 (2001) (describing opposition by U.S. mining firms to the U.N. convention).

[106] *See* The Antarctic Treaty, Dec. 1, 1959, 12 U.S.T. 794, T.I.A.S. No. 4780, 402 U.N.T.S. 71, art. I(1) (restricting use of Antarctica to peaceful, international uses "in the interest of all mankind"); Ellen S. Tenenbaum, Note, *A World Park in Antarctica: The Common Heritage of Mankind*, 10 Va. Envtl. L.J. 109 (1990).

[107] *See* Agreement Governing the Activities of States on the Moon and Other Celestial Bodies, G.A. Res. 34/68, 34 U.N. GAOR 34th Sess., Supp. No. 46, at 79, U.N. Doc. A/34/664 (1979); Spectar, *supra* note 105.

[108] *See* Sturges, *supra* note 103, at 246; *cf.* Universal Declaration on the Human Genome and Human Rights, U.N. Educational, Scientific and Cultural Organization, 29th Sess., 29C/Resolution 19, art. 12(a).(Nov. 11, 1997) ("Benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard to the dignity and human rights of each individual.").

[109] *See* Utility Guidelines, *supra* note 182, at 1093 cmt. 3 ("descriptive sequence information alone is not patentable subject matter").

[110] Lockwood v. American Airlines, 107 F.3d 1565, 1572 (Fed. Cir. 1997).

that, in the case of claims to specific DNA molecules, generally entails placing full sequence information in the public domain.[111]

Second, DNA patent claims do not cover life, the human genome, or the genetic alphabet. Instead, DNA patent claims are typically directed to one or more specified DNA molecules in "isolated and purified" form. A DNA molecule is generally considered to be "isolated" if it has been removed from its natural environment, and "purified" if it is in an environment that is substantially free of other large molecules.[112] Thus, DNA patents do not purport to cover the natural behavior or identity of

[111] *See* Stephen A. Bent & Paul M. Booth, Genomics Race Raises Ownership Boundary Issue, Nat'l L.J., Jan. 26, 1998, at C3 (predicting that "gene claims supported by anything less than a disclosure of the full-length sequence probably will get a rough reception" in the Federal Circuit); Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences*, 49 EMORY L.J. 783, 787-88 (2000) (noting that patent claims on DNA molecules "do not prevent anyone from perceiving, using, and analyzing information about what the DNA sequence is"); *but see* Utility Guidelines, supra note 163, at 1095 cmt. 14 (stating Patent Office's policy that a sequence listing "is one method of describing a DNA molecule but it is not the only [acceptable] method").

Notably, there have been some recent efforts to patent computer-readable media containing genetic sequence information. A pending patent application by Human Genome Sciences Inc. claims, *inter alia*, a "computer-readable medium having recorded thereon the nucleotide sequence" disclosed in the patent specification. *See* Gary Stix, *Code of the Code*, SCI. AM., Apr. 2001, at 37 (describing HGS application and suggesting that alternative intellectual property regimes may be necessary to protect informational value of DNA sequences). In addition, biotechnology business method patents issued to Incyte Genomics, Inc., while not claiming sequence information itself, may have the practical effect of foreclosing access to sequence information. *See* U.S. Patent No. 6,023,659 (issued Feb. 8, 2000) (claiming a database system for searching biomolecular sequences); U.S. Patent No. 5,966,712 (issued Oct. 12, 1999) (claiming a database system for searching genomic sequence libraries). The validity of such patents is in question. *See* Incyte Genomics v. Gene Logic, Inc., C00-20876 (N.D. Cal. filed Aug. 18, 2000) (infringement suit, settled in January 2001, in which defendant challenged validity of '659 patent); Eisenberg, *supra* note 111, at 786-91 (arguing that Human Genome Sciences's patent application and other efforts to extend § 101 subject matter to cover DNA sequence information are deeply inconsistent with patent policy); Anthony Shadid, *Battle Turns Fierce Over Biotech Patents*, BOSTON GLOBE, July 18, 2001, at D1 (describing an apparently successful search for prior art to invalidate the '712 patent, sponsored by the BountyQuest.com Web site). Even if such patents may effectively preclude certain computationally intensive uses of genetic sequence information in bioinformatics research, however, such concerns are of no direct consequence for the question of DNA patenting.

[112] *See, e.g.*, U.S. Patent No. 6,214,797 (issued April 10, 2001). The terms of a patent claim are to be construed with the meaning with which the patent applicant has presented them in the patent specification. *See* Bell Atl. Network Servs., Inc. v. Covad Communications Group, Inc., 262 F.3d 1258, 1267-68 (Fed. Cir. 2001); Multiform Dessicants, Inc. v. Medzam, Ltd., 133 F.3d 1473, 1477 (Fed. Cir. 1998); Gen. Am. Transp. Corp. v. Cryo-Trans, Inc., 93 F.3d 766, 770 (Fed. Cir. 1996). Thus, commentators are not free to supply their own definitions of "isolated" and "purified" to suit their particular critiques of DNA patents. As one postmodern theorist notes, patent doctrine grants "hegemonic" status to the term construction favored by those of skill in the art. *See* Jonathan Kahn, *What's the Use? Law and Authority in Patenting Human Genetic Material*, STAN. L. & POL'Y REV. 417, 443 (2003) ("The social constructions of the meaning of 'isolated and purified' human genetic material put forth by science and the market simply overwhelms [*sic*] those put forth by dignitary critics."); *see also* Specialty Composites v. Cabot Corp., 845 F.2d 981, 986 (Fed. Cir. 1988) ("Claim terms must be construed as they would be understood by a person of ordinary skill in the art to which the invention pertains.").

any living organism,[113] the entirety of the human genome,[114] or the four-letter "alphabet" of individual nucleotides that comprise DNA.[115]

Finally, the Patent Act fully contemplates the possibility that a patent might result in the creation of a monopoly.[116] A patent can confer monopoly power only when it is so broad in scope that the owner can profitably restrict output of the patented product without fear that consumers will turn to substitutes and competitors.[117] Such a situation is widely thought to be rare.[118] Moreover, even in such cases, a patentee

[113] As one colleague has noted, some patents include claims directed to transgenic organisms that expresss one or more specified DNA molecules together with claims directed to the isolated and purified DNA molecules themselves. Mimi Yang, Intellectual Property/Technology Law, personal communication. This Article is addressed solely to the patenting of DNA molecules and does not purport to draw any conclusions regarding the patenting of transgenic animals or other living organisms.

[114] *See* Oak Ridge National Laboratory, *Genome Glossary* <http://www.ornl.gov/TechResources/Human_Genome/glossary/> (visited June 17, 2002) (defining genome as "All the genetic material in the chromosomes of a particular organism. . . .").

[115] *See infra* section II.A.

In the interest of precision, this article will also avoid referring to DNA patents as "gene patents." While most patented DNA molecules are structurally or functionally related to genes, most are not themselves genes. Whereas there are more than two million patented DNA molecules, *see* Derwent GENESEQ, *supra* note 41, there are estimated to be fewer than 100,000 genes in the human genome. *See* Eli Kintisch, *So What's the Score?*, NEW SCIENTIST, May 12, 2001, at 16 (reviewing widely varying recent estimates of the number of human genes). Relatively few genes have yet been definitively identified, let alone patented. *See, e.g.*, Herman T. Blumenthal, *Milestone or Genomania?*, 56A J. GERONTOLOGY SERIES A 529 (2001) (explaining that even after the sequencing of the human genome, identifying the genes associated with human aging will likely require several decades of research).

[116] *See, e.g.*, Morton Salt Co. v. G.S. Suppiger, Co., 314 U.S. 488, 492 (1942) ("The grant to the inventor of the special privilege of a patent monopoly carries out a public policy adopted by the Constitution and laws of the United States, 'to promote the Progress of Science and useful Arts.'"); Kendall v. Winsor, 62 U.S. 322, 329 (1859) (referring to patent grant as a "limited and temporary monopoly").

[117] *See* Nuno Pires de Carvalho, *The Primary Function of Patents*, 2001 J. L. TECH. & POL'Y 25, 61-66.

[118] *See, e.g.*, Northern Pacific R.R. Co. v. United States, 356 U.S. 1, 10 n.8 (1958) ("Of course it is common knowledge that a patent does not confer a monopoly over a particular commodity."); ROBERT M. SHERWOOD, INTELLECTUAL PROPERTY AND ECONOMIC DEVELOPMENT 51-52 (1990); Carvalho, *supra* note 117, at 62 ("Only a few patents do afford monopoly power"); Lori M. Berg, Comment, *The North American Free Trade Agreement and Protection of Intellectual Property: A Converging View*, 5 TRANSNAT'L L. & POL'Y 99 (1995) ("Rarely is a patent on a single product the equivalent of a marketplace monopoly"); Kenneth W. Dam, *The Economic Underpinnings of Patent Law*, 23 J. LEGAL STUD. 247, 249-50 (1994) ("Indeed, without the benefit of empirical research, it is entirely plausible to conclude that in the great bulk of instances no significant market power is granted."); J. Paul McGrath, *Patent Licensing: A Fresh Look at Antitrust Principles in a Changing Economic Environment*, 27 PAT., TRADEMARK & COPYRIGHT J. (BNA) 624, 626 (1984) ("[T]he exclusive rights to patents rarely give their owners anything approaching a monopoly"); *see also* Nickola v. Peterson, 580 F.2d 898, 914 n.25 (6th Cir. 1978) (Markey, J.) ("Of course it is common knowledge that a patent does not always confer a monopoly over a particular commodity."); *but cf.* In re ISOs Antitrust Litigation, 964 F. Supp. 1479, 1488 (D. Kan. 1997) (holding that antitrust law does not forbid "a single 'patent monopoly' [to] be used to secure multiple 'economic monopolies,' i.e., monopolies in more than one relevant antitrust market"); Ramon A. Klitzke, *Patents and Monopolization: The Role of Patents Under Section Two of the Sherman Act*, 68 MARQ. L. REV. 557, 595 (1985) ("Section Two of the Sherman Act, the antimonopolization statute, stands in polar opposition to the monopoly granted by the Patent Act.")

may be precluded from practicing the claimed invention by third-party patents or other circumstances, because a patent confers the right to exclude others from patenting the invention (a negative right), and not the exclusive right to practice the invention (a positive right). This distinction is often neglected in the characterization of a patent as the positive grant of a monopoly.[119]

C. DNA Molecules and Patentable Subject Matter

To be eligible for a patent, an invention must fit within one of the statutory categories of patentable subject matter established in § 101 of the Patent Act:

> 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.[120]

This list of categories, which has origins in the earliest U.S. patent statutes,[121] has been interpreted as implementing the constitutional requirement that patent protection be limited to "the useful Arts"; i.e., in modern terms, the "technological arts."[122]

While DNA molecules are material substances, and are therefore compositions of matter in a literal sense, not all material substances are considered patentable "compositions of matter" within the meaning of § 101. Products of nature[123] and discoveries in nontechnological fields,

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[119] *See, e.g.*, Bonito Boats Inc. v. Thunder Craft Boats Inc., 489 U.S. 141, 150-51 (1989) (describing the patent right as "the exclusive right to practice the invention for a period of years").

[120] 35 U.S.C. § 101 (emphasis added).

[121] See Act of Apr. 10, 1790, ch. 7, 1 Stat. 109 (authorizing patents for "any useful art, manufacture, engine, machine, or device, or any improvement therein not before known or used"); Act of Feb. 21, 1793, ch. 11, 1 Stat. 318 (amending statutory categories of patentable subject matter to "any useful art, machine, manufacture, or composition of matter, or any new and useful improvement [thereon], not known or used before the application").

[122] *See* In re Bergy, 596 F.2d 952, 958 (C.C.P.A. 1979), *aff'd sub. nom.* Diamond v. Chakrabarty, 447 U.S. 303 (1980) ("the present day equivalent of the term 'useful arts' employed by the Founding Fathers is 'technological arts.'"); In re Toma, 575 F.2d 872, 877 (C.C.P.A. 1978) (stating that claim must be directed to "technological arts" to be patentable subject matter); In re Waldbaum, 457 F.2d 997, 1003 (C.C.P.A. 1971) (same); *see generally* John R. Thomas, *The Patenting of the Liberal Professions*, 40 B.C. L. Rev. 1139 (1999) (examining various definitions of technological arts as alternative approaches to delineating patentable subject matter).

[123] *See* Diamond v. Diehr, 450 U.S. 175, 185 (1981) ("Excluded from such patent protection [under § 101] are laws of nature, natural phenomena, and abstract ideas."); Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948) ("He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of which the law recognizes. If there is to be invention from such a discovery, it must come from the application of the law of nature to a new and useful end."); American Wood-Paper Co. v. Fiber Disintegrating Co., 90 U.S. (23 Wall.) 566 (1874); Ex parte Latimer, 1889 C.D. 123, 46 O.G. 1638 (Comm'r Pat. 1889); *see also* Conley & Makowski, supra note 142 , at __ (describing the application of the product of nature doctrine to biological and chemical substances in the pre-biotechnology era).

such as pure mathematics[124] and the liberal arts,[125] are specifically excluded from patentability. As the Supreme Court famously noted in *Diamond v. Chakrabarty* (1980),[126] these categorical exclusions are strictly construed, permitting patents to issue on "anything under the sun that is made by man."[127] In *Chakrabarty*, the Court interpreted the term "composition of matter" to include "all compositions of two or more substances and . . . all composite articles, whether they be the results of chemical union, or of mechanical mixture, or whether they be gases, fluids, powders or solids."[128] The Court concluded that a genetically-altered bacterium did not fall within the "product of nature" exclusion as it was "not nature's handiwork, but [Chakrabarty's] own; accordingly, it is patentable subject matter."[129]

The *Chakrabarty* decision and its progeny have represented a general trend by the courts, most notably the United States Court of Appeals for the Federal Circuit, toward an increasingly expansive (and controversial[130]) interpretation of patentable subject matter.[131] Since

[124] *See, e.g.*, Gottschalk v. Benson, 409 U.S. 63, 71-72 (1972) (holding that an invention consisting of the use of a mathematical algorithm is a "mental process[]" and therefore not patentable subject matter under § 101).

[125] *See, e.g.*, In re Toma, 575 F.2d at 877; In re Waldbaum, 457 F.2d at 1003.

[126] 447 U.S. 303 (1980).

[127] Id. at 309.

[128] Id. at 308 (quoting Shell Dev. Co. v. Watson, 149 F. Supp. 279, 280 (D.D.C. 1957), aff'd, 252 F.2d 861 (D.C. Cir. 1958).

[129] Id. at 310.

[130] *See e.g.*, Brian P. Biddinger, Note, *Limiting the Business Method Patent*, 69 FORDHAM L. REV. 2523, 2528-34 (criticizing *State Street Bank*); Conley & Makowski, *supra* note 142, at __; Eisenberg, *supra* note 111, at 793-94 (suggesting that Federal Circuit's "momentum" toward more expansive interpretation of patentable subject matter would yield incorrect decision regarding patentability of DNA databases); Thomas, *supra* note 122, at 1163-70 (arguing that business method patents threaten to destabilize fundamental understandings of which arts are "technological").

[131] *Cf.* In re Alappat, 33 F.3d 1526 (Fed. Cir. 1994) (en banc) (holding that a claim directed to a computer programmed to execute a mathematical algorithm satisfies § 101 subject matter requirement), *with* Diamond v. Diehr, 450 U.S. 175, 186 (1981) (holding mathematical algorithms unpatentable) and Gottschalk, 409 U.S. at 71-72 (same); *cf.* State Street Bank & Trust v. Signature Financial Group, 149 F.3d 1368 (Fed. Cir. 1998), *cert. denied*, 525 U.S. 1093 (1999) (holding that business methods are patentable subject matter) *with* Hotel Security Checking Co. v. Lorraine Co., 160 F. 467, 469 (2nd Cir. 1908) (holding that a system of transacting business, even if novel, is not a patentable "art"); *and cf.* J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred International, Inc., 534 U.S. 124 (2001) (holding that seeds are patentable subject matter) *with* Ex parte Latimer, 1889 Dec. Comm'n Patent 123 (1889) (holding plant tissues to be unpatentable). The Patent Office has begun issuing patents on "sports moves." *See, e.g.*, U.S. Patent 5,776,016 (issued July 7, 1998) (method of putting a golf ball using a putter with a reflective surface); U.S. Patent 5,498,162 (issued March 12, 1996) (method of demonstrating a weightlifting technique); Kukkomen, *Be a Good Sport and Refrain from Using My Patented Putt: Intellectual Property Protection for Sports Related Movements*, 80 J. PAT. & TRADEMARK OFF. SOC'Y 808 (1998); Note, *It's Your Move — No It's Not! The Application of Patent Law to Sports Moves*, 70 U. COLO. L. REV. 1051 (1999).

The Federal Circuit itself has remarked on this trend, attributing it to the court's recognition of the need for the law "to adapt to new and innovative concepts, while remaining true to basic principles." AT&T Corp. v. Excel Communications, Inc., 172 F.3d 1352, 1356 (Fed. Cir. 1999); see also J.E.M. AG Supply, 534 U.S. 124, ___ (2001) (attributing broad interpretation of § 101 to "the forward-looking perspective of the utility patent statute").

Chakrabarty, the scope of patentable subject matter under § 101 has been extended to cover an ever-widening range of biological materials that have been genetically altered, purified, or otherwise changed through human intervention into forms not found in nature.[132] These developments have obliterated any distinction between animate and inanimate compositions of matter for purposes of the product of nature inquiry.[133]

Doctrinal support for the patentability of DNA is grounded in the structural and functional distinctions between an isolated, purified DNA molecule[134] and its naturally-occurring, impure counterpart. Under the 1952 Patent Act, the courts have generally regarded the purification of natural substances as one of the many forms of human intervention that are capable of producing a "new and useful . . . composition of matter" within the meaning of § 101.[135] While it has been long settled that the mere fact of purification is not sufficient to confer patentability on a substance,[136] over the years there has been a divergence of opinion as to the further conditions that a purified substance must meet in order to distinguish it from an unpatentable impure substance and thereby qualify as patentable subject matter under § 101.[137] One line of cases has held that the purified substance qualifies as a patentable "new . . . composition of matter" within the meaning of § 101 provided that the

[132] *See, e.g.*, J.E.M. AG Supply, 534 U.S. 124 (2001) (newly developed plant breeds); Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200 (Fed. Cir. 1991) (isolated and purified DNA molecules); Ex parte Allen, 2 U.S.P.Q.2d (BNA) 1425 (B.P.A.I. 1987), *aff'd*, 846 F.2d 77 (Fed. Cir. 1988) (genetically modified oysters); U.S. Patent 4,736,866 (issued Apr. 12, 1988) (genetically altered mice); U.S. Patent 5,817,479 (issued Oct. 6, 1998) (expressed sequence tags); *see also* In re Bergy, 596 F.2d 952 (C.C.P.A. 1979) (biologically pure culture of a microorganism).

[133] *See* In re Bergy, 596 F.2d 952, 975 (C.C.P.A. 1979) ("In fact, we see no [l]egally significant difference between active chemicals which are classified as 'dead' and organisms used for their [c]hemical reactions which take place because they are 'alive.' Life is largely chemistry."); KENNETH J. BURCHFIEL, BIOTECHNOLOGY AND THE FEDERAL CIRCUIT § 3.2, at 41 (1995) ("The product of nature doctrine survives as a limitation on patentable subject matter, but the doctrine draws no distinction between animate and inanimate naturally occurring products.").

[134] *See supra* note 112 and accompanying text.

[135] *See* Merck & Co., Inc. v. Olin Mathieson Chem. Corp., 253 F.2d 156, 161, 163 (4th Cir. 1958) ("All of the tangible things . . . for which patent protection is granted are products of nature in the sense that nature provides the source materials. . . . The fact . . . that a new and useful product is the result of processes of extraction, concentration and purification of natural materials does not defeat its patentability.").

[136] *See, e.g.*, Risdon Locomotive Works v. Medart, 158 U.S. 68, 81 (1895); In re Michalek, 161 F.2d 253 (C.C.P.A. 1947); In re Crosley, 159 F.2d 735 (C.C.P.A. 1947); In re King, 107 F.2d 618, 620 (C.C.P.A. 1939); In re Macallum, 102 F.2d 614 (C.C.P.A. 1939); In re Merz, 97 F.2d 599 (C.C.P.A. 1939).

[137] *See* DONALD S. CHISUM, 1 CHISUM ON PATENTS § 1.02[9], at 1-75 (describing the two lines of cases as taking "fundamentally different approach[es] to the purity problem"); *but see* John Conley & Roberte Makowski, *Going Back to Square One: Biotechnology Patents and the Product of Nature Doctrine*, 85 J. PAT. & TRADEMARK OFF. SOC'Y 301, 330 n. 198 (arguing that both lines of doctrine are "implicit but nonetheless clear in the *Merck* analysis").

substance satisfies the novelty requirement of § 102.[138] The other line of cases has held that the pure substance must differ from the impure substance "in kind" as well as "in degree,"[139] meaning that the purification must yield an entirely new utility that is specific to the purified substance.[140] This requirement, that the asserted utility for the purified substance be one that is not possessed by its naturally-occurring counterpart, is somewhat more stringent than the generally applicable utility requirement of § 101.[141]

Some commentators contend that the mere isolation and purification of a substance from its naturally occurring environment should not yield a patentable "new . . . composition of matter" within the meaning of § 101 of the Patent Act.[142] John Conley and Roberte Makowski contend that an isolated and purified DNA molecule should be viewed as an unpatentable product of nature because it "is not, and cannot be, distinguished from [its naturally occurring counterpart] by any physical

[138] *See* Scripps Clinic & Research Foundation v. Genentech Inc., 666 F. Supp. 1379, 1389 n.6 (N.D. Calif. 1987), *rev'd in part on other grounds*, 927 F.2d 1565 (Fed. Cir. 1991) ("Although Factor VIII:C molecules occur in nature, a purified and concentrated preparation of Factor VIII:C as claimed in the patent constitutes a new form or combination not existing in nature, and hence is patentable under 35 U.S.C. § 101."); In re Bergstrom, 427 F.2d 1394, 1401-02 (C.C.P.A. 1970) ("[B]y definition, pure materials necessarily differ from less pure or impure materials and, if the latter are the only ones existing and available as a standard of reference . . . perforce the 'pure' materials are 'new' with respect to them."); *but see* General Electric Co. v. De Forest Radio Co., 17 F.2d 90 (D.Del. 1927) (affirming rejection of claim to "[s]ubstantially pure tungsten" as unpatentable product of nature).

[139] *See* Merck & Co. v. Olin Mathieson Chemical Corp., 253 F.2d 156, 162 (4th Cir. 1958) (describing product of nature doctrine as barring the patenting of "a new [purified] substance [that] differs from the old 'merely in degree, and not in kind.'"); Parke-Davis & Co. v. H.K. Mulford & Co., 189 F. 95, 103 (S.D.N.Y. 1911), *aff'd*, 196 F. 496 (2d Cir. 1912) (Learned Hand, J.) (characterizing the product of nature inquiry with respect to purified substances as the drawing of a "line between different substances and degrees of the same substance").

[140] *See, e.g.*, Merck, 253 F.2d at 164 (4th Cir. 1958) (upholding patentability of purified Vitamin B-12 based on transformation of the chemical "from complete uselessness to great and perfected utility"); Parke-Davis, 189 F. at 103 (upholding patentability of purified adrenalin compound based on new commercial and therapeutic uses); Kuehmsted v. Farbenfabriken of Elberfeld, 179 F. 701 (7th Cir. 1910) (upholding patentability of purified acytyl salicylic acid (aspirin) based on new utility as therapeutic agent); *cf.* Chakrabarty, 447 U.S. at 310 (citing "potential for significant utility" to support the conclusion that a genetically-altered bacterium is patentable subject matter under § 101); Funk Bros., 333 U.S. at 132 (1948) (citing lack of new utility to support the conclusion that the mere combination of various species of bacteria is an unpatentable product of nature).

See Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences*, 49 EMORY L.J. 783, 786 & n. 17 (citing *Merck*); *but cf.* Conley & Makowski, supra note 142, at ___ (criticizing *Merck* and citing *General Electric*).

[141] *See supra* Section III.A.

[142] *See* Utility Guidelines, *supra* note 163, at 1093 cmt. 2; Ned Hettinger, *Patenting Life: Biotechnology, Intellectual Property, and Environmental Ethics*, 22 B.C. ENVTL. AFF. L. REV. 267 (1995); John Conley & Roberte Makowski, *Going Back to Square One: Biotechnology Patents and the Product of Nature Doctrine* (manuscript).

characteristic."[143] Ned Hettinger, noting that isolating a gene does not change the traits that are expressed when the gene is returned to an *in vivo* setting,[144] asserts that "[t]rue invention of a gene would involve creating a gene coding for a characteristic that no organism possesses."[145] Linda Demaine and Aaron Fellmeth argue that absent a "substantial transformation" of biological function, purification does not change a naturally occurring DNA molecule into a "new" product.[146]

An implicit premise of these comments is that no legal significance under § 101 should attach to the isolation and purification of a composition of matter. For Conley and Makowski, the isolated and purified condition of a DNA molecule should not count as a "distinguish[ing] . . . physical characteristic." For Hettinger, a claimed DNA molecule is characterized solely by its *in vivo* behavior; the structure and function of the molecule in its isolated, purified, *in vitro* state should play no part in its characterization under § 101. Demaine and Fellmeth conclude that purification merely confers "a change of context, not a [fundamental] transformation of biological function," on a naturally occurring DNA molecule.[147] Similarly, another commentator, Burton Ong, argues that isolation and purification alone should not be found to convert "nature's handiwork" into a patentable invention if the resulting organic substance merely "performs a biological function . . . which it would otherwise carry out elsewhere in nature."[148]

Other commentators, including Jon Merz and Mildred Cho, contend that DNA patent disclosures provide the public with nothing more than an "observation of a state of nature" (e.g., a disease-gene association) that could have been made by anyone skilled in molecular biology using well-known and generally applicable techniques.[149] According to this view, § 101 should be read to exclude not only naturally occurring substances, but also any invention whose disclosure provides no more information than could have been found by observing nature.

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[143] *See* Conley & Makowski, *supra* note 142, at __ (quoting Ex parte Lattimer, 1889 Comm'n Dec. 123, 124 (1889) (rejecting a patent claim that failed to set forth "physical characteristics" distinguishing a claimed fiber from other naturally-occurring fibers).

[144] *See* Hettinger, *supra* note 142, at 289 & n. 116.

[145] *See id.* at 289 & n.114.

[146] Linda J. Demaine & Aaron Xavier Fellmeth, *Reinventing the Double Helix: A Novel and Nonobvious Reconceptualization of the Biotechnology Patent*, 55 STAN. L. REV. 303, 393-400 (2002).

[147] *See id.* at 400 (arguing that purification of natural proteins is "merely a change of context" and stating that "[t]he same analysis applies to DNA molecules").

[148] Burton T. Ong, *Patenting the Biological Bounty of Nature: Re-Examining the Status of Organic Inventions as Patentable Subject Matter*, 8 MARQ. INTELL. PROP. L. REV. 1, 19-20 (2004).

[149] Merz et al., *supra* note 69, at 300; Jon F. Merz & Mildred K. Cho, *Disease Genes Are Not Patentable: A Rebuttal of McGee*, 7 CAMBRIDGE QUARTERLY OF HEALTHCARE ETHICS 425 (1998).

Critics have described the Federal Circuit's permissive approach to the patentable subject matter requirement in this context as an evisceration, rather than an elaboration, of the principles underlying the product of nature doctrine.[150] Some have even questioned the court's motivations.[151] Perhaps a more charitable view is that the court has demurred on the essentially philosophical question of whether "nature" encompasses all, some, or none of the substances that can be derived from it through human acts of isolation and purification,[152] and has focused instead on promoting "Progress" by holding claimants to such purified substances to the terms of the patent bargain.

None of these commentators has expressed any expectation that the courts will actually reverse the Federal Circuit's position that artificial isolation and purification distinguish DNA molecules over products of nature. Legislative and administrative initiatives to restrict patenting activity in biotechnology[153] have often deferred to the courts on the issue of patentable subject matter[154] and have become rarer in recent years.[155] Donna Gitter has gone so far as to conclude that "arguments against the patentability of human DNA sequences, *per se*, are a dead letter under U.S. law."[156] Of course, it is not necessary to reach that conclusion in order to justify an investigation into the long-term impacts of DNA patents on specific research methods, but this Article does proceed under the

[150] See Conley, *supra* note 137, at __ (citing In re Bergy, 596 F.2d at 960) (arguing that under *Bergy*, the product of nature doctrine requires a "freestanding inquiry" that is entirely separate and distinct from the utility, novelty and nonobviousness requirements); John M. Golden, *Biotechnology, Technology Policy, and Patentability: Natural Products and Invention in the American System*, 50 EMORY L.J. 112, 127 (2001) (describing the product of nature doctrine as "effectively toothless" because the "'purification exception' tends to swallow the rule").

[151] *See* Conley, *supra* note 137, at __.

[152] *See* Parke-Davis, 189 F. at 103 (concluding that the product of nature inquiry with respect to purified substances is a distinction "to be drawn rather from the common usages of men than from nice considerations of dialectic").

[153] *See* Barry S. Edwards, Note, . . . *And On His Farm He Had a Geep: Patenting Transgenic Animals*, 2 MINN. INTELL. PROP. REV. 89, 113-18 (2001) (reviewing failed legislative responses to the patenting of transgenic organisms); Sigrid Sterckx, *European Patent Law and Biotechnological Inventions*, *in* BIOTECHNOLOGY, PATENTS AND MORALITY 1, 18-19 (Sigrid Sterckx ed., 1997) (same); Utility Guidelines, supra note 163.

[154] *See generally* Utility Guidelines, supra note 163, at 1092-97 (dismissing public concerns about extending patentable subject matter to cover DNA molecules); Edwards, supra note 153, at 116-17 (reviewing failed legislation to modify substantive rights under biotechnology patents); *but see* H.R. 4989, 102nd Cong. (1992) § 2(b) (providing for a five-year period during which animals would be excluded from patentable subject matter). In contrast, many European Union member states are vigorously resisting an EU directive to extend patentability to human DNA sequences. *See* Gitter, *supra* note 8, at 1644-49.

[155] See Edwards, supra note 153, at 117.

[156] Gitter, *supra* note 8, at 1651; but see Edwards, supra note 153 (suggesting that growing public awareness may spur congressional action on biotechnology patents).

working hypothesis that patent claims covering microarray probes will, as a category, be found to be legally operative for the foreseeable future.

It is sufficient for present purposes to note that both of these lines of cases have rejected an approach to the § 101 subject matter requirement that would classify entire categories of purified substances as unpatentable products of nature,[157] in favor of a particularized inquiry into whether a claimed purified substance is "new" and/or "useful."[158] For isolated and purified DNA molecules, this means that the product of nature doctrine retains little independent significance in the patentability analysis, and simply collapses into the generally applicable § 102 novelty requirement[159] and a slightly stricter version of the § 101 utility requirement.[160] Under prevailing doctrine, then, the patentability of DNA molecules is to be governed not by a "new and activist" genetic exceptionalism,[161] but by a case-by case approach in which "[t]he same patentability analysis is conducted for every patent application, regardless of whether the application is for a computer chip, a mechanical apparatus, a pharmaceutical, or a piece of DNA."[162]

D. The Patent Office's View of the Controversy

In January 2001, the Patent Office took the opportunity to address various criticisms of DNA patenting in connection with the issuance of two sets of guidelines for the examination of patent applications under the Patent Act.[163] The guidelines elaborate the prevailing legal standards for the utility requirement under § 101 and § 112, ¶ 1 and the written description requirement under § 112, ¶ 1. To satisfy the utility requirement, a claimed invention must have at least one "specific and substantial utility" that would be found credible by one of ordinary skill in the art.[164] To satisfy the written description requirement, the

[157] *See, e.g.*, In re Bergy, 596 F.2d at 976 (rejecting a categorical approach to the patentability of "all living things").

[158] *See* Merck, 253 F.2d at 161 ("There is nothing in the language of the [1952] Act which precludes the issuance of a patent upon a 'product of nature' when it is a 'new and useful composition of matter' and there is compliance with the specified conditions for patentability.")

[159] *See supra* Section III.A.

[160] *See id.*

[161] *See, e.g.*, Glenn McGee, *Foreword: Genetic Exceptionalism*, 11 HARV. J. L. & TECH. 565, 569 (1998) ("Those preparing to litigate existing claims to human gene patents have before them a significant new challenge: developing jurisprudence that either incorporates genetic information and processes into other conventional matters, or holds that genes are not patentable subject matter. Here too, the question is at once difficult and urgent: do we need new and activist genetic policy, or can traditional norms be shaped in the courts to accommodate new problems?").

[162] John J. Doll, *The Patenting of DNA*, 280 SCIENCE 689, 689 (1998).

[163] Utility Guidelines, *supra* note 5; United States Patent & Trademark Office, Written Description Guidelines, 66 Fed. Reg. 1099 (Jan. 5, 2001) [hereinafter Written Description Guidelines].

[164] *See* Utility Guidelines, *supra* note 5, ¶¶ 1-2, at 1098.

specification of the patent application must "describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention."[165] The guidelines serve in part to provide general procedures for allocating the burdens of proof between the applicant and the examiner relating to these standards.

In a preface to the guidelines, the agency published an extensive discussion of public comments on DNA patents received during the previous year, including arguments against DNA patents from each of the three groups discussed above.[166] The Patent Office responded to these comments by citing leading precedents, mainly from the Supreme Court and the Federal Circuit.

The Patent Office received numerous comments regarding the fairness of the patent bargain in the case of claims to DNA molecules. Some commentators argued that DNA patents would delay medical research and further exploratory research using the claimed DNA molecules without providing a commensurate societal benefit from the molecules' discovery and disclosure.[167] The Patent Office rejected these arguments, noting that the Patent Act requires the issuance of any patent that satisfies the statutory conditions for patentability.[168] Thus, beyond examining patents for compliance with these conditions, the agency lacks discretion to evaluate the private value of the patent grant or the social value of the invention disclosure.[169] The Patent Office proceeded to defend the continued issuance of DNA patents by asserting the following premises:

> 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. . . . Other researchers may discover higher, better or more practical uses, but they are advantaged by the starting point that the original disclosure provides.[170]

[165] See Written Description Guidelines, supra note 163, at 1104.

[166] *See id.*

[167] See id. at 1094-95 cmts. 7-8, 12-13.

[168] See id. at 1094 cmt. 7.

[169] See id. ("As long as one specific, substantial and credible use [of the DNA molecule] is disclosed and the statutory requirements are met, the USPTO is not authorized to withhold the patent until another, or better, use is discovered.").

[170] Id. at 1094 cmt. 7.

Several commentators noted that in certain cases, the discovery of a claimed DNA molecule could have been achieved using well-known, routine methods.[171] The Patent Office responded by distinguishing between such general methodological knowledge in the prior art and the patent disclosure's teaching of the DNA molecule's specific structural formula. Citing the Federal Circuit's *In re Deuel* decision,[172] the agency stated that "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."[173]

The Patent Office also received various comments expressing the concern that patents were being issued over a part of the human body, a piece of our common human heritage, and a basic aspect of human identity.[174] The agency responded by observing that the invention claimed in a DNA patent was the isolated and purified DNA molecule — a composition of matter — and not DNA sequence information or the DNA as it occurs in the human body.[175]

Several commentators also objected to the patenting of genes because genes exist in nature.[176] They argued that genes are discovered, not invented,[177] and that genes are products of nature.[178] The Patent

[171] *See id.* at 1095 cmt. 13.

[172] 51 F.3d 1552, 1559 (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, 785 (Fed. Cir. 1993) ("[T]he issue is the obviousness of the claimed compositions, not of the method by which they are made."); *but see* Ex parte Goldgaber, 41 U.S.P.Q.2d 1172 (Bd. Pat. App. & Int. 1995) (unpublished opinion) ("[W]e find nothing wrong, however, in the application of methodology in rejecting product claims under 35 U.S.C. §103, depending on the particular facts of the case.").

[173] Utility Guidelines, *supra* note 5, at 1095 cmt. 13.

Several commentators have criticized the Federal Circuit's *Bell* and *Deuel* decisions, arguing that general methods exist for cloning DNA molecules from known proteins and amino acids with a reasonable expectation of success. *See, e.g.*, NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, A PATENT SYSTEM FOR THE 21ST CENTURY 91-93 (Stephen A. Merrill et al. eds., 2004); Philippe Ducor, *Recombinant Products and Nonobviousness: A Typology*, 13 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 43-48 (1997); Kate H. Murashige, *Genome Research and Traditional Intellectual Property Protection: A Bad Fit?*, 7 RISK: HEALTH SAFETY & ENV'T 231, 233-35 (1996); Arti K. Rai, *Intellectual Property Rights in Biotechnology: Addressing New Technology*, 34 WAKE FOREST L. REV. 827, 833-34 (1999); *see also* Jeffrey S. Dillen, Comment, *DNA Patentability: Anything But Obvious*, 1997 WIS. L. REV. 1023, 1044-45 (1997) (suggesting that the technological rationales for *Deuel*'s obviousness analysis are eroding). Such arguments appeal to the general rule that a claimed invention is obvious if the prior art provides motivation for the invention and enables one of ordinary skill in the art to make the invention with a reasonable expectation of success. *See* In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991).

[174] *See id.* at 1093 cmt. 2.

[175] *See id.*

[176] *See id.*

[177] *See id.* at 1092 cmt. 1.

[178] See id. at 1093 cmt. 2.

Office responded by noting that Section 101 of the Patent Act expressly permits the grant of a patent to a person who "invents or discovers any new and useful . . . composition of matter."[179] The agency also observed that compounds isolated and purified from nature are not found in the human body and have long been patentable.[180] For example, Judge Learned Hand held in 1911 that adrenaline when isolated and purified from the adrenal gland "became for every practical purpose a new thing commercially and therapeutically" and was therefore patentable.[181]

E. SUMMARY

While there appears to be widespread public concern about deoxyribonucleic acid ("DNA") patents, very few people actually know what DNA patents are,[182] and even fewer know what effects they will have on genetic research.[183] Defenders of DNA patents argue that they will promote research by providing scientists with incentives to invent and discover;[184] critics contend that they will impede research by depriving scientists of basic tools and techniques.[185]

The United States patent system has not waited for a definitive resolution of this debate. It has not needed to wait. Although the

[179] See id. at 1093 cmt. 1 (quoting 35 U.S.C. § 101).

[180] See id. at 1093 cmt. 2.

[181] See Parke-Davis & Co. v. H.K. Mulford Co., 189 F. 95, 103 (S.D.N.Y. 1911).

[182] Even recent law review articles on the subject of DNA patents devote several pages to introducing basic concepts in genetics and patent law. *See, e.g.*, Mary Breen Smith, Comment, *An End to Gene Patents? The Human Genome Project Versus the United States Patent and Trademark Office's 1999 Utility Guidelines*, 73 U. COLO. L. REV. 747 (2002); Scott McBride, Comment, *Patentability of Human Genes: Our Patent System Can Address the Issues Without Modification*, 85 MARQ. L. REV. 511 (2001); David B. Reznik, *DNA Patents and Human Dignity*, 29 J.L. MED. & ETHICS 152 (2001); Mattias Luukkonen, Note, *Gene Patents: How Useful Are the New Utility Requirements?*, 23 THOMAS JEFFERSON L. REV. 337 (2001). Unfortunately, misconceptions are still common in the literature. *See generally supra* Section III.B (describing common misconceptions about DNA patents and their effects); United States Patent & Trademark Office, Utility Examination Guidelines, 66 Fed. Reg. 1092 *passim* (Jan. 5, 2001) [hereinafter Utility Guidelines] (rejecting public comments as based on erroneous legal premises). It has therefore also been necessary to provide an extensive introduction to DNA patents in this Article.

[183] *See* Timothy Caulfield et al., *Patenting Human Genetic Material: Refocusing the Debate*, 1 NATURE REV. GENETICS 227, 230 (2000) ("[M]ore research is needed on the actual benefits and harms of human gene patents. Much of the public debate seems to be based on broad assumptions that patents either encourage innovation and product development or that they are bad for society generally. As much as possible, reform initiatives should be based on credible evidence."); *see generally* George Priest, *What Economists Can Tell Lawyers About Intellectual Property*, 8 RESEARCH ON L. & ECON. 19 (1986) ("Economists know almost nothing about the effect on social welfare of the patent system or . . . other intellectual property.").

[184] *See, e.g.*, John J. Doll, *The Patenting of DNA*, 280 SCIENCE 689, 690 (1998); John Murray, Note, *Owning Genes: Disputes Involving DNA Sequence Patents*, 75 CHI.-KENT L. REV. 231, 254-56 (1999).

[185] *See* John F. Merz et al., *Diagnostic Testing Fails the Test*, 415 NATURE 577 (2002) (reporting that several labs have canceled genetic testing projects in response to exclusive licensing of DNA patents); A. Schissel et al., *Survey Confirms Fears About Licensing of Genetic Tests*, 402 NATURE 118 (1999) (same).

constitutional purpose for the issuance of patents is to "promote the Progress of . . . useful Arts,"[186] no law requires the Patent Office or the courts to balance the research a patent motivates against the research it forecloses.[187] The Patent Act[188] requires the Patent Office to issue a patent upon every application claiming a DNA molecule that meets the statutory requirements for a patent,[189] and in doing so, discharges its constitutional duty to "promote . . . Progress."[190]

The Utility Guidelines make clear that as long as DNA molecules are eligible subject matter under the Patent Act,[191] the Patent Office will continue to treat the issuance of DNA patents as an end in itself.[192] The scientific community might consider the use of a well-known general method to obtain the structural formula for a specific DNA molecule to be a routine undertaking, but the patent system must recognize such trivial work as "Progress."[193] And, if the interests of medical research ultimately diverge from the patent system's concept of "Progress,"[194] then so much the worse for medical research.[195] The more valid and enforceable DNA patents are issued, the more "Progress" is promoted, as Congress has elaborated and the courts and the Patent Office have given effect to that term: namely, *the discovery and disclosure of structural formulae for new, nonobvious and useful DNA molecules.*[196]

The self-justifying logic of "Progress" has resisted a steady barrage of economic,[197] moral,[198] and metaphysical[199] objections. The principal criticisms of DNA patents have been categorical: they have drawn no distinctions among the various molecules that might be encompassed within a DNA patent claim. As such, they represent an unduly radical

[186] U.S. CONST., art. I, § 8, cl. 8.

[187] *See generally* section III.A.

[188] 35 U.S.C. §§ 1-376.

[189] 35 U.S.C. § 131; Utility Guidelines, *supra* note 182, a't 1094 cmt. 7.

[190] *See* Graham v. John Deere Co., 383 U.S. 1, 6 (1966) ("It is the duty of the Commissioner of Patents and of the courts in the administration of the patent system to give effect to the constitutional standard by appropriate application, in each case, of the statutory scheme of the Congress.").

[191] *See generally infra* section III.C.

[192] *See generally infra* section III.D; *cf.* Jon F. Merz et al., *Disease Gene Patenting is a Bad Innovation*, 2 MOLECULAR DIAGNOSIS 299, 301 (1997) (arguing that the pursuit of DNA patents as an end goal is preventing important downstream clinical research).

[193] *See supra* text accompanying notes 171-173.

[194] *See supra* text accompanying notes 66-69.

[195] *See* Utility Guidelines, *supra* note 182, at 1094 cmt. 7 (stating Patent Office's view that the discovery and disclosure of "genetic inventions" promotes progress, regardless of subsequent medical research).

[196] *See id.* at 1094 cmt. 5 (stating Patent Office's view that patents for DNA, as for other chemical compounds, promote progress by providing incentives for the original inventor and others to discover new, nonobvious and useful chemical compounds).

[197] *See supra* section III.A.

[198] *See supra* section III.B.

[199] *See supra* section III.C.

strategy on the part of those who are concerned about the social costs of DNA patenting. For the courts and the Patent Office to account for the relatively limited social value of a disclosed DNA sequence, to give effect to the moral claims of human subjects and religious leaders, or to exclude substances isolated from the human body from patentable subject matter, they would need to distinguish DNA molecules categorically from other compositions of matter, in effect reading a fact-specific "genetic exception" into the Patent Act. They have repeatedly declined to do so.[200] Absent such a development, critical challenges to the patenting of DNA molecules should focus instead on challenging the factual premise that DNA patenting promotes the patent system's concept of "Progress."

IV. CHALLENGING THE PATENT SYSTEM'S PURSUIT OF "PROGRESS" IN OLIGONUCLEOTIDE RESEARCH

As I have argued in Part III, the patent system has effectively evaded previous objections to the apparent imbalance in the DNA patent bargain by maintaining the position that every valid DNA patent issued under the Patent Act promotes the "Progress of . . . Useful Arts," where "Progress" is understood as the discovery and disclosure of structural formulae for new, nonobvious and useful DNA molecules. In particular, the patent system purports to promote this concept of "Progress" when it allows a composition-of-matter claim to an oligonucleotide based on the discovery of one specific and substantial utility.[201]

The patentability of DNA molecules as compositions of matter effectively allows the discoverer of one use of an oligonucleotide to exclude the public from all uses. This may be particularly problematic for scientists, given the remarkable versatility of oligonucleotides in genetic research. As the analysis in this Part will show, oligonucleotide patents may actually undermine the patent system's concept of

[200] Federal Circuit Judge Randall Rader, joined twice by Judges Arthur J. Gajarsa and Richard Linn, has filed dissenting opinions vigorously criticizing the court's favoring of structural over methodological disclosures of DNA molecules under the § 112 written description requirement. *See* Univ. of Rochester v. G.D. Searle & Co., Inc., 375 F.3d 1303, 1307-24 (Fed. Cir. 2004) (Rader, J., dissenting); Enzo Biochem, Inc. v. Gen-Probe, Inc., 323 F.3d 956, 976-83 (Fed. Cir. 2002) (Rader, J., dissenting); *see also* Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1322-27 (Fed. Cir. 2003) (Rader, J., concurring). The remaining judges on the court by now have had ample opportunity to consider Judge Rader's arguments and do not yet appear to have been persuaded. As Arti Rai has suggested, it is possible that Judge Rader's position will eventually prevail, and even be extended to the court's § 102 and § 103 jurisprudence. Arti Rai, personal communication, on file with author. The position of this Article, however, is that there exist important avenues for challenging the issuance of DNA patents that do not rely on such a broad reversal of current Federal Circuit doctrine.

[201] *See supra* text accompanying note 170.

"Progress" by impeding particular genetic research procedures, including some promising approaches to the discovery of patentable oligonucleotides.

Section IV. A surveys the sequence-specific uses of oligonucleotides that are most commonly recited in support of patent claims covering those oligonucleotides: probes for DNA molecules of known sequence, PCR primers, aptamers, antisense therapies, and oligonucleotide-directed mutagenesis. Section IV.B describes experimental procedures that use certain oligonucleotides and that may lead to the discovery of other useful oligonucleotides: e.g., RAPD-PCR primers, random primers for the synthesis of radiolabeled probes, sequencing by hybridization, and gene expression studies.

In assessing the extent to which existing oligonucleotide patents may be impeding the future discovery of patentable oligonucleotides, it is helpful to identify conditions under which the exclusion of patented oligonucleotide probes will degrade the performance of particular experimental procedures. Section IV.C examines the effect of oligonucleotide patenting on two such procedures: sequencing by hybridization and clustering of gene expression data. Building on previous work in the field of bioinformatics, I provide quantitative evidence that a significant degree of guaranteed public access to oligonucleotides is critically necessary to facilitate future oligonucleotide research.

Of course, the fact that a patent confers an exclusionary right to the patentee does not imply that the public will necessarily be excluded from practicing the claimed invention during the patent term. As various commentators have pointed out, a DNA patent merely represents an initial entitlement that can be reallocated to appropriate research institutions through licensing.[202] Critics of DNA patents, however, have noted that where diagnostic tests and therapies require the use of numerous DNA molecules patented by many different

[202] *See* ZWEIGER, *supra* note 68, at 173-74 (arguing that "[d]ealmaking, cross-licensing, mergers, and acquisitions" are likely to overcome any obstacles to research in the "very dynamic" genomics industry, "particularly when companies' survival and people's incomes and investments are at stake"); Kenneth W. Dam, *Intellectual Property and the Academic Enterprise* 11-12 (Univ. of Chicago John M. Olin Law & Econ. Working Paper, No. 68, 1999) <http://www.law.uchicago.edu/Publications/Working/index.html> (arguing that voluntary industry-wide cross-licensing of intellectual property should be preferred as a solution to the problem of technology access in the biomedical field).

[203] *See* Bobrow & Thomas, *supra* note 69, at ("If the DNA sequences of all of these components are identified and then treated as separate 'inventions,' any useful product is highly likely to cross the boundaries of several patents."); Heller & Eisenberg, *supra* note 69, at 699 ("Foreseeable commercial products, such as therapeutic proteins or genetic diagnostic tests, are more likely to require the use of multiple [gene] fragments."). This situation is commonly described as "patent stacking." Heller & Eisenberg, *supra* note 69, at 699.

firms,[203] the costs of the necessary licensing transactions can be prohibitive.[204] Such licensing difficulties may force scientists to alter or even abandon promising biomedical research projects.[205] More generally, to the extent that standards of patentability differ from generally accepted standards of excellence in the scientific community,[206] economic pressures in the market for DNA patents may also distort the agendas of research scientists.

Available data on DNA patent licensing is too limited to draw definitive conclusions regarding the extent to which existing and future DNA patents may result in the exclusion of DNA molecules from specific research procedures. A recent study by the National Research Council of the National Academy of Sciences, however, found that most biotechnology researchers had found "working solutions" in response to the existence of patents on DNA probes and other research tools.[207] Researchers were able to pay reasonable prices to license at least those patented research tools that were "nonrival-in-use"; i.e., those tending not to lead to the development of competing products.[208] Other researchers were able to work with non-infringing research tools or to

[204] *See* John Barton, *Reforming the Patent System*, 287 SCIENCE 1933, 1933 (2000) ("Those who wish to introduce a new pharmaceutical product must negotiate an unwieldy number of licenses with firms that have patents on various steps in the research . . . . The problem is likely to become increasingly serious in biotechnology . . . where the practical limit of claim breadth seems to be only the imagination of the claim drafter."); Rebecca Eisenberg, *Do EST Patents Matter?*, 14 TRENDS IN GENETICS 379, 380 & nn. 14-15 (1998) (describing failures of research institutions to negotiate cross-licenses); *see also* Rebecca S. Eisenberg, *Symposium: A Technology Policy Perspective on the NIH Gene Patenting Controversy*, 55 U. PITT. L. REV. 633, 647 (1994) (describing onerous terms, such as exclusivity, reach-through obligations and disclosure requirements, that are likely to discourage patent licensing transactions); Rebecca S. Eisenberg, *Technology Transfer and the Genome Project: Problems With Patenting Research Tools*, 5 RISK: HEALTH, SAFETY & ENVIRONMENT 163, 171-72 (1994) [hereinafter Eisenberg, *Technology Transfer*] (same); Heller & Eisenberg, *supra* note 69, at 700-01 (arguing that uncertainty of research outcomes, limited resources of public research institutions, heterogeneity of patent rights and rights holders, and cognitive biases will tend to complicate licensing negotiations); *see generally* Clarisa Long, *Proprietary Rights and Why Initial Allocations Matter*, 49 EMORY L.J. 823 (2000) (describing costs of drafting and negotiating multiple license agreements in the face of uncertainty); Andrew Pollack, *U.S. Hopes to Stem Rush Toward Patenting of Genes*, N.Y. TIMES, June 28, 2000, at __ (reporting Bob Levy's description of the gene patenting situation as a "minefield"); see also DONALD S. CHISUM, 1 CHISUM ON PATENTS § 3.01, at 3-5 (2002) ("The social cost [imposed by a patent] is higher prices for and underutilization of the patented process or product during the period of the monopoly."); *but see* Dam, *supra* note 202, at 10-11 (arguing that patent licensing transaction costs, while significant, pose "less of a risk than that insufficient patent protection will be granted where it is most needed [to encourage research]").

[205] *See* Heller & Eisenberg, supra note 69, at 699 ("Unable to procure a complete set of licenses, firms choose between diverting resources to less promising projects with fewer licensing obstacles or proceeding to animal and then clinical testing on the basis of incomplete information.").

[206] *See infra* notes 171-173 and accompanying text.

[207] NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, A PATENT SYSTEM FOR THE 21ST CENTURY 72 (Stephen A. Merrill et al. eds., 2004).

[208] *See id.* at 72-73.

locate research work outside the United States.[209] For many scientists, however, the "solution" to the problem posed by existing patents was to proceed under the assumption that they faced no legal liability for conducting infringing research activities,[210] even though this belief was often misplaced.[211] The study concludes that "it is clear that investigators and their institutions must now pay closer attention to the intellectual property issues involved in their work, with an attendant increase in its cost."[212]

The present analysis does not attempt to address current attitudes or responses of the research community to the problem of DNA patents. Instead, the critical focus of this analysis is on the granting of exclusionary rights to oligonucleotide probes as a legal precondition for the preclusive effects on research described in Section IV.C. To appreciate the potential significance of these results, it is sufficient in this context to recognize that the cost of DNA patent licensing is already influencing the selection of oligonucleotide probes that are currently being used to conduct basic research on the functional characterization of genes. In particular, Affymetrix's selection of probes for its GeneChip products[213] has affected the design of thousands of gene expression experiments around the world.[214] At a symposium in 2002, Affymetrix's general counsel, Barbara Caulfield, stated in response to a question from the author:

> We have defensively licensed, to protect ourselves and our freedom to operate. It is costly, because . . . when you're looking generally at whole-genomic, multiprobe, multigenic, you know, setting the groundwork, people get very self-motivated about how they give you a license, and they have a right to do it, and they should do it, and the price is high. And the more you want it, the higher the price. And we are very sophisticated players in the licensing field, there's no two ways about it. We

[209] *See id.* at 72.

[210] *See id.* at 72-76.

[211] It might be thought that the public has legal immunity to perform experimental procedures using patented oligonucleotides under the "experimental use" exception to patent infringement; however, such a conception of the experimental use doctrine would be "overly broad." *See* Madey v. Duke University, 307 F.3d 1351 (Fed. Cir. 2002) (reversing district court's holding that "the experimental use defense inoculated uses that 'were solely for research, academic, or experimental purposes," and emphasizing that defense applies only to uses "solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry").

[212] NATIONAL RESEARCH COUNCIL OF THE NATIONAL ACADEMIES, *supra* note 207, at 77.

[213] *See Affymetrix — GeneChip® Probe Selection and Array Design*, available at < http://www.affymetrix.com/technology/design/index.affx> (visited March 1, 2005).

[214] *See Affymetrix Scores First Profitable Year*, available at <http://www.bio-itworld.com/news/012904_report4273.html> (visited March 1, 2005) (reporting GeneChip sales of $42.5 million in the fourth quarter of 2003).

do it every day, I do it every day. We run quite remarkable economic models. But there's limited resources.[215]

A. Utilities for Claimed Oligonucleotides

Probes for DNA Molecules of Known Sequence. Oligonucleotide probes may be used to detect the presence or absence of particular DNA molecules that contain a reverse-complementary subsequence. For example, a researcher who knows the sequence of a gene can design and synthesize an oligonucleotide probe that hybridizes specifically to one strand of the gene.[216] An unknown sample of DNA molecules can be broken into single strands ("denatured") and combined with the probe under conditions favorable to hybridization.[217] Observations of hybridization products will then indicate the presence and prevalence of the targeted gene. For example, synthetic oligonucleotide probes have been designed that are specific to genes of E. coli[218] and E. coli toxins,[219] cholera toxins,[220] HIV-1,[221] hepatitis C,[222] anthrax,[223] listeria,[224] staphylococcus,[225] shigella,[226] and the Lyme disease bacterium.[227]

PCR Primers. The polymerase chain reaction ("PCR"), for which Kary Mullis received the 1993 Nobel Prize in chemistry, provides a method for rapidly synthesizing numerous copies of ("amplifying") a DNA molecule.[228] The technique exploits the ability of each strand of a

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[215] *See Symposium on Commercialization of Human Genomics: Consequences for Science and Humanity*, Duke University, Sept. 27, 2002 (visited October 15, 2004) <http://www.law.duke.edu/conference/gelp/program.html> (providing archived Webcast of symposium). Caulfield's remarks occur at approximately one hour and 42 minutes into Panel 2.

[216] *See generally* GEORGE H. KELLER & MARK M. MANAK, DNA PROBES (1993); SAMBROOK, *supra* note 21, at 10.1-.10.

[217] *See* SAMBROOK, *supra* note 21, at 10.2-.4

[218] *See* U.S. Patent 5,041,372 (issued Aug. 20, 1991).

[219] *See* T. Yamamoto et al., *Sequence Analysis of the Heat Labile Enterotoxin Subunit B Gene Originating in Human Enterotoxigenic Escherichia Coli*, 152 J. BACTERIOLOGY 506 (1982).

[220] See S. Hanchalay et al., *Non-Ol Vibrio Cholerae in Thailand: Homology with Cloned Cholera Toxin Genes*, 21 J. CLINICAL MICROBIOLOGY 288 (1985)

[221] See U.S. Patent No. 5,599,662 (issued Feb. 4, 1997).

[222] *See* U.S. Patent No. 5,527,669 (issued June 18, 1996).

[223] *See* U.S. Patent No. 6,087,104 (issued July 11, 2000) ("Oligonucleotides for Detection of Bacillus Cereus Group Bacteria Harmful to Mammals, and Method of Detection with the Oligonucleotides.")

[224] *See* A.R. Datta et al., *Cloning of the Literiolysin O Gene and Development of Specific Gene Probes for Listeria Monocytogenes*, 56 APPLIED ENVIRONMENTAL MICROBIOLOGY 3874 (1990).

[225] *See* S. Notermans et al., *Synthetic Enterotoxin B DNA Probes for Detection of Enterotoxigenic Staphylococcus Aureus Strains*, 54 APPLIED ENVIRONMENTAL MICROBIOLOGY 531 (1988).

[226] *See* U.S. Patent No. 5,041,372 (issued Aug. 20, 1991).

[227] *See* U.S. Patent No. 5,977,339 (issued Nov. 2, 1999).

[228] *See* Kary Mullis et al., *Specific Enzymatic Amplification of DNA in Vitro: The Polymerase Chain Reaction*, 51 COLD SPRING HARBOR SYMPOSIUM ON QUANTITATIVE BIOLOGY 263 (1986). For detailed descriptions of the polymerase chain reaction, see, e.g., M.J. MCPHERSON & S. G. MOLLER, PCR (2000); NICHOLL, *supra* note 20, ch. 7.

DNA molecule to serve as the template for the synthesis of its reverse complement. As shown in Figure 1, the DNA to be copied (the "target" DNA) is initially denatured in a solution containing an excess of each of the four kinds of nucleotides and a special kind of enzyme known as a "polymerase." To begin the copying, an oligonucleotide (called a "primer" in this context) must hybridize with each of the single strands of the target DNA, so that the exposed 3' end of the oligonucleotide is

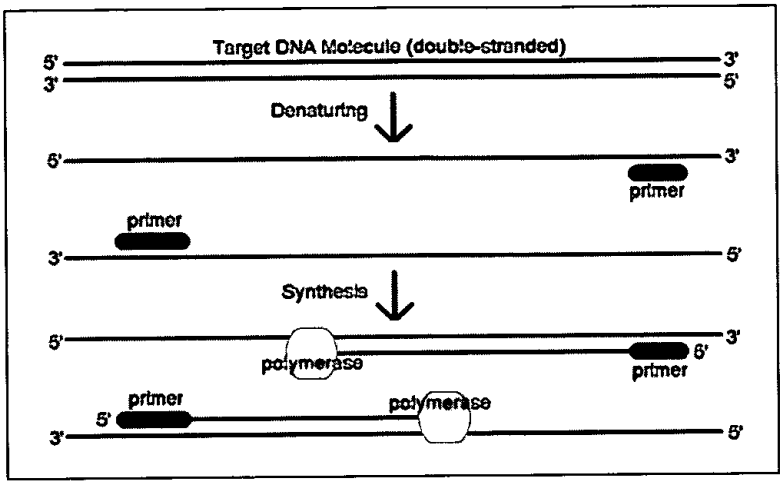

Figure 1. One cycle of the polymerase chain reaction in progress. Each strand of the target DNA molecule serves as a template for the synthesis of its reverse complement, yielding a product of two double-stranded molecules.

adjacent to an unmatched nucleotide on the target strand. Since the two strands have different nucleotide sequences, PCR uses a pair of different primers for this purpose. The polymerase then extends the 3' end of the attached primer by adding nucleotides one at a time complementary to the adjacent nucleotides on the target DNA, until a complete double-stranded DNA molecule has been assembled. The molecule can be denatured and the procedure repeated. The entire process takes place in a machine called a "thermal cycler," which produces the temperatures necessary for the different chemical reactions to occur. Since each PCR cycle doubles the number of copies of the target DNA, the procedure is capable of rapidly producing any desired quantity.

For an oligonucleotide to serve as an appropriate primer, it must hybridize specifically to the appropriate strand of the target DNA during each PCR cycle.[229] Thus, in designing a pair of PCR primers,

[229] *See* SAMBROOK, *supra* note 21, at 8.13.

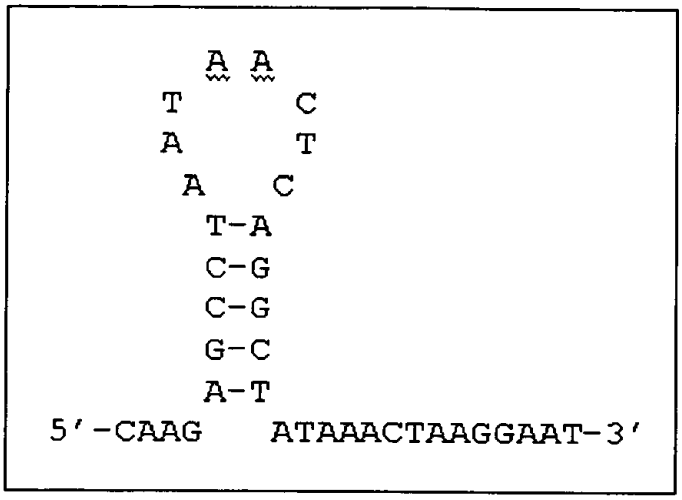

Figure 2. Formation of a hairpin loop in the oligonucleotide whose sequence is 5'-CAAGAGCCTAATAACTCAGGCTATAAACTAAGGAAT-3'. The loop results from the self-complementary regions AGCCT and AGGCT occurring at bases 5-9 and 18-22 of the sequence, respectively.

laboratories must consider not only the sequence of the target molecule, but also the primer's thermodynamic properties and the possibility of unwanted hybridization reactions. As Figure 2 illustrates, if a primer contains segments that are reverse complements of each other, hydrogen bonds can form between them, causing unwanted folds, loops, and other topological features known as "nonlinear secondary structures" to occur in the molecule.

During the denaturing step, bonds between A and T nucleotides separate at a lower temperature than bonds between G and C nucleotides. As a rule of thumb, a primer may be expected to denature and hybridize correctly during PCR if it is composed of between 40 and 60 percent G and C nucleotides and it contains no self-complementary sequences of four or more nucleotides.[230] The preferred length for a PCR primer is between 18 and 25 nucleotides,[231] although oligonucleotides as short as 10 nucleotides may be appropriate in some cases.[232] Many other heuristics for designing PCR primers have been

[230] *See id.* at 8.13-.15.

[231] *See id.* at 8.14.

[232] *See* U.S. Patent No. 5,976,791, claims 1 & 15 (issued Nov. 2, 1999) (claiming, inter alia, a PCR primer comprising an oligonucleotide "having at least eight consecutive nucleotides" from a group of disclosed sequences); U.S. Patent No. 6,004,754, claim 5 (issued Dec. 21, 1999) (claiming, *inter alia*, a new use for a PCR procedure using a primer "consisting of at least 10 consecutive nucleotides" of a disclosed sequence).

developed, thereby providing a systematic procedure for the amplification of virtually any DNA molecule.[233]

As the public has been aware ever since the O.J. Simpson trial, PCR can be used to enhance the sensitivity of tests for detecting the target DNA, including oligonucleotide probes.[234] By increasing the prevalence of the target DNA relative to other DNA molecules that may be in the solution, PCR can effectively "amplify" the target DNA to a detectable level. As a burgeoning literature indicates, the research community is continuing to discover many other applications for PCR.[235]

Until recently, the potential usefulness of PCR to the scientific community was been constrained somewhat by the fact that it was a patented procedure. Patents covering the use of PCR to amplify, detect, and differentiate DNA molecules were issued to Mullis and his colleagues in 1987 and assigned to their employer, Cetus Corporation,[236] and were subsequently acquired by Hoffman-La Roche, Inc. ("Roche") in 1991.[237] In licensing and enforcing the PCR patents, Roche was often seen as responsive to public pressure and the concerns of the scientific

[233] *See* SAMBROOK, *supra* note 21, at 8.13-.15.

[234] *See, e.g.*, Gerald D. Robin, *DNA Evidence in Court: The Odds Aren't Even*, CRIMINAL JUSTICE, Fall 1994, at 8.

[233] *See* SAMBROOK, *supra* note 21, at 8.13-.15.

[234] *See, e.g.*, Gerald D. Robin, *DNA Evidence in Court: The Odds Aren't Even*, CRIMINAL JUSTICE, Fall 1994, at 8.

[235] *See* MCPHERSON & MOLLER, *supra* note 228 (charting the rapid increase in the number of publications citing PCR between 1985 and 1999); 2 ESSENTIAL MOLECULAR BIOLOGY: A PRACTICAL APPROACH 11-12 (T.A. Brown ed., 1991) ("New applications for PCR are being discovered virtually every month.").

[236] *See* U.S. Patent No. 4,683,202 (issued July 28, 1987) (claiming a process for using PCR to "amplify[] at least one specific nucleic acid sequence contained in a nucleic acid or a mixture of nucleic acids"); U.S. Patent No. 4,683,195 (issued July 28, 1987) (claiming a process for using PCR to "detect[] the presence or absence of at least one specific nucleic acid sequence in a sample containing a nucleic acid or mixture of nucleic acids, or distinguishing between two different sequences in said sample, wherein the sample is suspected of containing said sequence or sequences").

The PCR technique was independently described more than a decade before Mullis's work by Gobind Khorana, *see* K. Kleppe et al., *Studies on Polynucleotides XCVI: Repair Replications of Short Synthetic DNA's as Catalyzed by DNA Polymerases*, 56 J. MOLECULAR BIOLOGY 341 (1971), although not in sufficient detail to invalidate any claims in the '202 patent. *See* E.I. du Pont de Nemours & Co. v. Cetus Corp., 19 U.S.P.Q.2d 1174 (N.D. Calif. 1990).

[237] *See Chiron Cleared to Acquire Cetus Corp. in Stock Swap*, WALL ST. J., Dec. 11, 1991, at B3. Another Roche patent, claiming a particular form of polymerase that can be used in PCR, has been held unenforceable for inequitable conduct. *See* Hoffman-La Roche, Inc. v. Promega Corp., 1999 WL 1797330 (N.D. Cal. 1999). The decision is on appeal to the Federal Circuit; oral argument was heard on May 10, 2001.

community,[238] although not to the satisfaction of some commentators.[239] The patents expired in July 2004.[240]

Aptamers. Although secondary structures are generally undesirable in oligonucleotides that are to be used as primers, certain strands of DNA and RNA known as "aptamers" possess secondary structures that, because of their unique shapes, are useful for identifying and binding with specific sites on nucleic acid or protein structures ("ligands"). For example, given a protein that is necessary for a virus to function, it may be possible to synthesize an oligonucleotide that serves as an aptamer for binding the protein, thereby inhibiting the virus.[241] Oligonucleotide aptamers can also be used as probes for the detection of particular ligands, although the principle of target recognition in this case is ligation rather than hybridization.[242]

Oligonucleotides that bind specifically with a particular ligand can be derived from a pool of random oligonucleotides through an iterative process, reminiscent of natural selection, known as "systematic evolution of ligands by exponential enrichment" ("SELEX").[243] Generally, oligonucleotides at least 30 to 40 nucleotides in length are used in order to assure the occurrence of secondary structures that can bind tightly with the target ligand.[244] Random oligonucleotides can be generated on a DNA synthesizer by using mixtures of nucleotides in place of

[238] *See* Janice M. Mueller, *No "Dilettante Affair": Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools*, 76 WASH. L. REV. 1, 3 (2000) (discussing Roche's decision not to name "pure research" scientists as defendants in its PCR patent infringement suits); Ron Winslow, *Biotechnology: Hoffman-La Roche to Ease Curb on Gene Technology*, WALL ST. J., Jan. 27, 1992, at B1 (reporting Roche's decision to ease restrictions on licensing of PCR to academic and private diagnostic labs); *PCR and Taq Polymerase: A Patented Research Tool for Which Licensing Arrangements Were Controversial*, *in* NATIONAL RESEARCH COUNCIL, INTELLECTUAL PROPERTY RIGHTS AND RESEARCH TOOLS IN MOLECULAR BIOLOGY ch. 5 (1997) [hereinafter "PCR Case Study"] (reporting opinion of Tom Caskey, senior vice-president for Research at Merck Research Laboratories, that Roche "has behaved fantastically" with regard to granting access to PCR for scientific research).

[239] *See* Mueller, *supra* note 238, at 3 (citation omitted) (reporting Nobel laureate Arthur Kornberg's criticism of Roche's patent enforcement activity as "violat[ing] practices and principles basic to the advancement of knowledge for the public welfare."); PCR Case Study, *supra* note 238 (describing scientific community's continuing dissatisfaction with the high cost of Taq polymerase, and "dismay" as an aftereffect of Cetus's initial licensing terms, which included reach-through royalties on second-generation products derived through PCR).

[240] *See* U.S. Patent No. 4,683,202 (issued July 28, 1987) (disclaiming portion of patent term subsequent to July 28, 2004); U.S. Patent No. 4,683,195 (issued July 28, 1987) (same).

[241] *See* Scott E. Osborne et al., *Aptamers as Therapeutic and Diagnostic Reagents: Problems and Prospects*, 1 CURRENT OPINION IN CHEMICAL BIOLOGY 5, 5-6 (1997).

[242] *See id.* at 7-8; V.A. Spiridonova & A.M. Kopylov, *DNA Aptamers as Radically New Recognition Elements for Biosensors*, 67 BIOCHEMISTRY (MOSCOW) 706 (2002).

[243] *See* Craig Tuerk & Larry Gold, *Systematic Evolution of Ligands by Exponential Enrichment*, 249 SCIENCE 505 (1990).

[244] *See id.* at 6.

individual nucleotides at appropriate stages of the synthesis process.[245] By incorporating random nucleotides into 30 or more positions of the synthesized oligonucleotides, researchers can produce mixtures of trillions of individual species.[246] From this diverse population of nucleic acids, those that bind with the target ligand can be selected (using a technique known as an "affinity column") and amplified (using PCR and/or reverse transcription). By repeating this process, researchers can eventually refine the mixture to contain only the nucleic acids that bind most strongly and specifically to the ligand.

The principal advantage of the SELEX procedure is that it requires no prior knowledge of the geometric relationship between the ligand and aptamer molecular structures.[247] Instead of designing an aptamer around the ligand's molecular structure, a researcher can simply generate a sufficiently large pool of candidates and let the SELEX procedure identify and synthesize those that that can serve as aptamers.[248] The procedure's inventors, Craig Tuerk and Larry Gold, have suggested that the method "heralds a new era in novel molecular design" and will be capable of generating "nucleic acids and proteins with any number of targeted functions."[249]

Antisense Therapies. As described above, protein synthesis in the cell requires the transcription of the sense strand of an exon into mRNA, which is then translated by a ribosome into a protein.[250] If an oligonucleotide having the same sequence as the antisense strand of the exon is introduced into the cell, it may be able to interrupt the translation process by hybridizing with the mRNA before a ribosome can act on it. In this way, oligonucleotides can inhibit the expression of particular genes. The first commercialized drug based on antisense oligonucleotides, Vitravene[251] (fomivirsen), is a treatment for cytomegaloviral retinitis (a viral infection of the eye).[252] Antisense therapies for HIV-AIDS, asthma, hair loss, acne, and certain forms of cancer and cardiovascular disease are currently under development.[253]

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[245] *See, e.g.*, U.S. Patent No. 5,808,022 (issued Sept. 15, 1998); U.S. Patent No. 5,639,595 (issued June 17, 1997) (Christopher K. Mirabelli et al.).

[246] *See* Tuerk & Gold, *supra* note 243, at 505 & n.9.

[247] *See id.* at 510 ("[W]e require no scorable phenotype other than binding to the partitioning agent...").

[248] *See id.* (concluding that the SELEX procedure "can be used to determine the optimal binding sequences for any nucleic acid binding protein").

[249] *See id.*

[250] *See supra* section II.A.

[251] Vitravene is a registered trademark of Isis Pharmaceuticals, Inc.

[252] *See* Justin Gillis, *Researchers Cheer Approval of Drug That Targets Genes*, WASH. POST, Aug. 28, 1998, at A2.

[253] *See* Douglas W. Green et al., *Antisense Oligonucleotides: An Evolving Technology for the Modulation of Gene Expression in Human Disease*, 191 J. AM. COLL. SURGEONS 93 (2000); Janice Kane, *The Promise of Antisense Drugs*, CHEMICAL MARKET REP., Nov. 9, 1998, at FR11.

Effectiveness and safety requirements raise special considerations for the design of antisense oligonucleotides for therapeutic use. Such oligonucleotides must be short enough to maintain a high likelihood of hybridization, yet long enough to ensure that they bind only to the target mRNA; i.e., generally between 12 and 20 nucleotides.[254] Often the oligonucleotides are modified to increase the likelihood that they will enter the target cells and hybridize with the target mRNA.[255]

Oligonucleotide-Directed Mutagenesis. The study of mutations, or changes in an organism's DNA, is yielding important insights into the relationship between DNA sequences and protein functions. A major problem in protein engineering is determining the effect of a mutation on the physical structure of the resulting protein. Researchers have not yet developed computational models that can accurately predict such effects. For this reason, researchers find it useful to have a procedure for inducing specified mutations ("mutagenesis") in the laboratory.

An oligonucleotide carrying a particular mutation can be synthesized and incorporated into the template that is used by the polymerase in the *in vitro* synthesis of DNA. The resulting double-stranded DNA, which carries the mutation, can then be inserted into a gene to be expressed as a mutant protein.[256] The traits of the resulting mutant organism may then provide a clue to the function of the mutated gene.[257] Oligonucleotides used in this procedure need to include a sufficient number of unchanged bases on both sides of the mutation so that they will hybridize at the appropriate location on the target molecule.[258] Depending on the complexity of the desired mutation, oligonucleotides of between 25 and 80 bases in length may be required.[259]

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[254] *See* Green, *supra* note 253, at 96 ("Sequences 15 to 20 bases long, and even longer, have traditionally been used in antisense studies, in part to avoid the possibility of a similar sequence being present in an unrelated gene."); Susanna Wu-Pong, Oligonucleotides: Opportunities for Drug Therapy and Research, BioPharm, Nov. 1, 1994, at 20 (stating that a minimum length of 12 nucleotides is necessary to ensure acceptable specificity); P.C. Zamecnik & M.L. Stephenson, *Inhibition of Rous Sarcoma Virus Replication and Cell Transformation by a Specific Oligodeoxynucleotide*, 75 PROC. NAT'L ACAD. SCI. USA 280 (1978) (describing an antisense therapy study involving a 13-mer).

[255] *See* DMITRI KNORRE, DESIGN AND TARGETED REACTIONS OF OLIGONUCLEOTIDE DERIVATIVES 263-98 (1994); Wu-Pong, *supra* note 254.

[256] *See generally* SAMBROOK, *supra* note 21, at 13.2-.10.

[257] See T.A. Kunkel et al., *Rapid and Efficient Site-Specific Mutagenesis Without Phenotypic Selection*, 154 METHODS ENZYMOL. 367 (1987)

[258] SAMBROOK, *supra* note 21, at 13.82-.83.

[259] Id. at 13.4.

B. Uses of Oligonucleotides for Further Oligonucleotide Research

RAPD-PCR Primers. A variation of the PCR technique known as "random amplified polymorphic DNA PCR" ("RAPD-PCR")[260] or "arbitrarily primed PCR" ("AP-PCR")[261] has been developed that permits the amplification of segments of a target molecule even when its nucleotide sequence is unknown. Instead of designing pairs of primers with reference to the sequence of the target molecule, researchers use a single primer with a known, randomly generated sequence. The PCR procedure is then run under "low stringency" conditions, which allow the primer to bind to one or more locations on the target molecule even though some pairs of adjacent nucleotides may be mismatched. The locations of the priming sites determine which segments of DNA are synthesized by the polymerase and amplified.

The list of molecules that are amplified by RAPD-PCR with a given primer forms a profile, or "fingerprint," that can be used to identify and differentiate among DNA samples.[262] For greater accuracy, a more detailed profile can be achieved by repeating the procedure with several different random primers. Qiagen Operon, Inc. markets various kits each containing 20 randomly generated 10-mers for use as primers in RAPD-PCR profiling.[263]

Random Primers for the Synthesis of Radiolabeled Probes. In genetic research, it is often desirable to label DNA probes with radioactivity so that hybridization reactions can be readily detected. The ability of polymerases to synthesize DNA strands that are reverse-complementary to regions of a given target DNA molecule[264] provides a convenient procedure for making radiolabeled probes.[265] The procedure resembles one cycle of PCR, except that some of the nucleotides in the initial solution have been made radioactive, and the procedure uses a

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[260] *See* J.G. Williams et al., *DNA Polymorphisms Amplified by Arbitrary Primers are Useful as Genetic Markers*, 18 Nucleic Acids Research 6531 (1990).

[261] *See* J. Welsh & M. McClelland, *Fingerprinting Genomes Using PCR With Arbitrary Primers*, 18 Nucleic Acids Research 7213 (1990).

[262] *See, e.g.*, I. Levin et al., Genetic Map of the Chicken Z Chromosome Using Random Amplified Polymorphic DNA (RAPD) Markers, 6 Genomics 224 (1993); B.B. Wardell et al., *The Identification of Y Chromosome-Linked Marker With Random Sequence Oligonucleotide Primer*, 4 Mammalian Genome 109 (1993).

[263] *See* Westburg BV, Oligos, RAPD Primers, available at <http://www.westburg.nl/htm/products/oligonucleotides/rapd_primers.htm> (visited August 22, 2002) (providing a link to an Excel spreadsheet listing the 10-mer sequences in Operon's RAPD-PCR primer kits).

[264] *See supra* text accompanying note 228.

[265] *See* Michael D. Brush, Probing Questions, The Scientist, May 1, 2000, at 24; A.P. Feinberg & B. Vogelstein, *A Technique for Radiolabeling DNA Restriction Endonuclease Fragments to High Specific Activity*, 132 Analytical Biochemistry 6 (1983).

mixture of different random primers instead of a single primer pair to hybridize at numerous sites along the target molecule.[266] When very short random primers (six to ten nucleotides in length) are used, the prevalence of hybridization reactions can be statistically predicted. By adjusting the concentration of primers used in the reaction, researchers can control the expected distance between primed sites on the target molecule, and thus also the expected length of the radiolabeled probes that are synthesized by the polymerase.[267]

Sequencing by Hybridization. The sequence of nucleotides in a DNA molecule entirely determines its chemical structure and biological function.[268] In an organism for which the nucleotide sequences of the entire genome is known, the sequence of a particular molecule can serve to locate it on a chromosome within the genome, thereby enabling researchers to integrate biological data regarding the molecule into the scientific community's genome-wide knowledge base.[269] For these reasons, procedures for "sequencing," or determining the sequence of nucleotides in a DNA molecule, are of considerable importance in genetic research.

The most common methods for DNA sequencing utilize a technique called "gel electrophoresis," wherein macromolecules are sorted according to length while passing through the matrix structure of an electrified gel.[270] To sequence a DNA molecule, chemical or enzymatic methods are used to generate a mixture of fragmented copies of the molecule, with longer fragments containing more of the original molecule's nucleotide sequence than shorter molecules. Next, fragments that contain the initial (5') end of the original molecule are isolated and sorted by length through gel electrophoresis. As long as the mixture is sufficiently diverse, there will be fragments on the gel that terminate at every position in the original nucleotide sequence. Finally, the sequence is read from the nucleotides at the terminal (3') end of each fragment in the order in which they have been sorted on the gel.

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[266] *See* SAMBROOK, *supra* note 21, at 9.4-9.6; Feinberg & Vogelstein, *supra* note 265.

[267] The expected number of nucleotides in a radiolabeled probe synthesized through random priming is proportional to , where is the concentration of the primer. *See* C.P. Hodgson & R.Z. Fisk, *Hybridization Probe Size Control: Optimized "Oligolabelling,"* 15 NUCLEIC ACIDS RESEARCH 6295 (1987).

[268] *See supra* section II.A.

[269] *See, e.g.*, C. Lee & K. Irizarry, *The GeneMine System for Genome/Proteome Annotation and Collaborative Data Mining*, 40 IBM SYSTEMS J. 592 (2001) (describing a computer implementation of a collaborative genome-wide knowledge base); D.D. Shoemaker et al., *Experimental Annotation of the Human Genome Using Microarray Technology*, 409 NATURE 922 (2001) (describing the use of genome-wide sequence information to identify authentic exons from among a set of DNA probes).

[270] *See generally* SAMBROOK, *supra* note 21, at 5.4-5.13.

Gel electrophoresis methods are limited by the gel's "resolution": i.e., its ability to distinguish between DNA molecules of different lengths. For example, to sequence a 600-nucleotide molecule, the gel must be able to separate 590-nucleotide fragments from 589-nucleotide fragments and 591-nucleotide fragments. While gel resolutions of up to 1000 nucleotides have recently been achieved,[271] the laws of thermodynamics are expected to limit further advances in this field.[272]

An alternative DNA sequencing technique, known as "sequencing by hybridization," combines the power of microarrays with high-speed data processing to determine the sequence of an unknown DNA molecule.[273] This patented procedure[274] uses a microarray containing all possible oligonucleotides of a given length; i.e., all 4^k possible k-mers. The molecule will hybridize to the oligonucleotides whose reverse complements occur somewhere within the unknown sequence. Observing which hybridization reactions take place thus yields a list of all the k-base sequences that occur as subsequences in the target molecule (the "k-spectrum" of the target molecule). Computers can efficiently reconstruct the unknown sequence from this hybridization data with high probability, provided that the length of the sequence n is not too large as a function of the oligonucleotide size k.[275]

In the example shown below, n=10 and k=3. When a sample consisting of an isolated and purified DNA molecule with sequence 5'–TGCGGCACAT–3' is reacted with a microarray containing all possible 3-mers, the hybridization reactions indicated in Figure 3 will occur in the wells shaded in Figure 4. From this pattern, it may be possible to identify the original sequence computationally, as I will discuss further in Section IV.C.

[271] *See* Y. Kim & E.S. Yeung, *DNA Sequencing Up to 1000 Bases By Using Poly(ethylene oxide)-Filled Capillary Electrophoresis*, 781 J. CHROMATOGRAPHY 315 (1997).

[272] *See* Gary W. Slater *et al.*, *Recent Developments in DNA Electrophoretic Separations*, 19 ELECTROPHORESIS 1525, 1525 (1998).

[273] *See* W. Bains & G.C. Smith, *A Novel Method for DNA Sequence Determination*, 135 J. THEOR. BIOL. 303 (1988); R. Drmanac et al., *Sequencing of Megabase Plus DNA by Hybridization: Theory of the Method*, 4 GENOMICS 114 (1989); Lysov et al., *DNA Sequencing by Hybridization with Oligonucleotides*, 303 DOKLADY ACAD. SCI. USSR 1508 (1988).

[274] *See, e.g.*, U.S. Patent No. 5,203,231 (issued April 13, 1993) ("Method of Sequencing of Genomes by Hybridization of Oligonucleotide Probes").

[275] *See infra* Section IV.C.1.

TGC GCA	(probes)
GTG CGC	(probes)
3'–TACACGGCGT–5'	(sample)
ATG GCC	(probes)
TGT CCG	(probes)

Figure 3. Out of the 64 possible 3-mers, eight will hybridize to a DNA molecule with the sequence 5'–TGCGGCACAT–3'.

AAA	ACA	AGA	ATA
AAA	ACC	AGC	ATC
AAG	ACG	AGG	**ATG**
AAT	ACT	AGT	ATT
CAA	CCA	CGA	CTA
CAC	CCC	**CGC**	CTC
CAG	**CCG**	CGG	CTG
CAT	CCT	CGT	CTT
GAA	**GCA**	GGA	GTA
GAC	**GCC**	GGC	GTC
GAG	GCG	GGG	**GTG**
GAT	GCT	GGT	GTT
TAA	TCA	TGA	TTA
TAC	TCC	**TGC**	TTC
TAG	TCG	TGG	TTG
TAT	TCT	**TGT**	TTT

Figure 4. Example of a microarray used in a sequencing by hybridization experiment. Probes that hybridize to the DNA sample (top) are shaded (below). Using a computer algorithm, the sequence of the DNA molecule can be reconstructed from the pattern of hybridization reactions on the microarray.

Cluster Analysis of Gene Expression Data. Oligonucleotide microarrays can be used to measure the extent to which various genes are expressed in a clinical sample; i.e., by providing the necessary DNA sequence information for the synthesis of the proteins in the sample. In a gene expression study, each microarray probe detects the prevalence of a corresponding mRNA molecule in the sample.[276] The simultaneous measurement of gene expression levels comprises a detailed molecular snapshot of the cell in a specific state, also known as a "gene expression profile."[277] By comparing gene expression profiles of various clinical samples under different conditions, biologists have been able to infer statistical relationships between genes and metabolic processes, drug sensitivity and resistance, tissue types, and disease state.[278]

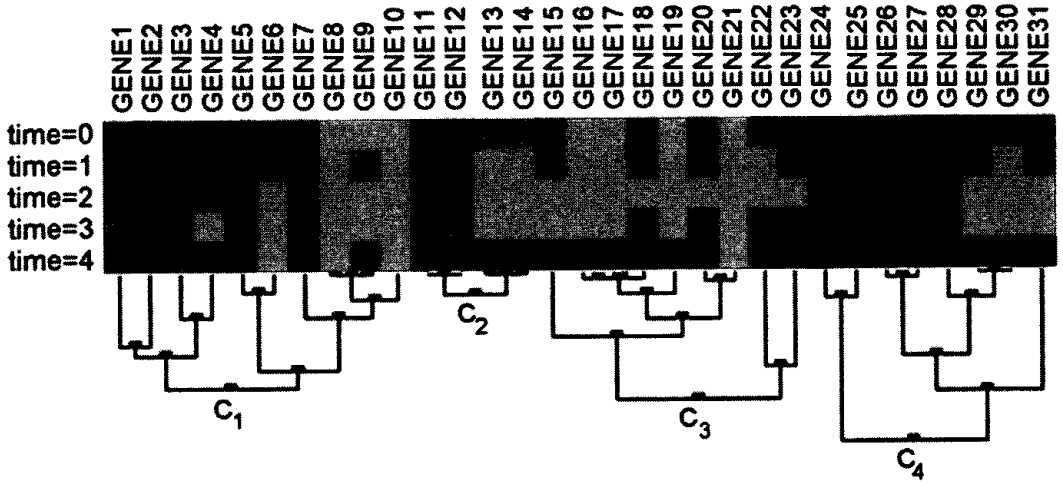

Figure 5. Hierarchical clustering of thirty-one genes based on five observed expression levels.

"Cluster analysis" is a common statistical technique that can be applied to gene expression data in order to classify previously uncharacterized genes and clinical samples.[279] Scientists can use cluster analysis to identify groups of genes that exhibit similar expression patterns across a given range of samples and conditions, or alternatively, to identify groups of clinical samples that have similar expression

[276] *See* HELEN C. CAUSTON ET AL., MICROARRAY GENE EXPRESSION DATA ANALYSIS: A BEGINNER'S GUIDE 4 (2003).

[277] *See id.* at 6.

[278] *See id.* at 5-6.

[279] *See* MEI-LING TING LEE, ANALYSIS OF MICROARRAY GENE EXPRESSION DATA 237 (2004).

patterns with respect to a particular set of genes.[280] For example, in Figure 5, the grid of shaded blocks illustrates the expression levels of thirty-one genes measured at five different times during an experimental procedure. By successively combining groups of genes that exhibit similar patterns of expression across the five observations, it is possible to classify the genes into four clusters .

Geneticists have found that genes of similar function tend to cluster together,[281] and this observation has supported the identification of functions for previously uncharacterized genes.[282] Cluster analysis has also revealed clinically significant genotypical distinctions among phenotypically similar tissue samples,[283] raising the possibility of differentiated or even individualized approaches to medical treatment.[284]

C. *Degradation of Research Performance by Excluded Probes*

Since the 1970s, computer scientists, statisticians, and biologists have worked together to analyze biological sequence data, creating the interdisciplinary field that is known today as bioinformatics.[285] In recent years, bioinformaticians have extensively examined the utility of microarrays as research tools for the sequencing and classification of DNA samples, both by developing algorithms for selecting probes and processing hybridization data[286] and by establishing theoretical limits to the performance of such research approaches.[287] Some of these results are immediately applicable; others will gain importance as continuing improvements in microfabrication enable larger-scale investigations.

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[280] See id. at 238.

[281] *See* CAUSTON, *supra* note 276, at 5; *see also* ERNST WIT & JOHN MCCLURE, STATISTICS FOR MICROARRAYS 160 (2004).

[282] *See* Michael B. Eisen, *Cluster Analysis and Display of Genome-Wide Expression Patterns*, 95 PROC. NAT'L ACAD. SCI. USA 14863, 14865-67 (1998).

[283] *See* WIT & MCCLURE, *supra* note 281, at 137.

[284] *See id.* at 138; CAUSTON, *supra* note 276, at 6.

[285] For a brief history of bioinformatics research, see DAVID W. MOUNT, BIOINFORMATICS: SEQUENCE AND GENOME ANALYSIS 2-15 (2001).

[286] *See, e.g.*, F.P. Preparata & E. Upfal, *Sequencing-by-Hybridization at the Information-Theory Bound: An Optimal Algorithm, in* PROC. 4TH ANNUAL INT'L CONF. ON COMPUTATIONAL MOLECULAR BIOLOGY (RECOMB-00), at 245 (Ron Shamir et al., eds., 2000) (sequencing); R. Sharan et al., *Cluster Analysis and Its Applications to Gene Expression Data*, unpublished manuscript <available on the Web> (clustering).

[287] *See, e.g.*, P.A. Pevzner et al., *Improved Chips for Sequencing By Hybridization*, 9 J. BIOMOLECULAR STRUCTURE & DYNAMICS 399 (1991) (showing that a particular microarray yields an accurate DNA sequence in only 94 out of 100 cases); Martin Dyer et al., *The Probability of Unique Solutions of Sequencing By Hybridization*, 1 J. COMPUTATIONAL BIOLOGY 105 (1994) (showing that the probability that a particular microarray accurately sequences a randomly chosen DNA sequence tends to zero as the length of the sequence increases).

Bioinformatics provides a useful lens through which to examine the potential impediments posed by the patenting of oligonucleotides. If the public is legally excluded from using a particular oligonucleotide as a microarray probe, it will be more difficult or even impossible for researchers to obtain the hybridization data corresponding to that probe. Bioinformaticians have recognized in other contexts that genetic research sometimes must contend with missing or incomplete hybridization data, and have analyzed some of the computational difficulties that may arise as a result. By extending their analysis, it is possible to determine how existing patents on oligonucleotides might impair the future search for patentable DNA molecules, including other oligonucleotides.

1. SEQUENCING BY HYBRIDIZATION

Discoveries of patentable DNA molecules often result from the application of standard research techniques to new genetic and biological phenomena. For example, libraries consisting of the DNA molecules that are expressed in a cell under particular conditions can be sequenced and compared with other DNA sequences for which a common utility has been established. While the question of patentable utility is fact-specific, the Patent Office has indicated that at least in some cases, a patent applicant may credibly assert a specific and substantial utility for a claimed DNA molecule based upon the showing of a sufficiently high degree of homology to sequences with known utility.[288] Discovering such a patentable DNA molecule from within a large library requires the capability for efficient large-scale DNA sequencing.

Sequencing by hybridization has recently attracted interest as an approach to large-scale DNA sequencing that can exploit massive parallelism for improved efficiency.[289] Already Nuvelo, Inc., the owner of numerous sequencing-by-hybridization patents, has developed a chip

[288] *See* U.S. Patent & Trademark Office, Revised *Interim Utility Guidelines Training Materials*, at 53-55 <http://www.uspto.gov/web/menu/utility.pdf> (visited Nov. 15, 2004). As an example of a disclosure that satisfies the § 112 utility requirement, the Patent Office describes sequencing 5,000 cDNA molecules prepared from human kidney epithelial cells, and claiming one that encodes an amino acid sequence with 95% homology to a DNA ligase (a catalyst for the formation of a bond linking two DNA strands). *See id.* at 53-54. *Cf.* Utility Guidelines, *supra* note 163, at 1096 cmt. 19 ("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.").

[289] *See* CHARLES R. CANTOR & CASSANDRA L. SMITH, GENOMICS: THE SCIENCE AND TECHNOLOGY BEHIND THE HUMAN GENOME PROJECT 394-432 (1999); *see also* supra text accompanying notes 26-32 (discussing the massive parallelism provided by microarray technology).

that can be used to sequence a 3,000-nucleotide DNA molecule in a single procedure.[290] Given continuing improvements in microarray fabrication[291] and the availability of efficient, scalable computer algorithms for reconstructing DNA sequences from sequencing-by-hybridization data, it is foreseeable that oligonucleotide microarrays will become increasingly important, if not essential, as a tool for large-scale DNA sequencing.

As discussed in Section IV.B, sequencing by hybridization on a microarray that contains all k-mers yields the k-spectrum of the target molecule. The total number of bases n in the target molecule can be determined using standard gel electrophoresis methods.[292] The biochemical problem of sequencing a DNA molecule is thus reduced to the purely computational problem of reconstructing the n-base sequence of the target molecule from its k-spectrum.

This problem is a special case of the more general task of assembling a collection of randomly generated molecular fragments whose sequences are known but whose locations on the larger molecule are unknown. Such "shotgun" sequencing techniques are well established and have been used recently in connection with the development of genome sequence databases for humans[293] and other species of interest to genetic researchers.[294] Even with this background, however, reconstructing the sequence of a target molecule from its k-spectrum has turned out to be a complex and challenging problem.

The principal difficulty is that some k-spectra correspond to two or more different sequences, so that the actual sequence of the target molecule cannot be uniquely determined from the available data. Bioinformatics research has produced essentially three approaches to addressing this difficulty:

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[290] *See* Press Release, Hyseq, Inc., *Hyseq Announces DNA Sequencing Chip Breakthrough* (Jan. 12, 2000), < http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=NUVO&script=412&layout=-6&item_id=228567> (visited Nov. 15, 2004). Nuvelo, Inc. was formed by the merger of Hyseq., Inc. and VARIAGENICS, Inc. in 2003. *See* Press Release, Nuvelo, Inc., *Hyseq and VARIAGENICS Merge to Form New Company, Nuvelo* (Feb. 3, 2003), < http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=NUVO&script=411&layout=-6&item_id=377600> (visited Nov. 15, 2004).

[291] *See supra* note 29 and accompanying text.

[292] *See* J. Sambrook, et al., *Gel Electrophoresis of DNA*, *in* SAMBROOK, *supra* note 21, at ch. 6.

[293] *See E.W. Myers, Is Whole Genome Sequencing Feasible?*, in COMPUTATOINAL METHODS IN GENOME RESEARCH (S. Suhai ed. 1997); *but see* P. Green, *Against a Whole-Genome Shotgun*, 7 GENOME RESEARCH 410 (1997) (arguing that the human genome contains too many repetitive sequences to be sequenced accurately using shotgun techniques).

[294] *See, e.g.*, R.D. Fleischmann et al., *Whole-Genome Random Sequencing and Assembly of* Haemophilus Influenzae *Rd.*, 269 SCIENCE 496 (1995) (influenza bacterium); E.W. Myers et al., *A Whole-Genome Assembly of* Drosophila, 287 SCIENCE 2196 (2000) (fruitfly).

First, research has shown that the problem of ambiguous k-spectra is rare in practice. Specifically, if n does not grow too quickly as a function of k, then almost all n-base sequences have unique k-spectra.[295]

Second, researchers often have partial information about a DNA molecule's sequence prior to performing the sequencing-by-hybridization experiment. For example, this is the case when examining a target molecule that may exhibit a single-nucleotide polymorphism (SNP) with respect to a known reference sequence.[296] Given this or other prior knowledge of partial information, it is possible to resolve many of the cases where ambiguous k-spectra occur.[297]

Third, in addition to the four DNA bases, microarray probes may also include a "universal base" capable of bonding with any of the four bases occurring at the corresponding position on the target molecule.[298] Research has shown that fewer probes are necessary to perform sequencing by hybridization on microarrays that include universal bases than on microarrays that do not.[299]

Although each of these approaches goes some way toward resolving the problem of ambiguous k-spectra, DNA patents present a further difficulty by excluding the public from using certain molecules as microarray probes in sequencing procedures. I will examine the impact of DNA patents on specific procedures that follow the first two of these sequencing approaches. With respect to the third, there is already a pending patent application that appears to claim *any* use of universal bases in sequencing microarrays.[300] If these patents are held valid, they are likely to impede the development and use of many advanced sequencing by hybridization technologies.

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[295] *See* R. Arratia et al., *Poisson Process Approximation for Sequence Repeats, and Sequencing by Hybridization*, 3 J. COMPUTATIONAL BIOLOGY 425 (1996); Martin Dyer et al., *The Probability of Unique Solutions of Sequencing by Hybridization*, 1 J. COMPUTATIONAL BIOLOGY 105 (1994).

[296] I. Pe'er & R. Shamir, *Spectrum Alignment: Efficient Resequencing by Hybridization*, *in* PROC. 8TH INT'L CONF. ON INTELLIGENT SYSTEMS IN MOLECULAR BIOLOGY 260, 261 (2000).

[297] *See* Pe'er & Shamir, supra note 296 (addressing case where target sequence is highly similar to a known sequence); *cf.* A. Ben-Dor et al., *On the Complexity of Positional Sequencing by Hybridization*, *in* PROC. 10TH ANN. SYMP. ON COMBINATORIAL PATTERN MATCHING 88 (Springer-Verlag Lecture Notes in Computer Science No. 1645, 1999) (addressing case where there is partial knowledge about the locations of hybridization sites on the target molecule); Dimitris Margaritis & Steven S. Skiena, *Reconstructing Strings from Substrings in Rounds*, in PROC. 36TH IEEE SYMP. ON FOUNDATIONS OF COMPUTER SCIENCE 613 (1995).

[298] *See* D. Loakes & D.M. Brown, *5-Nitroindole as a Universal Base Analogue*, 22 NUCLEIC ACIDS RESEARCH 4039 (1994).

[299] See A.M. Frieze et al., *Optimal Reconstruction of a Sequence From Its Probes*, 6 COMPUTATIONAL BIOLOGY 361 (1999); Franco P. Preparata & Eli Upfal, *Sequencing-by-Hybridization at the Information-Theory Bound: An Optimal Algorithm*, 7 COMPUTATIONAL BIOLOGY 621 (2000).

[300] U.S. Patent Application No. 20010004728, at 23 (filed June 21, 2001) (claiming, *inter alia*, "[a] sequencing chip, comprising a substrate, and a set of nucleic acid probes disposed thereon, where in each probe comprises an instance of a pattern of universal and designate nucleotides such that the set comprises a plurality of instances of the pattern").

A microarray whose probes are all of the possible sequences of k bases can be used in a trivial manner to identify the sequence of any target molecule with k bases. The target molecule hybridizes to exactly one of the probes, and there is no ambiguity in the resulting data. The problem of ambiguous k-spectra gradually emerges as the number of bases n in the target molecule grows (as a function of k), and eventually imposes a strict limit on the size of molecules that can be sequenced using the microarray. Bioinformaticians have shown that the maximum sequence length of a target molecule that can be uniquely reconstructed with high probability $(1-o(1))$ from its k-spectrum is proportional to 2^k.[301] This result can be stated more precisely as follows:

Theorem 1. Let $\Sigma=\{A,T,G,C\}$ and let $n:Z^+\rightarrow Z^+$ be an integer-valued function with $n(k)>k$ for all $k\in Z^+$. For any string σ, let $\Gamma_k(\sigma)$ denote the k-spectrum of σ. Let ξ be a string chosen uniformly at random from Σ^n. As $k\rightarrow\infty$, the probability that there is some string $\xi'\in\Sigma^n, \xi\neq\xi$, such that $\Gamma_k(\xi')=\Gamma_k(\xi)$ approaches:

$$\begin{cases} 0 \text{ if } n(k)=o(2^k) \\ 1 \text{ if } n(k)=\omega(2^k) \end{cases}.$$

Proof. Dyer[302] has shown that for $k=\lfloor log_s(n^2/2c)\rfloor$, where $s=|\Sigma|$ and $c>0$ is a constant,

$$\lim_{m\rightarrow\infty} \Pr(\xi \text{ is k - recoverable}) = \sum_{i=0}^{\infty} \frac{e^{-\lambda}(2\lambda)^i}{i!(i+1)!},$$

where $\lambda=(s-1)c$. Dyer also notes that the value of the right hand side of the above equation is 0 if $c=c_n\rightarrow\infty$, and 1 if $c=c_n\rightarrow 0$. But $c=\Theta\left(\frac{n^2}{4^k}\right)$, whence the result follows. ■

Patents on k-mer probes introduce a further difficulty for the sequence reconstruction problem, in that they may impede the identification of subsequences complementary to the probes in question. Even where the target molecule is short enough that the probability of an ambiguous k-spectrum is negligible, a small number of excluded probes may result in a significant probability that the observed k-spectrum will have missing subsequences. This observation is formalized in the following theorem.

[301] See Arratia, supra note 295; Dyer, supra note 295.
[302] Dyer, *supra* note 295.

Theorem 2. In addition to the hypotheses in Theorem 1, suppose that $n(k)=o(2^k)$ and $n(k)=w(k)$. Let $F=F(k)$ represent a random set of $p=p(k)$ excluded probes $F=\{\phi^1,\phi^2,...,\phi^p\}\subseteq\Sigma^k$, where $p:Z^+\to Z^+$ is an integer-valued function with $p(k)=0\left(\frac{4^k}{n(k)}\right)$. Let $T\subseteq\Sigma^{n(k)}$ be the set of sequences of length $n(k)$ that hybridize to at least one of the probes in F. Then $E(|T|)=\Omega(4^{n(k)-k}p(k)n(k))$.

Proof. For $\xi\in\Sigma^{n(k)}$, call g a substring of ξ if there is an $i,0\le i\le n(k)-1$, such that for all $j,1\le j\le k$,

$$g_j=\begin{cases}\xi_{i+j} \text{ if } i+j\le n(k)\\ \xi_{i+j-n(k)} \text{ if } i+j>n(k)\end{cases}.$$

We estimate $E(|T|)$ by the inclusion-exclusion principle. Note that $E(|T|)$ is a nondecreasing function of p. An upper bound on $E(|T|)$ is

$$S_1=pn(k)4^{n(k)-k}, \qquad (1)$$

where the first factor p represents the number of substrings complementary to the probes in F, the second factor $n(k)$ accounts for the possible locations of each such substring within the target sequence, and the third factor $4^{n(k)-k}$ accounts for the base combinations not determined by this substring.

The quantity S_1 defined in (1) overcounts the target sequences that hybridize to two or more of the probes in F. To adjust for this, we calculate an upper bound on the expected number of these sequences as the sum S_2+S_3, where S_2 and S_3 count sequences that have disjoint and overlapping regions complementary to some (unordered) pair of probes in F, respectively. We have $S_2=p(p-1)n(k)(n(k)-2k)4^{n(k)-2k}$ and

$$\begin{aligned}S_3&=n(k)4^{n(k)-k}\sum_{t=1}^{k}\frac{\left|\left\{(i,j)\,|\,\mu(\phi^i,\phi^j)=t\right\}\right|}{4^t}\\&\le n(k)4^{n(k)-k}\left(\frac{p^2}{4\cdot4^{k-1}}+\sum_{t=2}^{k}\frac{p^2}{4^k}\cdot\frac{4-2}{(4-1)4^{k-t}}\right)\\&=p^2n(k)4^{n(k)-2k}\left(1+\frac{2(k-1)}{3}\right).\end{aligned}$$

By the inclusion-exclusion principle, we have

$$E(|T|) \geq S_1 - (S_2 + S_3)$$
$$\geq pn(k)4^{n(k)-k}\left(1 - \frac{p(n(k)-2k)}{4^k} - \frac{p}{4^k}\left(1 + \frac{2(k-1)}{3}\right)\right).$$

For all $p = o\left(\frac{4^k}{n(k)}\right)$, we have

$$E(|T|) = \Omega\left(\frac{p}{n(k)}4^{n(k)}\right). \qquad (2)$$

We prove that equation (2) holds more generally for all $p = O\left(\frac{4^k}{n(k)}\right)$ by contradiction. Suppose to the contrary that there is a $p_0(k)$ such $p_0(k) = \Theta\left(\frac{4^k}{n(k)}\right)$ that and $E(|T|) = o\left(\frac{p_0(k)}{n(k)}4^{n(k)}\right)$.

Then there is a $p_1(k) = o(p_0(k)) = o\left(\frac{4^k}{n(k)}\right)$

for which $E(|T|) = \Theta\left(\frac{p_1(k)}{n(k)}4^{n(k)}\right)$. But $E(|T|)$ is nondecreasing in p,

so (2) cannot hold for the case, $p = \sqrt{p_0(k)p_1(k)} = o(p_0(k))$

a contradiction. ■

Theorem 1 teaches that a random target sequence of length can be reconstructed unambiguously from a complete k-spectrum with high probability (i.e.,1-o(1)) provided that the function $n(k)$ grows more slowly than 2^k; i.e., $n(k)=o(2^k)$. Theorem 2, however, shows that only slightly more than 2^k excluded probes $\left(\text{i.e., } \Theta\left(\frac{4^k}{n(k)}\right)\right)$ may be sufficient to prevent the sequencing by hybridization procedure from generating a complete k-spectrum with high probability from an unknown sequence of $n(k)$ nucleotides. Together, these results demonstrate that patents on even a negligible fraction of the oligonucleotide probes of a given length can have a dramatic effect on the maximum size of target DNA molecules that are amenable to standard sequencing by hybridization procedures.[303]

2. Cluster Analysis of Gene Expression Data

Recent patent applications have claimed oligonucleotide probes based on their utilities for targeting genes that have been functionally characterized through the use of hierarchical cluster analysis methods.[304] The accuracy of such functional characterizations depends on the quality of the underlying gene expression data, in which statistical similarities between the newly characterized gene and genes of known function may be observed. If DNA patents preclude the use of oligonucleotide probes targeting one or more genes in a gene expression study, the resulting loss of data may distort the results of any ensuing cluster analysis, thereby impeding the discovery of gene functions and of patentable utilities for other oligonucleotides.

[303] Because other, more fault-tolerant, procedures are available, the inability to observe one or more subsequences occurring in the k-spectrum of a target molecule is not necessarily fatal for sequencing efforts. Bioinformatics researchers have recognized that experimental errors may cause the set of observed hybridization reactions to differ from the k-spectrum of the target molecule. *See* J. B∏a˜ewicz et al., *DNA Sequencing With Positive and Negative Errors*, 6 J. Computational Biology 113 (1999); Ron Shamir & Dekel Tsur, *Large Scale Sequencing By Hybridization*, Proc. 5th Ann. Int'l Conf. on Computational Biology 269 (2001). The microarray may either detect extraneous subsequences (positive errors) or fail to detect actual subsequences (negative errors) of the target sequence. In this context, patented probes may be treated as a persistent source of negative errors in sequencing-by-hybridization experiments.

[304] *See, e.g.*, U.S. Patent App. 20040214325, Ser. No. 10/712,795 at ¶ 514 (published Oct. 28, 2004) ("Antisense Modulation Of Apolipoprotein B Expression"); U.S. Patent App. 20040120956, Ser. No. 10/603,283 at ¶ 264 (published June 24, 2004) ("CNGH0004 Polypeptides, Antibodies, Compositions, Methods and Uses"); U.S. Patent App. 20040009553, Ser. No. 10/426,776 at ¶ 1,482 (published Jan. 15, 2004) ("Novel . . . Molecules And Uses Therefor").

In more specific terms, cluster analysis seeks to identify groups of objects that are close to each other with respect to a particular distance or similarity measure. For example, two genes or clinical samples may be regarded as similar if their corresponding expression patterns are positively correlated.[305] Various methods have been used to agglomerate objects into clusters of similar objects. One common approach, known as "single linkage hierarchical clustering," starts with each object in its own "singleton" cluster and then iteratively combines the closest pair of clusters until the desired number of clusters have been formed (where the distance between two clusters is calculated as the distance between their closest members, one from each cluster).[306] The example in Figure 5 illustrates the single linkage hierarchical clustering method. The clustering of gene expression profiles by this method is sensitive to omissions of relevant data, however, such as may result from the exclusion of patented oligonucleotide probes. We can formalize this statement in the following theorem.

Theorem 3. Let U be a set of objects on which a distance measure d is defined, where $d(a,b)$ denotes the distance between the objects a and b. Assume also that no pair of objects is separated by exactly the same distance. Let $\Gamma(U,d,k)$ denote a collection of $k \geq 2$ nonempty clusters $\Gamma(U,d,k)=\{C_1, C_2,\ldots,C_k\}$ formed from U using the single linkage hierarchical clustering approach. Let C_i be any cluster with $|C_i| \geq 2$. Then there exists an object $x \in C_i$ such that at least one of the following two conditions holds:

(a) for all $u,v \in C_i, z \notin C_i, d(u,x)<d(v,z)$, or

(b) there exists a subset $C' \subset C_i$ of objects with $x \notin C'$ such that $C_i \backslash C' \notin \Gamma(U \backslash C', d, k)$ for any collection of k clusters $\Gamma(U \backslash C', d, k)$ formed from $U \backslash C'$ using the single linkage hierarchical clustering approach.

Proof. First note that single linkage hierarchical clustering proceeds to combine objects into clusters in the same manner in which vertices are connected into components by Kruskal's minimum spanning tree ("MST") algorithm.[307] Let $T(U,d)$ represent the MST produced by

[305] *See* LEE, *supra* note 279, at 242-43 (describing the use of the Pearson correlation coefficient as a similarity measure for purposes of clustering).

[306] *See id.* at 244-45.

[307] *See, e.g.*, Herbert Edelsbrunner, *Minimum Spanning Trees* (lecture notes for Duke University computer science course on the Design and Analysis of Algorithms) (October 21, 2003) (visited Jan. 15, 2005) <http://www.cs.duke.edu/courses/fall03/cps230/L-15.ps> (noting that the evolution of the construction of a minimum spanning tree by Kruskal's algorithm can be interpreted as a hierarchical clustering of the vertices); J.B. Kruskal, *On the Shortest Spanning Subtree of a Graph and the Traveling Salesman Problem*, 7 PROC. AM. MATH. SOC'Y 48 (1956) (describing and proving the correctness of Kruskal's algorithm).

Kruskal's algorithm on a complete graph with vertices U and edge lengths given by $d(a,b)$ for all $a,b \in U$.

Let (x,y) be the unique edge in $T(U,d)$ that traverses the "cut" between C and the other clusters in $\Gamma(U,d,k)$; i.e., let x be the unique vertex such that $(x,y) \in T(U,d)$ and $x \in C_i, x \notin C_i$. Since (x,y) must be a minimum edge across the cut,[308] for all $v \in C_i z \notin C_i, d(x,y)$.

Now suppose that condition (a) in the theorem fails to hold. Then there are $u,v \in C_i, z \notin C_i$ such that $d(u,x) > d(v,z) \geq d(x,y)$. Set $= \{t \in C_i \mid 0 < d(t,x) \leq d(x,y)\}$. Then for all $s \in C_i \setminus C', s \neq x$ we have $d(s,x) > d(x,y)$.

We now claim that condition (b) in the theorem holds with respect to this C'. Suppose not; then $C_i \setminus C' \in \Gamma(U \setminus C', d, k)$. Since $x \in C_i \setminus C'$ and $|C_i \setminus C'| \geq 2$, there must be some vertex $a \in C_i \setminus C'$ with $(a,x) \in T(U \setminus C', d)$. But $d(a,x > d(x,y)$. In single-linkage clustering, this implies that x and y must have been clustered together before x and a were clustered together. But this would require that $y \in C_i \setminus C'$, a contradiction.

In the context of cluster analysis of microarray data, condition (b) in Theorem 3 describes a situation where the exclusion of certain probes in a cluster (i.e., the set represented by) would result in a change in the characterization of the remaining probes in the *same* cluster. This condition can be avoided only if condition (a) holds for all clusters in $\Gamma(U,d,k)$.

Condition (a) is related to some of the validity measures that are commonly used to indicate the quality of a given clustering. For example, the simplest form of Dunn's validation index V is given by,

$$V(\Gamma) = \min_{1 \leq i \leq c} \left\{ \min_{\substack{1 \leq j \leq c \\ j \neq i}} \left\{ \frac{\delta(C_i, C_j)}{\max_{1 \leq k \leq c} \{\Delta(C_k)\}} \right\} \right\}$$

where $\delta(S,T) = \min_{x \in S, y \in T} \{d(x,y)\}$ and $\Delta(S) = \max_{x,y \in S} \{d(x,y)\}$.

[308] *See* THOMAS H. CORMEN ET AL., INTRODUCTION TO ALGORITHMS 501-02 (1990).

Provided that the distance metric d satisfies the triangle inequality, it is straightforward to show that condition (a) can hold for all clusters in Γ only if $V(\Gamma) \geq 1/2$. Many gene expression profiles, however, do not result in clusters that satisfy this condition. For example, Azuaje and Bolshakova[309] found Dunn's indices of between 0.26 and 0.31 for a recent clustering study on diffuse large B-cell lymphoma.[310]

The above results are consistent with the informal observation of Troyanskaya et al. that hierarchical clustering methods in general "may lose effectiveness even with a few missing values."[311] As the leading researchers addressing this problem, Troyanskaya et al. have evaluated various methods for imputing gene expression data in cases where readings for a given probe are missing in some but not all of a series of experiments, e.g., as a result of "insufficient resolution, image corruption, . . . dust or scratches on the [microarray,] . . . [or] the robotic methods used to create [the microarray]."[312] In these algorithms, missing expression levels in the compromised experiments are inferred, *inter alia*, from the available values in the other experiments.[313] These imputation methods could not be used at all in a situation where the patenting of an oligonucleotide probe precluded the measurement of an expression level in *every* experiment in the series. In the absence of suitable methods for adjusting clusters to compensate for the exclusion of patented probes, Theorem 3 indicates that significant errors in the functional characterization of DNA molecules will go undetected and uncorrected.

V. CONCLUSIONS

This Article has identified a new beachhead from which DNA patenting can be challenged in the context of rapid changes in biotechnology. To contest the premise that DNA patents promote the discovery and disclosure of structural formulae for patentable DNA molecules, critics of DNA patents may undertake to demonstrate that the

[309] *See* Francisco Azuaje & Nadia Bolshakova, *Clustering Genomic Expression Data: Design and Evaluation Principles*, *in* UNDERSTANDING AND USING MICROARRAY ANALYSIS TECHNIQUES: A PRACTICAL GUIDE (D. Berrar et al., eds., 2002) (referring to data in Table 13.3 for validity index V_{11}).

[310] See A.A. Alizadeh et al., Distinct Types of Diffuse Large B-Cell Lymphoma Identified by Gene Expression Profiling, 400 NATURE 503 (2000).

[311] Olga Troyanskaya et al., Missing Value Estimation Methods for DNA Microarrays, 17 BIOINFORMATICS 520 (2001).

[312] See id.

[313] See id. at 521-22.

patenting of DNA molecules will have the effect of retarding the identification and sequencing of so many other useful DNA molecules that patent-driven DNA research is a self-defeating enterprise. This Article has served to initiate such a project by showing that the assertion of a relatively small number of oligonucleotide patents would impair two of the most promising procedures involved in the future discovery of patentable oligonucleotides and other DNA molecules. Although alternative avenues of discovery exist, the cumulative effect of these impediments may be to postpone or prevent the further discovery and patenting of many DNA molecules by foreclosing the most efficient and widely applicable approaches. Even if the findings presented in this Article do not yet provide a conclusive basis for condemning DNA patents as inimical to "Progress," it is likely that many extensions and refinements of these results can be achieved. Such results may ultimately reveal irreconcilable contradictions in the internal logic of DNA patentability doctrine.

Most of the legal and public policy literature addressing the controversy over DNA patents has regarded such patents as a unitary category, without engaging in a particularized analysis of the validity and enforceability of individual patents and patent claims.[314] As this scholarship begins to focus more closely on oligonucleotide patents and their consequences for genetic research, however, it will become necessary to consider specific patented molecules and the specific laboratory procedures that call for their use. In both form and substance, scholarship on the merits of DNA patents will become much more particularized to the actual work of the genetic scientists who are conducting their research in the shadow of DNA patents.

This Article has drawn its methodologies and motivation principally from genetic engineering and bioinformatics. In doing so, it has sought to establish a new interdisciplinary space wherein the technological consequences of DNA patenting can be rigorously described and studied. This work directly addresses the constitutional requirement that patents are to promote technological progress,[315] as opposed to auxiliary economic or ethical objectives. This approach also responds to recent public appeals by Supreme Court Justice Stephen Breyer[316] and the Bio

[314] See infra Part III.

[315] See supra text accompanying note 186.

[316] See Richard Willing, Breyer Makes a Rare Appeal: Justice Calls for a "Conversation" on Genetics and Law, USA TODAY, Nov. 24, 2000, at 10A.

Judiciary Project[317] for the integration of scientific teachings into biotechnology jurisprudence. As Breyer has said:

> Traditionally, some have believed that we need not know science but only law to make decisions. This view is increasingly unrealistic. Since the implications of our decisions in the real world often can and should play a role in our legal decisions, the clearer our understanding of the relevant science, the better.[318]

A full critical examination of the technological premises of DNA patent law is likely to require contributions from medicine, molecular biology, statistics, computer science, and bioinformatics. Whether or not this work ultimately succeeds in motivating a comprehensive judicial or administrative review of DNA patent doctrine, it will bring needed light to bear on the future of research in the shadow of DNA patents.

[317] "The Bio Judiciary Project's mission is to provide judges, courts and court-related personnel with knowledge tools necessary to address pressing questions emerging from the intersection of biotechnology and the law." See Objectives <http://www.biojudiciary.org/about/obj.asp> (visited Sept. 26, 2002).

[318] Willing, supra note 316 (quoting Justice Breyer).

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