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LIMITS ON PATENTABILITY IN LIFE SCIENCES: CLAIMS COVERING EXPRESSED SEQUENCE TAGS

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I. INTRODUCTION

In June 1991, scientists from the U.S. National Institutes of Health (NIH) published a research paper detailing the discovery of short genetic sequences that could be used to find and map specific genes, and to explore gene functions, in a remarkably rapid and cost-effective manner.[1] Terming their new discovery "expressed sequence tags" (ESTs), the NIH scientists boldly predicted that ESTs would revolutionize the field of genetics by facilitating "the tagging of most human genes in a few years at a fraction of the cost of complete genome sequencing," by providing "new genetic markers," and by serving "as a resource in diverse biological research fields."[2]

Those predictions, though wildly aggressive, ultimately proved to be true. Today, the discovery of ESTs is widely credited for completion of the Human Genome Project significantly ahead of schedule and well below budget.[3] ESTs now serve as standard laboratory research tools that are frequently employed by geneticists to probe and explore the genomes of a variety of organisms.[4] The critical importance of ESTs is further underscored by the explosive growth of a commercial industry premised on the usefulness of ESTs. Over the last decade, sophisticated entities and individuals have dedicated hundreds of millions of dollars to locate and organize ESTs into libraries, and to license databases of ESTs discovered by others.[5]

Despite the obvious and considerable value of ESTs to the field of genetics, a fierce controversy surrounding the patentability of ESTs has raged from the start. Those hoping to protect their significant investment in developing ESTs by securing patents have faced stiff opposition grounded in a variety of moral, social, economic, and scientific concerns.[6] Opponents, however, are far from united in their proposed treatment of ESTs. For example, some contend that ESTs should be dedicated to the public domain and placed entirely outside the scope of patent protection. Others join in opposing the patenting of ESTs, but instead propose that ESTs should receive protection under non-patent forms of intellectual property (e.g., copyright law or forced registration and licensing schemes).[7]

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1 *See* M.D. Adams et al., *Complementary DNA Sequencing: Expressed Sequence Tags and Human Genome Project,* SCIENCE, June 21, 1991, at 1651.

2 *Id.*

3 When the Human Genome Project started in 1990, experts estimated that the project would be completed by the end of 2005 at a cost of $3 billion. The project ultimately concluded in April 2003 - two and a half years ahead of schedule and $300 million under budget. *See* Press Release, National Human Genome Research Institute, International Consortium Completes Human Genome Project (Apr. 14, 2003), http://www.ornl.gov/sci/techresources/Human_Genome/project/50yr/press4_2003.shtml.

4 *See, infra* Section II(B)-(C).

5 *See infra* Section VI(C).

6 *See infra* Section III(A)-(B).

7 *See infra* Section III(C).

Those supporting the patenting of ESTs are equally divided. Some supporters maintain that ESTs should be subjected to the same patentability standards, and afforded the same patent rights, as any other new, useful, and nonobvious invention. Meanwhile, other proponents argue that EST patents should issue, but only after meeting heightened patentability requirements or with fewer rights than afforded to other types of patented inventions (e.g., claims with limited scope, duration, and/or enforcement rights).[8]

Notwithstanding more than a decade of heated debate, Congress and the courts have done nothing to preclude, limit, or otherwise affect the patenting of ESTs. In 2001, however, the U.S. Patent and Trademark Office (PTO) placed itself at the center of the EST debate by issuing Utility Examination Guidelines that announced a new heightened standard for utility under 35 U.S.C. Section 101.[9] On its face, the new, more stringent standard purports to apply to all inventions. In practice, however, the PTO has applied a heightened utility standard to EST patent applications, while continuing to judge the utility of other inventions under a more lenient test. This result should come as little surprise. From the start, the PTO openly has conceded that it raised the utility bar solely to preclude the patenting of most ESTs.[10] That policy has achieved its intended purpose - the PTO's newly crafted utility standard has all but halted the filing and issuance of patents covering ESTs.[11]

The PTO's unilateral attempt to bring an end to this long-standing controversy through the uneven application of the utility standard finds no support in the plain language or legislative history of the patent laws, or in the decisions of the courts. Rather, those statutory and judicial sources make clear that the standard for utility under 35 U.S.C. Section 101 is a minimal one that is fixed by law and made applicable to *all* inventions - including ESTs. Simply put, the PTO lacks the authority to impose a heightened utility requirement, or to apply that requirement selectively to some inventions, but not to others.[12] If the utility standard is to be elevated for any particular category of inventions, it is Congress that should do it.

When properly applied, the utility requirement established by Section 101 in no way precludes the patenting of ESTs - to the contrary, *all* ESTs are inherently capable of meeting the minimal threshold of utility established by the statute. As a matter of scientific truth, *every* EST can be used as a research tool to provide the public with a host of specific, substantial, and commercially valuable benefits. This is all that the minimal utility requirement of 35 U.S.C. Section 101 demands.[13]

II. WHAT ARE EST'S?

A. Basic Principles of Molecular Genetics[14]

Proteins are essential to the proper growth, development, and function of every life form. For example, in humans, proteins are responsible for a wide variety of critical functions ranging from routine (e.g., fingernail and hair growth) to complex (e.g., processing nutrients, controlling muscle function, and stimulating brain activity).[15] Failures in the protein-generation process can result in serious problems, including improper development, disease, and even death.

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8 *See id.*
9 *See* Utility Examination Guidelines, 66 Fed. Reg. 1092-99 (2001).
10 *See* Molly A. Holman and Stephen R. Munzer, *Intellectual Property Rights in Genes and Gene Fragments: A Registration Solution for Expressed Sequence Tags,* 85 IOWA LAW REV. 735, 759 ("[A high-ranking PTO official] has clarified to us that the intended impact of the Revised Utility Examination Guidelines on EST applications is to heighten the utility requirement . . . .").
11 *See* Jennifer Van Brunt, *Next Move in the Patent Game,* SIGNALS MAGAZINE, *at* http://www.signalsmag.com/signalsmag.nsf/657b06742b5748e888256570005cba01/5bff0c004db8303f88256a390080aa36?OpenDocument&Highlight=0,EST (Apr. 26, 2001) (noting that the initial flood of patent applications on ESTs decreased dramatically beginning around the time the PTO issued interim Utility Guidelines in 1999 that were a precursor of the final Guidelines issued in 2001).
12 *See infra* Section V.
13 This article is limited to a discussion of the utility requirement under 35 U.S.C. Section 101. It does not address whether ESTs are capable of satisfying the remaining requirements for patentability.
14 The Federal Circuit repeatedly has addressed many of the basic principles of molecular genetics set forth here. *See, e.g., In re Deuel*, 51 F.3d 1552, 1554-55 (Fed. Cir. 1995); *Amgen, Inc. v. Chugai Pharm. Co., Ltd.,* 927 F.2d 1200, 1207-08 (Fed. Cir. 1991); *In re O'Farrell*, 853 F.2d 894, 895-99 (Fed. Cir. 1988).
15 *See* D. PETER SNUSTAD & MICHAEL J. SIMMONS, PRINCIPLES OF GENETICS 17-18, 77 (3d ed. 2003). Proteins play an equally important role in the development and daily functioning of other animals, as well as in plants and microorganisms. *See id.*

In recent decades, scientists have started to explore the complex genetic underpinnings of the intricate process used by various organisms to synthesize proteins. These efforts have resulted in a greater understanding of the genomes of hundreds of organisms, leading to the development of new disease-fighting drugs, genetically improved plants, and other important products. Efforts to explore and further understand the genomes of humans and other organisms continue today.

1. The Role of Chromosomes and Genes

The billions of cells found in the human body (as well as the cells of other life forms) are comprised largely of proteins. The specific proteins produced by the cells of an organism are determined by the genetic code, or genome, of the organism. This genetic information is chemically stored within the nucleus of each of the organism's cells in long, densely coiled strands of deoxyribonucleic acid (DNA) called "chromosomes." The number of chromosomes that reside within each cell varies by organism. For instance, a normal human cell contains twenty-three pairs of chromosomes, a maize plant cell contains only ten pairs, and baker's yeast contains sixteen chromosomes.[16]

The portion of a chromosome that contains the genetic coding information necessary to make a particular protein is called a "gene." Structurally, genes are comprised of several components, including: (1) regulatory regions that affect the "expression" (i.e., synthesis) of a particular protein; (2) exons, which are the coding sequences of a gene that serve as the template for protein expression; and (3) introns, which are non-protein-coding sequences that exist between exons. The number of genes also varies significantly between organisms. By way of example, human chromosomes contain 30,000 to 40,000 genes, maize plants contain about 50,000 genes, and baker's yeast contains about 6,000 genes.[17]

2. The Role of DNA

DNA acts as the blueprint for all protein-driven activities that are necessary for an organism to develop, grow, and live. DNA molecules are comprised of repeating units called nucleotides that link together into long strands. The four nucleotides found in DNA - adenine (A), guanine (G), cystosine (C), and thymine (T) - are called bases, and the particular order of the linked nucleotide bases is referred to as the DNA sequence.[18]

Each DNA molecule is comprised of two strands of nucleotide bases. The sequence of nucleotide bases found in one strand will "hybridize" (i.e., pair or bind) with the complementary sequence of nucleotide bases found in the other strand; adenine will hybridize with thymine (A-T), and guanine will hybridize with cystosine (G-C). This hybridization of nucleotide bases results in a two-stranded DNA molecule that takes the form of a twisting double helix. Because of the unique hybridization properties of the four DNA nucleotide bases, the known sequence of one strand can be used to predict the complimentary sequence of the other strand.[19]

The DNA sequence of a gene ("genomic" DNA) contains all of the coding information necessary to produce a particular protein. However, the entire sequence is not translated directly into protein. Rather, only the protein-coding regions (the exons) of the gene are used as a template for protein synthesis.[20] Within that protein-coding region, sequential groupings of three nucleotides called codons code for single amino acids, which are the building blocks of proteins. The sequence of codons determines the chain of amino acids in the resulting protein.[21]

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16 *See* JEREMY M. BERG ET AL., BIOCHEMISTRY III-31.2 (5th ed. 2002), *available at* http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowSection&rid=stryer.section.4452; Enrique Martinez-Perez & Graham Moore, *Promiscuous Maize Chromosomes*, SCIENCE, Jan. 2, 2004, at 49, 50.

17 *See* SNUSTAD & SIMMONS, *supra note* 15, at 277, 529; Edward R. Winstead, *Sizing Up the Genomes: Amoeba is King*, GENOME NEWS NETWORK, Feb. 12, 2001.

18 *See* SNUSTAD & SIMMONS, *supra note* 15, at 209-12.

19 *See id.* at 12-15. For example, human DNA is comprised of 3.12 to 3.15 billion nucleotide base pairs, maize DNA contains approximately 2.5 billion base pairs, and baker's yeast contains about 12 million base pairs. *See* KEVIN DAVIES, CRACKING THE GENOME 239-41 (2001); Katherine Miller, *The Challenges of Maize Genetics, at* http://www.mutransposon.org/project/RescueMu/zmdb/education/challenge.php (last visited Oct. 7, 2004); Winstead, *supra* note 17. Interestingly, the microscopic *Amoeba dubia* has the largest known genome, spanning 670 billion base pairs - more than 200 times the size of the human genome. *See id.* In contrast, the HIV virus has less than 20,000 base pairs. *See id.*

20 *See* SNUSTAD & SIMMONS, *supra* note 15, at 292-99.

21 *See id.* at 320-27. The four DNA bases can be arranged into 64 possible codon combinations, three of which are termination codons that signal the end of the amino acid chain being assembled. Since only 20 amino acids exist naturally, most amino acids are coded by more than one codon. This principle is known as redundancy. *See id.* at 325.

3. The Role of mRNA

Although genomic DNA contains all of the information necessary to generate a particular protein, the DNA molecule itself is not directly involved in creation of the protein. Instead, when a gene is expressed, the relevant DNA sequence first is "transcribed" (i.e., copied) into a new single strand of genetic material called messenger ribonucleic acid (mRNA).[22] After the transcription of genomic DNA into mRNA, the non-coding sequences (the introns) are removed in a process called "splicing," leaving the coding sequence (the exons) necessary to produce the specific protein that corresponds to the gene.[23] Once transcribed and spliced of introns, mRNA is transported outside of the cell nucleus and used to synthesize protein in a process called "translation;" the particular sequence of codons found in the mRNA is translated into a sequence of amino acids that comprises a protein.[24]

A cell generates mRNA only when a gene is being expressed. As such, scientists can determine that a particular gene is being expressed in certain tissue at a given point in time simply by confirming the existence of mRNA corresponding to the gene within the cells of the tissue.[25]

4. The Role of cDNA

Because mRNA contains the same protein-coding regions (the exons) found in the genomic DNA sequence from which it was derived, scientists can use mRNA as a tool to trace an expressed protein back to its originating gene. However, mRNA is quite unstable once extracted from a cell, making it a difficult object of study within a laboratory environment. Therefore, scientists typically use a process called "reverse transcription" (and a catalyst enzyme called "reverse transcriptase") to transcribe mRNA into a purified complementary DNA (cDNA) molecule commonly referred to as a "clone." Like naturally occurring DNA, a man-made cDNA clone is comprised of two strands of nucleotide bases that take the form of a twisting double helix - the first strand is generated from (and thus, is "complementary" to) the single-stranded mRNA molecule, and the second strand is synthesized from the first strand of the clone.[26]

A cDNA clone contains the same nucleotide sequence found in the mRNA from which it is generated; that is, the sequence derived from the exon portions of the corresponding gene.[27] Using a variety of different sequencing processes, geneticists can determine the full or partial sequence of nucleotides forming a cDNA clone.[28] Once the sequence of a cDNA clone is known, the codons found in that sequence can be used to determine the corresponding protein sequence. That information then can be used to study the specific function of the protein expressed by the gene to which the cDNA clone corresponds.[29]

5. The Role of cDNA Libraries

To study the specific genes being expressed in a specific tissue of an organism at a specific point in time, geneticists commonly construct a cDNA library for that tissue.[30] These libraries take advantage of the fact that cells generate mRNA only when one or more genes within the cell are being expressed.[31] Therefore, by extracting the mRNA from the cells of specific tissue at a certain point in time (and using reverse transcription to convert mRNA into cDNA), a library of cDNA clones for the tissue can be generated. By sequencing and studying the clones found in a tissue-specific cDNA library, scientists can determine which genes were being expressed in the tissue at the time of mRNA extraction.[32]

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22 *See id.* at 275-92.
23 *See id.* at 292-99.
24 *See id.* at 308-327. Like DNA, mRNA is comprised of chains of four nucleotide bases. DNA and mRNA share three of the same bases (adenine, guanine, and cystosine), but mRNA contains uracil in place of thymine. *See id.* at 210.
25 *See id.* at 275-82, 489-91.
26 *See id.* at 489-91.
27 *See id.*
28 *See id.* at 505-09.
29 *See id.* at 5-6, 518, 538.
30 *See id.* at 536.
31 *See id.*
32 *See id.* at 536-38.

B. The Role of Expressed Sequence Tags

To determine the full-length sequence of every clone stored in a typical cDNA library (and other similar collections of genetic material) would present an extremely time-consuming and costly endeavor.[33] As such, geneticists have sought to develop research tools to help screen genetic libraries for genes and gene fragments of interest in a rapid and cost-effective manner. Perhaps the most successful such tool is the "expressed sequence tag" (EST) - a short nucleotide sequence (usually 150 to 500 nucleotides in length) that uniquely represents a fragment of a cDNA clone, and thus, a fragment of the protein-coding portion of an expressed gene.[34]

An EST typically is generated by isolating a random clone from a cDNA library and then sequencing a small number of nucleotides from the end of one the clone's two strands.[35] When used as a probe and introduced into a sample containing a mixture of DNA (e.g., a cDNA library), a fragment of DNA corresponding to the EST sequence will hybridize under appropriate conditions with DNA molecules in the sample to which the EST uniquely corresponds.[36] Successful hybridization confirms that the gene corresponding to the EST was being expressed in the sample tissue at the time of mRNA extraction.[37]

Capitalizing upon this scientific property, geneticists routinely utilize ESTs to screen large cDNA libraries for the presence of expressed genes.[38] The information derived from these screens can be compiled into large digital databases and then analyzed with powerful computerized software tools in connection with a wide array of scientific applications, including, for example, activities such as genome mapping, linkage analysis, and other uses discussed below.[39]

C. Benefits Derived From the Use of ESTs

The vast majority of ESTs correspond to genes of unknown function. Nevertheless, even in the absence of any functional information, each EST can be used as a probe to screen cDNA libraries for the specific gene sequence to which the EST uniquely corresponds. The successful hybridization between an EST and its corresponding gene sequence confirms that the gene was being expressed in a certain tissue, at a certain time, by a certain organism. This information is useful to geneticists in a number of key respects - even where the specific function of the corresponding gene is unknown.[40]

For example, as detailed below, an EST can be used in research as a tool to: (1) serve as a molecular marker on a genetic or physical map; (2) identify the presence or absence of a polymorphism; (3) measure the level of mRNA in a sample; (4) serve as a source for primers; (5) isolate promoters; (6) control the expression levels of protein; and (7) locate genetic molecules of other organisms. In these ways, each EST provides the scientific community not only with a unique molecular tool for the targeting and isolation of novel genes, but also with practical utilities entirely separate from identifying the function of the gene corresponding to the EST.

1. The Use of ESTs as Molecular Markers

ESTs can be used as molecular markers on physical or genetic maps without knowing *anything* about the function of the corresponding gene.[41] More specifically, geneticists searching a genome typically utilize maps to guide them along through the many millions or billions of

33 *See id.* at 497.
34 *See* Adams, *supra* note 1 at 1651-56; SNUSTAD & SIMMONS, *supra* note 15, at 536-38. As noted above, ESTs were discovered in the early 1990s by a team of NIH scientists.
35 *See* SNUSTAD & SIMMONS, *supra* note 15, at 489, 519, 536-37.
36 *See id.* at 536-38.
37 *See id.* at 537-38. An EST probe can emit a visible light with a distinguishable wavelength after it binds to a complementary target sequence. S*ee id.*
38 *See id.* at 536-38.
See id. at 535-38. Prior to the development of ESTs, scientists used short DNA fragments called "sequenced tagged sites" (STSs) to screen large populations of genetic material. STSs are not necessarily derived from expressed genes. Therefore, although STSs can be used like ESTs in some respects, ESTs are more useful research tools than anonymous STSs because ESTs represent genes that are known to express protein in a specific tissue at a certain point in time. See Adams, *supra* note 1 at 1651-56.
40 *See generally* SNUSTAD & SIMMONS, *supra* note 15, at 489-91, 518-27; DAVIES, *supra* note 19, at 56-61. Indeed, it is standard practice in the field of genetics to use EST sequences to screen cDNA libraries for expressed genes without undertaking the time consuming and economically burdensome task of sequencing and characterizing the function of each and every located target gene. *See* DAVIES, *supra* note 19, at 57-58.
41 *See* SNUSTAD & SIMMONS, *supra* note 15, at 518-27 (describing genomics techniques utilizing ESTs and other markers to map and positionally clone genes).

base pairs found in the DNA of each cell. However, for a map to make navigational sense, it must include reliable landmarks or markers that help determine the order of genes and distances between sequences.[42]

ESTs can do just that. When an EST is introduced into a genetic sample and hybridizes with its target complementary DNA sequence, the specific location where the probe hybridizes can serve as a molecular marker on a physical or genetic map.[43] This landmark information is useful to scientists - even in the absence of information about the function of the gene corresponding to the EST. For instance, when considered in connection with other markers, the presence or absence of a molecular marker corresponding to a particular EST can be used to help determine the genetic heritage of an organism and to estimate its likely traits.[44] Molecular markers also are useful in other applications as well, such as linkage analysis.[45]

2. The Use of ESTs to Detect the Presence or Absence of a Polymorphism

Genomes naturally undergo spontaneous mutation in the course of a species's continuing evolution.[46] A "polymorphism" is a slight variation or difference in the nucleotide sequence of a gene that arises in the evolutionary process and appears in some members of a species.[47]

ESTs can be utilized as probes to identify the presence or absence of a polymorphism between two genetic samples. Knowledge of the presence of a polymorphism is useful, for example, to enable plant or animal breeders to determine the distribution of genetic material passed from one organism to another. Polymorphic information also is useful to relate a particular genetic deviation to a particular observable trait for purposes of tracking the trait or predicting the likelihood of the trait being present or absent in other organisms.[48]

In some organisms with high rates of polymorphic variation in their genetic sequences, such as corn, it is a matter of near statistical certainty that any EST will contain at least one polymorphism. Plant breeders can physically map the polymorphic information obtained from ESTs and then correlate the data in a meaningful way with existing genetic trait maps, even in the absence of gene function knowledge. This process allows breeders to utilize polymorphic ESTs as diagnostic molecular markers for traits whose underlying genes are physically proximate to the polymorphisms based on genetic linkage.[49] Using ESTs as diagnostic markers - which allows traits to be tracked at the seed stage on a molecular level - provides plant breeders with a huge advance in efficiency over other breeding techniques that require raising crops to maturity to observe their phenotypic traits.

Use of an EST to confirm the *absence* of a polymorphism also is useful to scientists. This information typically demonstrates that the two or more populations being compared share a common genetic heritage. Confirming the absence of a polymorphism also is useful in constructing genomic maps and assessing relationships between various traits and polymorphic markers.[50]

3. The Use of ESTs to Detect and Measure mRNA Levels

ESTs also can be used to confirm the presence and quantitative measurement of an mRNA molecule within a particular tissue or cell sample. To do so, the EST is used as a probe to screen a sample of genetic material. Hybridization between the EST, which is specially marked, and

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42 *See id.* at 518-19.
43 *See id.* at 519.
44 *See id.* at 518-24; Davies, *supra* note 19, at 57-58 (describing techniques to correlate ESTs to known genes in other organisms).
45 *See* SNUSTAD & SIMMONS, *supra* note 15, at 157-59, 179-96. Linkage analysis involves studying the relationships among genes in the same chromosome. Genes that are "linked" are proximate to one another within the chromosome and tend to be inherited together. *See id.* at 157-59. In agriculture, using molecular markers and linkage analysis are used for marker-assisted breeding, transgenic crop production, crop monitoring, and diagnostic techniques, all of which allow for better quality, growth, and yield for crops and livestock. *See id.* at 12-15. In humans, linkage analysis is critical in understanding the genetic basis of disease. *See id.* at 188-96.
46 *See id.* at 730-32 (describing random genetic drift).
47 *See id.* at 75, 722; DAVIES, *supra* note 19, at 42-44.
48 *See generally* SNUSTAD & SIMMONS, *supra* note 15, at 722-39 (discussing the study of allele frequency, polymorphisms, and genetic drift). Once a polymorphism is discovered, ESTs can serve as markers that are genetically or physically linked to the polymorphic area. *See id.* at 518-24 (discussing the use of ESTs and other markers in restrict fragment-length polymorphism mapping and other genomic techniques).
49 *See supra* note 45.
50 *See id.* at 519-22.

complementary mRNA molecules present in the sample is indicative of the presence of the corresponding mRNA, and the amount of the EST-mRNA hybrid formed is proportional to the amount of mRNA in the sample.[51] Thus, ESTs may be used to ascertain whether a specific mRNA molecule is present in a sample, and if so, the level and extent of mRNA production by the cells or tissues under examination. This information can be used to identify the type or source of a particular tissue, or to help evaluate how a cell or tissue responds in a particular setting, such as when the organism is infected with a disease.[52]

In this manner, ESTs may be used in chips or microarray assays to create expression profile data for sample tissues. Even in the absence of knowledge about the gene to which an EST corresponds, many different ESTs may be used in combination with one another and with other gene fragments that have been characterized to provide extensive data profiles that are useful to geneticists in studying and characterizing tissues and their biological states.

4. The Use of ESTs as a Source of Primers

The complex process necessary to sequence a gene or gene fragment requires many copies of the target DNA molecule. A well-known method called "polymerase chain reaction" (PCR) utilizes "primers" to generate billions of copies of a target DNA molecule within a matter of hours.[53] ESTs - like primers - typically represent the coding sequence found at the end of one of the strands of a specific DNA molecule. Therefore, without knowledge of the underlying gene function, an EST can be used as a readily available template to design primers specific to a given gene, thereby allowing scientists to generate large sample populations of the corresponding gene sequence in a rapid and cost-efficient manner.[54]

5. The Use of ESTs to Isolate Promoters

A "promoter" is a specific region of a gene that regulates the expression of protein.[55] An EST can be used to isolate promoters in specific tissue, including, at a minimum, the promoter that regulates the expression of protein by the gene that corresponds to the EST.[56]

Techniques such as chromosome walking - a process that utilizes a known fragment of DNA (in this case, the EST) to isolate adjacent fragments of DNA - may be used to isolate promoters. In a chromosome walk, an EST or other fragment is introduced as a probe into a genomic library to screen for all clones that hybridize with the probe. The located clone that extends furthest away from the locus of the original fragment then is used as a probe on more distal regions of the DNA. The process then is repeated to "walk" down the target region of the chromosome. Chromosome walks using ESTs can help, for example, to sequence a DNA molecule or create a physical map of an organism's genome.[57] In this way, ESTs may be used as to initiate "backward" chromosome walks near the beginning of the expressed gene to which the EST corresponds to isolate and identify that gene's nearby promoter. Promoters isolated in this manner not only have valuable applications with respect to the genes with which they are naturally associated, but also may be utilized to regulate the expression levels of entiredly different genes.

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51 *See id.* at 501 (describing Northern blot hybridization techniques that may be utilized in such measurements).

52 *See id.* at 536-38 (describing RNA assays such as dot blot hybridizations and gene chips).

53 *See id.* at 503-04. A primer is a short, single-stranded DNA molecule that is complementary to the sequence found at one end of the target DNA strand. The short sequence typically is unique to the target DNA molecule; therefore, when introduced into a sample, the primer will anneal only to the target DNA molecule. In nature, primers are formed from the free nucleotides residing in a cell by an enzyme called DNA primase. Primers also can be synthesized in a lab environment. *See id.* at 248, 277.

PCR involves heating a DNA sample to separate the double-stranded target DNA molecule into two single strands. When the mixture cools, a primer in the sample will anneal (i.e., bind) to its complementary sequence on the first strand, and a second primer will anneal to its complementary sequence on the second strand. DNA polymerase (an enzyme that catalyzes the synthesis of nucleic acids) then is used in conjunction with the annealed primers to synthesize two new DNA strands that are complementary to the original two strands. The two newly created strands anneal to the two original strands of the target DNA molecule, resulting in two complete target DNA molecules. When the two target DNA molecules are subjected to another cycle of heating, the strands of both DNA molecules separate, resulting in four strands that each becomes a template for DNA replication using the primer method discussed above. This heating and cooling process is continued as necessary, with each cycle doubling the amount of target DNA.
See id. at 503-04.

54 ESTs also can be used to confirm whether the PCR process correctly duplicated cDNA clones. *See* Adams, *supra* note 1, at 1651-56.

55 *See* SNUSTAD & SIMMONS, *supra* note 15, at 279-82, 287-88.

56 ESTs may be used as hybridization probes to initiate "chromosome walks" near the beginning of an expressed gene to isolate and identify the gene's nearby promoter. *See id.* at 525-26.

57 *See id.*

6. The Use of ESTs in Modulating the Expression Levels of Protein

ESTs can be used to modulate the expression levels of protein by a gene. For example, an EST may be used to create antisense RNA that inhibits production of proteins encoded by the corresponding gene.[58] Conversely, promoters or enhancers[59] identified using ESTs could be modified to alter their control characteristics and induce greater expression levels of a protein by the gene.[60] The ability to modulate protein expression levels using ESTs allows scientists to monitor how cells behave when the level of a specific protein is eliminated, reduced, or exaggerated. The resulting protein expression patterns aid scientists in understanding the function of the expressed gene and how to affect the pathways that regulate disease and other traits.

7. The Use of ESTs to Locate Genetic Molecules of Other Organisms

The genes of one organism often express proteins that are the same as, or substantially similar to, the proteins expressed by other organisms. Therefore, an EST derived from one organism can be used to probe genetic libraries for gene sequences of interest found in other organisms.[61] If the EST hybridizes with a gene sequence, and the gene has a known function with respect to the other organism, that finding may serve as a shortcut to help determine how the gene functions in the organism from which the EST was derived.[62]

Similarly, the knowledge derived from hybridization between an EST and a gene sequence found in another organism is important even in the absence of knowledge about how the gene functions in the either organism. Such a correlation suggests, for instance, that the organisms under study may share a common genetic heritage.[63] For this reason, the mere knowledge that a gene corresponding to an EST exists in a different organism alone provides geneticists with valuable information from an evolutionary standpoint.

III. THE CONTROVERSY SURROUNDING EST PATENTS

Despite the obvious and important value of ESTs to the scientific community, controversy has surrounded the patenting of ESTs since their discovery.[64] When NIH scientists filed a series of patent applications in the early 1990s directed to about 3,000 ESTs (as well as to the full-length genes and proteins corresponding to the ESTs) the protests heard were loud and immediate.[65] Although the NIH ultimately withdrew those applications in response to significant public opposition, and has since issued statements condemning the patenting of ESTs,[66] the controversy has not abated.

A. Arguments Against the Patenting of ESTs

Scientific and legal commentary have condemned the patenting of ESTs based on a host of moral, social, economic, and scientific concerns. Those who oppose the patenting of ESTs principally argue that:

- ESTs fall outside the scope of patentable subject matter because "the sequence of the human genome is at the core of what it means to be human and no

58 *See id.* at 565-68. Antisense RNA is complementary to the mRNA molecules transcribed from a gene. When introduced to cells attempting to produce corresponding proteins, antisense RNA will bind to the mRNA and block translation of the protein for which the mRNA codes. *See id.*
59 An enhancer, in this context, is a DNA sequence that up-regulates transcription of a gene located nearby in the chromosome. *See id.* at 609.
60 *See id*. at 279-83, 287-88, 561-65, 608-10 (describing the role of promoters and enhancers and the introduction of synthetic, modified, and foreign genetic elements into plant and animal species); Kay et al., 236 SCIENCE 1299 (1987) (describing enhancer modifications).
61 *See* DAVIES, *supra* note 19, at 57-59.
62 *See id*.; Ricki Lewis, *Pufferfish Genome Probe Human Genes,* THE SCIENTIST, Mar. 18, 2002, at 22 (describing how the genomes of humans and the pufferfish are "at least 90% similar" and detailing efforts to probe the human genome with pufferfish DNA sequences).
63 *See generally* SNUSTAD & SIMMONS, *supra* note 15, at 720-45 (discussing populations and evolutionary genetics and the concepts of genetic divergence and conservation).
64 *See generally* Holman, *supra* note 10, at 750-54 (discussing controversy). Mark C. Farrell, *Designer DNA for Humans: Biotech Patent Law Made Interesting for the Average Lawyer,* 35 GONZ. L. REV. 515, 518 (2000) (discussing filing of NIH patent applications and those who "protested loudly").
65 *See* Mark C. Farrell, *Designer DNA for Humans: Biotech Patent Law Made Interesting for the Average Lawyer,* 35 GONZ. L. REV. 515, 518 (1999) (discussing filing of NIH patent applications and those who "protested loudly"); Holman, *supra* note 10, at 750-754.
66 *See* Christopher Anderson, *NIH Drops Bid for Gene Patents,* 263 SCIENCE 909, 910 (1994) (noting that the NIH ultimately abandoned its EST applications because it no longer considered them to be "in the best interests of the public or science").

person should be able to own/control something so basic"[67] and "the patenting of ESTs . . . is contrary to indigenous law";[68]

- The existence of EST patents will block and significantly hamper necessary and important genetic research;[69]

- EST patents "may result in suboptimal allocation of research resources" by focusing development efforts on easily discovered ESTs rather than on the more important, but also more difficult, task of determining the function of genes and proteins;[70]

- Allowing the patenting of ESTs will encourage companies to expend large sums discovering ESTs, most of which will correspond to genes of no known function; this will lead to "an increase in the cost of developed products that reach the market" as these companies seek to recoup expenses directed to the discovery and patenting of their ESTs;[71]

- Large pharmaceutical and genomics companies will unfairly benefit from the widespread patenting of ESTs because those entities have detected far more ESTs than other entities, particularly with respect to the most important genomes (e.g., humans, crops);[72]

- Most meaningful uses of ESTs involve entire databases of thousands of ESTs; therefore, "the fragmented property rights, and the effort needed to integrate them into a useful product, may create transaction costs that deter biotechnological research and development";[73] and

- Most companies developing ESTs receive public funds, and as such, ESTs belong to the public.

B. Arguments in Favor of Patenting ESTs

In response, proponents of EST patents contend that ESTs are valuable inventions entitled to patent protection. These advocates typically maintain that:

- ESTs are new, useful, and nonobvious inventions, and despite more than a decade of intense debate, Congress has not provided any indication that ESTs should be treated differently from other inventions under the patent laws;[74]

- The issuance of EST patents is critical to biotechnology and genomics companies, especially emerging companies, which require patents to attract

67 *See* Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (2001); Farrell, *supra* note 65, at 528-32 (discussing "ethical problems" surrounding patenting of gene sequences); Peter J. Gardner, *U.S. Intellectual Property Law and the Biotech Challenge: Searching for an Elusive Balance,* 44 N.H. Bar J. 24 (Mar. 2003), http://ipmall.info/hosted_resources/NHBAIP/art_gardner_030414.pdf, at *3 (discussing the "religious" and "philosophical" arguments against EST patents).

68 66 Fed. Reg. at 1094.

69 *See id.* ("[P]atents should not issue for genes because patents on genes are delaying medical research."); Gardner, *supra* note 67, at *3 ("[A]cademic and basic researchers fear that proprietary rights to basic research results will hinder scientific progress by impeding access to fundamental information or by blocking the use of experimental tools."); Melanie J. Howlett and Andrew F. Christie, *An Analysis of the Approach of the European, Japanese and United States Patent Offices to Patenting Partial DNA Sequences (ESTs),* 34 INT'L REV. INDUS. PROP. & COPYRIGHT 581 (2004), http://ssrn.com/abstract=573184, at *8 ("The common view in scientific circles was that EST patents would impede research.").

70 Holman, *supra* note 10, at 776 (noting that many thousands of ESTs can be sequenced during the same amount of time it may take to accomplish other more important, but also more time consuming, genetic research); Farrell, *supra* note 65, at 527 ("[P]atenting useless things diverts resources and attention from the favored pursuit of genuine innovation."); Howlett, *supra* note 69, at *9 (noting concerns by the American Society of Human Genetics (ASHG) "that the patenting of ESTs would spur a race to isolate ESTs" at the cost of other valuable research).

71 Holman, *supra* note 10, at 777. *Accord* Howlett, *supra* note 69, at *9 ("[O]pportunity costs . . . , labor costs for EST production and sequencing, and the like would drive the cost of EST patent efforts well above the mere cost of patent applications.").

72 *See* Holman, *supra* note 10, at 782 ("[I]t is likely that the blocking power would be in the hands of a very few large entities. So the potential economic impact of blocking EST patents is great.").

73 *Id.* at 785 (discussing "tragedy of anticommons argument"); Gardner, *supra* note 67, at *3 ("The need to pay licensing fees, scientists say, will dissuade them from experimenting on patented genes.").

74 *See infra* Section V.

and retain investors and to protect their substantial investment in discovering ESTs;[75] and

- One of the core premises underlying the patent system is that society benefits from the public disclosure of inventions; the refusal to issue EST patents runs contrary to that premise, and will stifle further genomic research by forcing companies to keep their EST discoveries secret.[76]

C. Proposals Concerning the Protection of ESTs

This intense debate has given rise to a variety of proposed mechanisms intended to define the appropriate scope of property rights applicable to ESTs. Those arguing against the patenting of ESTs typically contend that all ESTs should: (1) be dedicated to the public domain[77] or (2) be made eligible for protection only under non-patent forms of intellectual property law (e.g., copyright law or forced registration and licensing schemes).[78]

Conversely, some proponents contend that EST patents should issue based on the same standards, and with the same resulting patent rights, as patents directed to claimed inventions in other technological fields.[79] Others agree that EST patents should issue, but disagree about the scope of resulting patent rights. These advocates often maintain that claims directed to ESTs should be limited in time or scope (e.g., limiting claims to uses expressly disclosed in the specification, or making claims unenforceable against experimental users).[80] And still others assert that EST patents should issue, but only after being subjected to heightened patentability standards under 35 U.S.C. Sections 101-03 and 112.[81]

IV. THE PTO'S CURRENT APPROACH TO EST PATENT CLAIMS: THE APPLICATION OF A HEIGHTENED UTILITY STANDARD UNDER 35 U.S.C. SECTION 101.

To date, neither Congress nor the courts have provided any explicit instruction concerning the proper treatment of ESTs under the patent laws - a silence that has left the PTO to face this fiery debate on its own. Unfortunately, the PTO's treatment of the issue has been far from consistent. After years of applying the same minimal standard of utility to ESTs and other claimed inventions, the PTO now applies a heightened standard of utility to ESTs - a standard that, as implemented by the PTO, effectively precludes the patenting of almost all ESTs.

A. The PTO's 1995 Utility Examination Guidelines

Under the 1995 version of its Utility Examination Guidelines ("the 1995 Guidelines"), the PTO instructed its examiners to find that the utility requirement of 35 U.S.C. Section 101 was satisfied where a patent application contained an assertion that "the claimed invention [was] useful for any particular purpose (i.e., a 'specific utility') and that assertion would be considered credible by a

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75 *See* Farrell, *supra* note 65, at 518 ("Patents are needed to reward those willing to undertake the painstaking and expensive labor of deciphering the makeup of genes."); Gardner, *supra* note 67, at *3 ("The biotech industry argues that without strong patent protection firms could not justify the risk, time, energy, and money necessary to create new pharmaceutical products.").

76 *See* 66 Fed. Reg. at 1094 ("The disclosure of genetic inventions provides new opportunities for further development."); *Brenner v. Manson*, 383 U.S. 519, 533 (1966) ("[O]ne of the purposes of the patent system is to encourage dissemination of information concerning discoveries and inventions."); John J. Doll, *The Patenting of DNA*, SCIENCE, May 1, 1998, at 689, 689-90 ("Issuance of patents to such products not only results in the dissemination of technological information to the scientific community for use as a basis for further research but also stimulates investment in the research, development, and commercialization of new biologics.").

77 *See* 66 Fed. Reg. at 1095 (rejecting comments that "DNA should be freely available for research"); Holman, *supra* note 10, at 805-809 (discussing the "public domain approach").

78 *See* Holman, *supra* note 10, at 815-17 (proposing registration system that would provide a brief period of exclusivity, a period of forced licensing, and then dedication to the public domain); Farrell, *supra* note 65, at 532-34 (discussing application of copyright law to gene sequences).

79 *See infra* Section V.

80 *See* 66 Fed. Reg. at 1094-95 (refusing to adopt comment that "patent claims directed to DNA should be limited to applications or methods of using DNA, and should not be allowed to encompass the DNA itself"); *id.* at 1095 (refusing to adopt comment that claims directed to genes "should be limited to uses disclosed in the patent application"); *id.* at 1096 (refusing to adopt comment that gene patents should "allow for others to learn from and improve the invention" without risk of infringement); Holman, *supra* note 10, at 809-13 (discussing theories to limit duration of EST patents).

81 *See* 66 Fed. Reg. at 1096 (discussing comments suggesting heightened utility standard); Nathan Machin, Comment, *Prospective Utility: The New Interpretation of the Utility Requirement of Section 101 of the Patent Act,* 87 CAL. L. REV. 421 (1999) (offering a new utility standard).

person of ordinary skill in the art . . . ."[82] Under this relaxed utility standard,[83] the PTO issued an increasing number of gene patents - including several directed to ESTs.[84] High-ranking PTO officials approved of this practice, publicly commenting that ESTs satisfied all of the patentability requirements, including utility:

> Although some . . . may not directly identify genes, they may still be extremely useful and thus satisfy the utility requirement. . . . ESTs may have specific utilities that are separate and distinct from the genes to which they correspond. For example, . . . ESTs can be used for chromosome identification and gene mapping. [ESTs] can be used to identify genes.[85]

B. The PTO's 2001 Utility Examination Guidelines

By the late 1990s, the PTO faced mounting pressure from the public and Clinton Administration to reverse its open willingness to issue EST patents - a policy that had caused applicants to burden the PTO's docket with applications directed to more than a million ESTs.[86] The PTO responded to these concerns by issuing its Revised Interim Utility Guidelines in 1999, and its Final Guidelines for Examination of Applications for Compliance With the Utility Requirement (the "2001 Guidelines") in January 2001.[87]

The new 2001 Guidelines expressly confirm that ESTs are patentable, provided that the requirements of patentability under 35 U.S.C. SectionSection 101-03 and 112 are met.[88] The 2001 Guidelines, however, announce a new utility standard that reverses course from the relaxed stance announced by the PTO only a few years earlier. More specifically, the 2001 Guidelines require applicants to satisfy a three-pronged test that conditions patentability upon the existence of at least one utility that is "specific, substantial, and credible."[89] As detailed below, the PTO's implementation of this standard effectively has precluded patents from issuing with respect to nearly all ESTs.

1. The "Specific Utility" Prong

The PTO defines a "specific utility" as one "that is *specific* to the subject matter claimed," unlike a "*general* utility that would be applicable to the broad class of the invention."[90] In contrast to prior public statements made by PTO officials, the PTO has construed this requirement to mean that:

> [A] claim to a polynucleotide [such as an EST] whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be *specific* in the absence of a disclosure of a specific DNA target. A general statement of

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82 Utility Examination Guidelines, 60 Fed. Reg. 36,263, 36,264 (1995).

83 *See* Andrew T. Kight, Note, *Pregnant With Ambiguity: Credibility and the PTO Utility Guidelines in Light of Brenner, 73* IND. L. J. 997, 999-1000 (1998) (concluding that the 1995 PTO utility guidelines "make utility-based rejections mere artifacts" because "[t]he guidelines establish the utility standard as 'credible,' which is far below that of 'substantial' as imposed . . . [in] *Brenner*").

84 For example, in October 1998, Incyte Pharmaceuticals received U.S. Patent No. 5,817,479 directed to ESTs concerning "human kinase homologs." By March 2000, the PTO had issued five patents covering ESTs. *See* Ken Garber, *Homestead 2000: The Genome,* SIGNALS (Mar. 2000), *at* http://www.signalsmag.com/signalsmag.nsf/publish/find?searchview&query=garber ("[O]nly five EST patents have issued to date.").

85 Doll, *supra* note 76, at 690. *Accord* Stephen P. Hoffert, *USPTO Issues Biotech Patent Guidelines,* THE SCIENTIST, Jul. 6, 1998 (quoting John J. Doll, director of biotechnology examination at the PTO: "Our position is that ESTs are clearly patentable subject matter. . . . They are nonobvious and have novelty and utility.").

86 *See* Pat Carson And Melissa Mandrgoc, *Gene-Based Drugs Challenge Patent Process,* N.Y.L.J., Oct. 15, 2001, Section 5 (noting that "public pressure" led to issuance of the new utility guidelines); Garber, *supra* note 84 (explaining that when the PTO "quit tracking" the number of pending ESTs in the mid-1990s, it "had about a half a million"); Leslie G. Restaino, et al., *Patenting DNA-Related Inventions in the European Union, United States, and Japan: A Trilateral Approach or a Study in Contrast?,* 2003 UCLA J.L. & TECH 2 ("[B]y the end of 2000, the USPTO had received patent applications on millions of gene fragments . . . ."). More recent estimates suggest that Incyte Pharmaceuticals and Hyseq alone have filed applications directed to more than two million ESTs. *See* Garber, *supra* note 84.

87 In 1996, the PTO sought to further limit the number of EST filings by precluding applicants from seeking to cover more than ten ESTs in a single application. *See* MPEP Section 803.04. The PTO is even more restrictive today: "the patent office will likely reject any filing claiming more than a single sequence of genetic code." Jeffrey Krasner, *Putting Patents in Their Place: Standards for Filing Claims on Genes Raised,* BOSTON GLOBE, Jan. 29, 2003, at C4.

88 Utility Examination Guidelines, 66 Fed. Reg. 1092, 1094 (2001) ("ESTs which meet the criteria for utility, novelty, and nonobviousness are eligible for patenting when the application teaches those of skill in the art how to make and use the invention.").

89 66 Fed. Reg. at 1093. The Guidelines do not expressly define the terms "specific," "substantial," and "credible," but do provide a few basic examples of when those requirements might be met by an EST. *See id.* at 1094 (EST may have utility if "it can be used to produce a useful protein or it hybridizes near and serves as a marker for a disease gene"); *id.* at 1095 (EST may have substantial and credible utility if "it has a gene-regulating activity"); *id.* at 1096 ("homology-based assertions" may satisfy utility requirement). Notably, an EST that corresponds to a gene of unknown function can satisfy none of these requirements.

90 MPEP Section 2107.01 (emphasis added).

diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.[91]

2. The "Substantial Utility" Prong

"Substantial utility" refers to a utility that "defines a 'real world' use."[92] "[T]hrow-away" utilities (e.g. "the use of a complex invention as landfill") are not substantial.[93] Moreover, the PTO has concluded that "[u]tilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities."[94] Examples of non-substantial uses include: (1) "studying the properties of the claimed product itself or the mechanisms in which the material is involved"; (2) "method[s] of treating an unspecified disease or condition"; (3) "method[s] of assaying for or identifying a material that itself has no specific and/or substantial utility"; (4) "method[s] of making a material that itself has no specific, substantial, or credible utility"; and (5) "claim[s] to an intermediate product for use in making a final product that has no specific, substantial and credible utility."[95]

3. The "Credible Utility" Prong

An asserted use that meets the specific and substantial utility prongs "cannot simply be dismissed by Office personnel as being 'wrong.'"[96] Instead, the examiner must accept a utility asserted by the applicant as "credible" unless: "(A) the logic underlying the assertion is seriously flawed, or (B) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion."[97] The determination of whether an invention has "credible utility" is "assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions."[98]

The examiner training materials make clear that, to the extent a claim directed to an EST satisfies the specific and substantial utility prongs, the claim typically will satisfy the credible utility prong as well: "[N]ucleic acids could be used as probes, chromosome markers, or forensic or diagnostic markers. Therefore, the credibility of such an assertion would not be questioned, although such a use might fail the *specific* and *substantial* tests . . . ."[99]

C. The PTO's Uneven Application of Its Heightened Utility Test

The PTO's present utility standard purports to apply equally to all inventions. The PTO's actual implementation of that standard, however, has been far from equal. In particular, while the PTO continues to assess the utility of inventions falling outside the field of genetics under a relaxed threshold of proof, at the same time, the PTO has applied a highly stringent test to ESTs, concluding that an EST fails the specific and substantial utility prongs in the absence of evidence showing some knowledge concerning the function of the gene or protein or an identified trait corresponding to the EST.

By directly equating the requirements of a specific and substantial utility with the level of knowledge concerning the function of a gene, protein, or trait that corresponds to an EST - a test that discards many important uses to which ESTs can be put - the PTO essentially has precluded the patenting of almost all ESTs.[100] This result should come as little surprise given the PTO's open

91 *Id.* (emphasis added).
92 *Id.*
93 66 Fed. Reg. at 1098.
94 MPEP Section 2107.01. *Accord id.* (confirming that "[m]any research tools such as . . . nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds)").
95 *Id.*
96 MPEP Section 2107.02.
97 *Id.*
98 *See* MPEP Section 2107.02. The failure of an applicant to demonstrate a utility that is specific and substantial is not immediately fatal to the application, if the claimed invention has a "well-established" utility. MPEP Section 2107.2. The PTO has concluded that ESTs corresponding to genes of unknown function do not have a well-established utility. *See* United States Patent and Trademark Office, *Revised Interim Utility Guidelines Training Materials,* at 50-51 (1999), *available at* http://www.uspto.gov/web/offices/pac/utility/utilityguide.pdf [hereinafter *Training Materials*].
99 *Id.* at 5.
100 *See* Carson, *supra* note 86 ("[T]he utility standard set forth by these guidelines should be a significant obstacle to the issuance of patents for partial and uncharacterized cDNA sequences . . . ."); Holman, *supra* note 10, at 758 ("[T]he utility requirement cannot be met in the vast majority of EST applications.").

concession that it enacted the 2001 Guidelines for the specific purpose of precluding the patenting of nearly all ESTs.[101]

V. THE PTO'S IMPOSITION OF A HEIGHTENED UTILITY STANDARD, AND ITS UNEVEN APPLICATION OF THAT STANDARD TO EST PATENT APPLICATIONS, RUNS CONTRARY TO ESTABLISHED LAW.

The utility standard established by 35 U.S.C. Section 101 is not a moving target that the PTO is entitled to adjust from time to time at its whim. Nor does the intensity of that standard rise or fall based on the PTO's desire to cleanse its docket or silence ongoing debate. Instead, the level of utility required by Section 101 is fixed by statute and court decisions to require just a minimal showing of usefulness. As detailed below, the PTO's effort to saddle EST applications with a heightened standard of utility runs contrary to this statutory and judicial precedent.[102]

A. The Minimal Threshold of Utility Established by 35 U.S.C. Section 101.

The concept of utility embodies "a fundamental requirement of American patent law" that finds its roots and purpose in the United States Constitution: That "[t]he Congress shall have Power … To Promote the Progress of Science and ***useful*** Arts."[103] Over the last two centuries, Congress has enacted a regime of patent laws to "promote this progress by offering inventors exclusive rights for a limited period as an incentive for their inventiveness and research efforts."[104] Since 1952, the constitutional requirement of "useful" inventions has been codified by 35 U.S.C. Section 101, which provides in relevant part that:

> 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 . . . .[105]

The legislative history unambiguously indicates that Congress intended for the "extremely broad"[106] language of Section 101 to "be given wide scope"[107] and "a broad construction"[108] so as to cover "anything under the sun that is made by man."[109] The goal of this legislative scheme was to foster "a positive effect on society through the introduction of new products and processes of manufacture into the economy, and the emanations by way of increased employment and better lives for our citizens."[110]

Given the expansive breadth of this statutory language and congressional intent, courts construing Section 101 (and predecessor versions of that statute) historically have ascribed a minimal standard to the requirement that an invention be "useful." For example, in a well-known decision now nearly two centuries old, Justice Story announced that:

> All that the law requires is, that the invention should not be frivolous or injurious to the well-being, good policy, or sound morals of society. The word

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101 *See* Holman, *supra* note 10, at 750-54. The uneven treatment of ESTs is evident in the PTO's own training materials, which discuss the treatment of a patent application that claims an EST that corresponds to a gene of unknown function and asserts that the EST can be used as a probe to obtain the full-length gene and study the corresponding protein - a use common to all ESTs. Examiners are instructed to reject the application for failure to satisfy both the specific and substantial utility prongs. According to the PTO, the EST would not meet the specificity prong because "[a]ny partial nucleic acid prepared from any cDNA may be used to as a probe in the preparation and or identification of a full-length cDNA," and would not satisfy the substantial utility prong because the corresponding gene and protein have no known utility and would require further research "to identify or reasonably confirm a 'real world' context of use." *Training Materials, supra* note 98, at 50-52.

102 *See In re* Krimmel, 292 F.2d 948, 954 (C.C.P.A. 1961) ("[T]he Patent Office has not been charged by Congress with the task of protecting the public against possible misuse of chemical patents."); *see also* 66 Fed. Reg. at 1095 ("The USPTO must administer the laws as Congress has enacted them and as the Federal courts have interpreted them.").

103 U.S. CONST., Art. I Section 8 (emphasis added); *see Stiftung v. Renishaw* PLC, 945 F.2d 1173, 1180 (Fed. Cir. 1991) ("The utility requirement has its origin in article I, section 8 of the Constitution, which indicates that the purpose of empowering Congress to authorize the granting of patents is 'to promote progress of . . . *useful* arts.'").

104 *Diamond v. Chakrabarty*, 447 U.S. 303, 307 (1980).

105 35 U.S.C. Section 101 (emphasis added).

106 *J.E.M. AG Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc.,* 534 U.S. 124, 130 (2001).

107 *Id.*

108 *Chakrabarty*, 447 U.S. at 380.

109 *Id.* at 308-09 (quoting S. REP. NO. 82-1979, at 5 (1952); H.R. REP. NO. 82-1923, at 6 (1952)).

110 *Kewanee Oil Co. v. Bicron Corp.,* 416 U.S. 470, 480 (1974).

> "useful," therefore, is incorporated into the act in contradistinction to mischievous or immoral.[111]

Even today, courts continue to cite Justice Story's minimalist view of utility with approval.[112]

1. The Requirement of "Substantial" or "Practical" Utility Established by *Brenner v. Manson*.

Nearly four decades ago, a divided Supreme Court addressed the standard of utility applicable to a chemical process or composition with no known utility "other than as a possible object of scientific inquiry."[113] After acknowledging the sometimes-difficult task of assessing the utility of inventions directed to chemical compositions,[114] the *Brenner* court determined that to be "useful" and patentable, inventions must provide the public with at least one identifiable benefit that is "substantial":

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention ***with substantial utility***.[115]

The Supreme Court further clarified that "substantial utility" does not exist "[u]nless and until . . . [a] specific benefit exists in currently available form."[116] Otherwise, "there is insufficient justification for permitting an applicant to engross what may prove to be a broad field."[117] "[A] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."[118]

In the several decades since *Brenner*, the Federal Circuit and its predecessor courts, the U.S. Court of Claims and the U.S. Court of Customs and Patent Appeals (C.C.P.A.), have implemented a two-prong analytical framework to assess whether an invention provides "substantial utility." First, the claimed invention must provide at least one specific, "identifiable benefit" - i.e., one that is not vague or unknown.[119] Second, the benefit must also be "substantial" or "practical"[120] - i.e., one that provides a measurable benefit in the "real-world."[121]

2. Even After *Brenner*, "The Threshold Of Utility Is Not High."

A number of commentators have suggested that Brenner marked a radical departure from Justice Story's minimalist view of utility.[122] It did not. More recent decisions of the Federal Circuit and its predecessor repeatedly have confirmed that the threshold to demonstrate "substantial utility" under Section 101 remains strikingly minimal, even today:

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111 *Lowell v. Lewis,* 15 F. Cas. 1018, 1019 (C.C. Mass. 1817) (No. 8568); *see also Bedford v. Hunt,* 3 F. Cas. 37, 37 (C.C. Mass. 1817) (No. 1217) ("By useful invention, in the statute, is meant such a one as may be applied to some beneficial use in society, in contradistinction to an invention, which is injurious to the morals, the health, or the good order of society.").

112 *See, e.g., Juicy Whip, Inc. v. Orange Bang, Inc.,* 185 F.3d 1364, 1366-67 (Fed. Cir. 1999) (noting that "[c]ourts have continued to recite Justice Story's formulation," but explaining that the prohibition on patenting inventions "principally designed to serve immoral or illegal purposes has not been applied broadly in recent years").

113 *Brenner v. Manson*, 383 U.S. 519, 529 (1966).

114 *Id.* at 533.

115 *Id.* at 534-35 (emphasis added).

116 *Id.* at 534.

117 *Id.* at 535.

118 *Id.* at 536.

119 *Juicy Whip, Inc. v. Orange Bang, Inc.,* 185 F.3d 1364, 1366 (Fed. Cir. 1999). *Accord In re Brana*, 51 F.3d 1560, 1565 (Fed. Cir. 1995); *In re Kirk*, 376 F.2d 936, 945 (C.C.P.A. 1967). Moreover, the utility requirement of Section 101 demands only ***one*** actual, identifiable benefit. *See Stiftung v. Renishaw PLC,* 945 F.2d 1173, 1180 (Fed. Cir. 1991) ("[W]hen a properly claimed invention meets at least one stated objective, utility under Section 101 is clearly shown."); *id.* (noting that the utility requirement does not "mean that a patented device must accomplish all objectives stated in the specification.").

120 *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996). The Federal Circuit has long-treated the terms "substantial utility" and "practical utility" interchangeably. *See, e.g., id.* 1563-64; Cross v. Iizuka, 753 F.2d 1040, 1047 n.13 (Fed. Cir. 1985).

121 *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980).

122 *See, e.g.*, Teresa M. Summers, Note, *The Scope of Utility in the Twenty-First Century: New Guidance for Gene-related Patents,* 91 GEO. L.J. 475, 479 (2003); Karen F. Lech, Note, *Human Genes Without Functions: Biotechnology Tests the Patent Utility Standard,* 27 SUFFOLK U. L. REV. 1631, 1643 (1993).

- Lack of utility is shown "when there is a ***complete absence of data*** supporting the statements which set forth the desired results of the claimed invention."[123]

- "The threshold of utility is ***not high***: An invention is 'useful' under section 101 if it is capable of providing ***some identifiable benefit.***"[124]

- "To violate Section 101 the claimed device must be ***totally incapable of achieving a useful result*** . . . ."[125]

- "[A] reasonable jury could not have found the '***total incapacity***' that is required to prevail on a lack of utility defense under Section 101."[126]

- "***Some degree of utility*** is sufficient for patentability."[127]

- "'Practical utility' is a shorthand way of attributing 'real-world' value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides ***some immediate benefit*** to the public."[128]

B. The PTO Cannot Selectively Target EST Patents Through a Heightened Utility Requirement.

The PTO has a plain and legitimate interest in providing patentees with a streamlined application process - a task that, prior to 2001, was made more difficult by the flood of pending claims directed to ESTs. The PTO also has an obvious interest in resolving any uncertainty surrounding the patentability of particular technologies, including ESTs. Nevertheless, it is inappropriate for the PTO to seek to accomplish either of those objectives through the arbitrary establishment of new patentability requirements.

Yet, that is exactly what has happened. Rather than apply the minimal standard of utility established by Congress and repeatedly applied by the courts - and PTO itself prior to 2001 - the PTO instead announced a new, more stringent utility standard applicable to ESTs - a standard that conditions patentability upon some undefined level of knowledge concerning corresponding gene function or trait. The PTO's enactment of a new utility standard impinges upon the role of the legislature. It is well established that Congress alone has been entrusted with the power to define the level of utility necessary to effectuate the constitutional requirement that patentable inventions be "useful",[129] a power that Congress has exercised through its enactment of 35 U.S.C. Section 101.

Moreover, nothing in the plain language of Section 101 or its legislative history in any way supports a claim that Congress expressly or impliedly intended to subject ESTs to a utility standard that is more stringent than the low utility standard applicable to other inventions. In fact, the decisions of the Federal Circuit make abundantly clear that an identical standard applies to all

123 *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999) (emphasis added) (quoting *Envirotech Corp. v. Al George, Inc.,* 730 F.2d 753, 762 (Fed. Cir. 1984)).
124 *Juicy Whip, Inc.,* 185 F.3d at 1366 (emphasis added) (citing *Brenner v. Manson*, 383 U.S. 519, 534 as direct support for holding).
125 *Brooktree Corp. v. Advanced Micro Devices, Inc.,* 977 F.2d 1555, 1571 (Fed. Cir. 1992) (emphasis added).
126 *Tol-O-Matic, Inc. v. Proma Produkt-Und Marketing GmbH,* 945 F.2d 1546, 1553 (Fed. Cir. 1991) (emphasis added), *abrogated on other grounds, Markman v. Westview Instruments, Inc.,* 52 F.3d 967 (Fed. Cir. 1995).
127 *Envirotech Corp. v. Al George, Inc.,* 730 F.2d 753, 762 (Fed. Cir. 1984) (emphasis added). *Accord id.* ("[T]he defense of non-utility cannot be sustained without *proof of total incapacity*.") (emphasis added).
128 *Nelson v. Bowler,* 626 F.2d 853, 856 (C.C.P.A. 1980) (emphasis added). The few post-*Brenner* cases actually finding lack of utility further confirm that the standard for utility remains minimal. *See, e.g., Newman v. Quigg,* 877 F.2d 1575, 1577, 1581-82 (Fed. Cir. 1989) (finding lack of utility where "perpetual motion machine" deemed "impossible" under the laws of thermodynamics); *Fregeau v. Mossinghoff,* 776 F.2d 1034, 1039 (Fed. Cir. 1985) (finding no utility for method to enhance the flavor of beverages using a magnetic field); *In re Houghton*, 433 F.2d 820, 820-21 (C.C.P.A. 1970) (finding no utility for "highly unusual" flapping flying machine based on bird and insect flight); *In re Eltgroth*, 419 F.2d 918, 920-21 (C.C.P.A. 1970) (no utility for "speculative" method of controlling the aging process); *In re Kirk*, 376 F.2d 936, 942-43 (C.C.P.A. 1967) (utility lacking for steroid compound where disclosed "possible use so general as to be meaningless").
129 *See, e.g.*, U.S. CONST., Art. I Section 8; *Diamond v. Chakrabarty*, 447 U.S. 303, 307 (1980); *Juicy Whip*, 185 F.3d at 1368.

inventions.[130] Continuing acceptance of the PTO's unequal treatment of ESTs will continue to lead to unjustifiable results. By way of example, a drink dispenser whose sole benefit is that it "look[s] like another" product will be deemed by the PTO to have patentable utility,[131] while nearly all ESTs will continue to be rejected by the PTO for lack of utility - even though ESTs have played, and continue to play, a critical role in helping scientists to develop new drug treatments, genetically improved crops, and other products beneficial to humanity. This unbalanced result simply highlights the danger of the PTO's unilateral decision to apply one standard of utility to certain classes of inventions and another standard of utility to others.

At bottom, the PTO simply does not have the authority or the expertise to usurp the role of Congress by rewriting the statutorily mandated standard for utility applicable under 35 U.S.C. Section 101. Accordingly, the courts should reject the PTO's newly manufactured and unequally applied utility test.

C. The PTO's Arguments in Favor of a Heightened Utility Standard.

The PTO has advanced a series of arguments in an effort to justify the imposition of a strict utility requirement to ESTs, but not to other inventions. None of these arguments can withstand scrutiny.

1. The PTO's *Brenner* Argument.

First, the PTO maintains that *Brenner* precludes a finding of substantial utility with respect to ESTs that correspond to genes of unknown function or that have not been correlated with a particular trait.[132] However, the attempt to equate ESTs with the chemical composition at issue in *Brenner* is misplaced. The *Brenner* chemical composition had no known utility other than as an object of further scientific research. In contrast, the utility of ESTs does not rest upon some mere interest in conducting further research upon the ESTs *themselves*. Rather, ESTs have utility because they can be used as research tools to conduct further scientific research on *other* chemical compositions (i.e., genes, gene fragments, proteins, etc.).[133]

Moreover, unlike the chemical composition at issue in *Brenner* - which possibly had no actual discoverable utility at all - ESTs correspond to expressed genes that synthesize proteins that an organism undoubtedly uses for some meaningful purpose. At a minimum, ESTs can be used to discover that unknown, but not unknowable, utility, as well as to conduct the variety of different research applications discussed above. These many uses collectively demonstrate that ESTs have significant value beyond further "use-testing" of the EST sequences themselves. Thus, *Brenner* is wholly inapplicable on this point.[134]

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130 *See, e.g., id.* (applying the same "substantial utility" standard to an imitation drink dispenser that the Supreme Court applied to the chemical composition at issue in *Brenner*).

131 *See Juicy Whip*, 185 F.3d at 1367.

132 *See, e.g., Ex parte Fisher*, Patent and Trademark Office Board of Patent Appeals and Interferences Appeal No. 2002-2046, at 19, 22 (Mar. 31, 2004).

Several commentators have written that *Brenner* precluded the patenting of basic research tools, such as ESTs. *See, e.g.,* Summers, *supra* note 122, at 479 ("In *Brenner v. Manson,* the Supreme Court maintained that the claimed invention must possess utility beyond being a basic tool for future research."); Lech, *supra* note 122, at 1642 ("The *Brenner* Court specifically denied patent protection to inventions whose only utility resided in their use in experimental research . . . ."). *Brenner* did no such thing. The Supreme Court held in that case that a composition did not have utility merely because scientists might have a reasonable interest in performing research on the composition itself. The Court said nothing about the patentability of the *tools* used to perform research on the composition.

133 The *Brenner* majority held that a chemical composition "whose sole 'utility' consists of its potential role as an object of use-testing" does not have substantial utility. *Brenner v. Manson*, 383 U.S. 519, 535 (1966). Writing for the dissent, Justice Harlan disagreed, noting that:

> Chemistry is a highly interrelated field and a tangible benefit for society may be the outcome of a number of different discoveries, one discovery building upon the next. To encourage one chemist or research facility to invent and disseminate new processes and products may be vital to progress, although the product or process be without 'utility' as the Court defines the term, because that discovery permits someone else to take a further but perhaps less difficult step leading to a commercially useful item. In my view, our awareness in this age of the importance of achieving and publicizing basic research should lead this Court to resolve uncertainties in its favor and uphold the respondent's position in this case.

Id. at 539 (Harlan, J., dissenting). Given the steep advances in the field of Chemistry over the last several decades, it is at least an open question as to whether the Supreme Court would adopt Justice Harlan's dissenting view if asked to revisit the issue presented in *Brenner*.

134 Nor is the PTO's treatment of ESTs justified in view of the Federal Circuit's decision in *In re Ziegler*, 992 F.2d 1197 (Fed. Cir. 1993). In that case, the court found that a claimed polypropylene lacked utility even though it could be pressed into a film because "Ziegler did not assert any practical use for the polypropylene or its film, and Ziegler did not disclose any characteristics of the polypropylene or its film that demonstrated its utility." *Id*. at 1203. By contrast, ESTs have utility as research tools, not as mere intermediates used to generate a substance of no known value.

2. The PTO's "Further Research" Argument.

Second, the PTO contends that any benefits derived from the use of an EST cannot be deemed "substantial" to the extent that "further research" is required to make sense of the information derived from the use.[135] The PTO's rationale, however, overlooks the series of Federal Circuit decisions holding that the need to conduct additional research to determine the significance of results obtained from the use of a compound in no way precludes a finding of utility.[136] In fact, those cases make abundantly clear that an "immediate benefit to the public" results from the use of a composition - like an EST - that "marshal[s] resources and direct[s] the expenditure of effort" for the very purpose of allowing *additional testing*.[137]

3. The PTO's "Single Data Point" Argument

Third, the PTO argues that ESTs lack patentable utility, in part, because the use of a single EST (e.g., as a molecular marker or to measure mRNA levels) results in just "a single data point among thousands or millions" and that "even if the thousands or millions of data points collectively are useful, [a single data point derived from a single EST] does not meet [the substantial utility] standard."[138] However, the authors of this article are unaware of any case - and the PTO has pointed to none - holding that a research tool lacks patentable utility simply because it provides just one data point among many others, or because the results derived from that tool must be used in connection with other data to be completely meaningful.

Indeed, if accepted, the PTO's rationale would have a profound impact on the patentability of numerous legitimate inventions that require the combination of multiple components or pieces of data to be completely useful. For example, if taken to its logical extreme, the Board's reasoning would preclude the patenting of inventions ranging from basic (e.g., a single LEGO block) to complex (e.g., gene mapping, surface mapping, CAD modeling, or semiconductor fabrication systems) simply because those applications require the combination of many other components or data points to work and have value. For obvious reasons, this is not the law.

4. The PTO's "Tragedy of the Anticommons" Argument

Finally, the PTO recently has relied upon a "tragedy of the anticommons argument" to justify the rejection of EST patent applications on utility grounds. That argument contends that, because ESTs are basic research tools that must be used in connection with thousands of other ESTs to have any meaningful value (e.g., in a microarray), the widespread patenting of ESTs will force scientists to conduct thousands of patent searches, and to negotiate and acquire thousands of patent licenses, prior to initiating even the most basic genetic research using ESTs.[139]

The PTO's "anticommons" argument is flawed in at least two key respects. First, even if the premise underlying the theory is accepted as true, the PTO has no legal authority to declare certain technologies outside the scope of the patent laws based on considerations of patent searching or licensing burdens. Congress, which has refused to take any course of action on the issue despite more than a decade of intense debate about the patenting of ESTs, alone is charged with that task.

Second, the need to conduct extensive patent searches and obtain licenses is in no way unique to ESTs. Rather, the PTO's "anticommons" argument applies just as equally to - and, therefore, if accepted, would preclude the patenting of - many other technologies that require the use of a substantial number of patented products and processes to work (e.g., semiconductor

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135 *See* MPEP Section 2107.01, at 2100-32 (describing "examples of situations that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use and, therefore, do not define 'substantial utilities'").

136 In those cases, the Federal Circuit held that the utility requirement of Section 101 can be met by compounds claiming a pharmacological effect in humans, even in the absence of evidence showing an in *vivo* pharmacological activity, and even though further research was required to prove *any* benefit for *in vivo* use. *See Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985) (holding that information derived from in vitro test results were sufficient to meet the requirement of substantial utility); *In re* Jolles, 628 F.2d 1322, 1327 (C.C.P.A. 1980) (finding utility without evidence of in vivo results); *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980) (same).

137 *Cross*, 753 F.2d at 1051. *Accord Nelson*, 626 F.2d at 856.

138 *Ex parte Fisher*, Patent and Trademark Office Board of Patent Appeals and Interferences Appeal No. 2002-2046, at 23 (Mar. 31, 2004).

139 *See, e.g., Ex parte Boukharov*, Patent and Trademark Office Board of Patent Appeals and Interferences Appeal No. 2003-1746, at 22 (June 30, 2004).

manufacturing). Therefore, to find that a "tragedy of the anticommons" argument justifies a ban on the patenting of ESTs, but not other similarly situated inventions, not only conflicts with established law, but also collides with common sense.

VI. ESTs INHERENTLY MEET THE UTILITY REQUIREMENT OF 35 U.S.C. SECTION 101.

Under a proper application of the law, there is no question that ***all*** ESTs satisfy the threshold for utility established by Section 101 - which "is not high."[140] ESTs are important research tools that can be put to a variety of specific, substantial, and commercially beneficial uses beyond mere use-testing. In other words, they have legal utility.

A. All ESTs Satisfy The "Specific Benefit" Prong of the Federal Circuit's Utility Analysis

All ESTs meet the first prong of the Federal Circuit's utility analysis: They provide the public with a number of specific, identifiable benefits that are not vague or unknown. Unlike the chemical process and the resulting compound at stake in *Brenner*, which had no known identifiable use other than as a subject of further scientific research, *all* ESTs necessarily correspond to a specific gene with a *knowable* function. Furthermore, all ESTs can be used as valuable research tools in connection with a host of scientific applications, including to: (1) serve as molecular markers on a genetic or physical map; (2) identify the presence or absence of a polymorphism; (3) measure the level of mRNA in a sample; (4) serve as a source for primers; (5) isolate promoters; (6) control the expression levels of protein; and (7) locate genetic molecules of other plants and organisms.

Each of these disclosed uses is "identifiable" and specific to a particular EST. In fact, because each EST uniquely corresponds to a specific gene segment, no other EST can be utilized for exactly the same purposes.[141] Accordingly, every EST meets the specificity prong of the Federal Circuit's substantial utility analysis.[142]

B. All ESTs Satisfy the "Substantial Benefit" Prong of the Federal Circuit's Utility Analysis.

All ESTs further satisfy the "substantial benefit" prong of the Federal Circuit's utility analysis - including ESTs that correspond to genes or proteins of unknown function. As a matter of scientific reality, when used as research probes to screen genetic samples for particular genes and gene fragments of interest, ESTs provide the public with a number of measurable benefits, including to:

- Serve as molecular markers for genes of interest, thereby assisting scientists to navigate through complex physical and genetic maps detailing the millions or billions of base pairs found in particular genomes;[143]

- Determine the presence or absence of polymorphic variations between two or more populations of genetic samples, which, among other things, provides scientists with important information for use in marker-assisted breeding and studying the nature of any shared genetic heritage between the samples;[144]

- Detect and monitor the quantitative levels and patterns of mRNA found in a particular cell or tissue sample, thus providing information pertinent to detecting expression changes in traits of interest;[145]

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140 *See Juicy Whip, Inc. v. Orange Bang, Inc.,* 185 F.3d 1364, 1366 (Fed. Cir. 1999).

141 As noted above, the Manual of Patenting Examining Procedure (MPEP) defines "specific utility" as a utility that "is *specific* to the subject matter claimed," and contrasts it with "a *general* utility that would be applicable to the broad class of the invention." MPEP Section 2107.01 (emphasis added). Because each EST uniquely corresponds to a particular segment of a particular gene, the utilities derived from an EST are not shared by any "broad class" of ESTs.

142 *See Juicy Whip*, 185 F.3d at 1366 ("An invention is 'useful' under section 101 if it is capable of providing *some identifiable benefit*.") (emphasis added); *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980) (finding that utility exists where "one skilled in the art can use a claimed discovery in a manner which provides *some immediate benefit* to the public") (emphasis added).

143 *See supra* Section II(C)(1).

144 *See supra* Section II(C)(4).

145 *See supra* Section II(C)(2).

- Serve as a source for synthetic PCR primers to enable the rapid and inexpensive duplication of a specific target gene;[146]

- Isolate promoters (such as the promoter of the genes corresponding to the claimed ESTs) by, for example, initiating a chromosome walk;[147]

- Modulate the expression levels of a gene to allow study of protein expression patterns and gene/protein function;[148] and

- Isolate nucleic acid molecules found in other organisms to allow comparative studies of located genes and their functions between organisms.[149]

Each of these uses furnishes the field of genetic science with *substantial* benefits that are capable of realization in the real world - regardless of the level of knowledge concerning the function of the underlying gene.[150]

As a practical matter, acceptance of the PTO's heightened utility standard would mean that other research tools of unquestionable and critical value to the scientific community similarly lack substantial utility. For example, in a number of key respects, ESTs are directly analogous to research tools such as microscopes, telescopes, and screening assays, all of which can be utilized to study, locate, and generate scientific data about samples with currently unknown properties. It would make little sense to conclude - as the logic of the PTO effectively requires - that a microscope has substantial utility when used to observe or analyze a sample of known function, but lacks substantial utility when used to observe or analyze a sample of unknown function. In fact, research tools arguably have even greater value when used to probe, examine, and understand the properties of a sample with an unknown function.

The same holds true here. When used as a probe to screen a genetic sample, every EST can be used like a microscope to locate, study, and derive information about a particular gene or gene fragment. That the gene under examination has no known function does not change this result. Like a microscope, regardless of whether used to examine genes of ***unknown*** function now, or genes of ***known*** function at some later date, ESTs serve specific, substantial, and scientifically valuable purposes. They have utility.

C. The Patentable Utility of ESTs is Further Confirmed by Considerations of Commercial Success.

As the Supreme Court noted decades ago in *Brenner*, the test for utility reflects the close relationship of the patent system "to the world of commerce rather than to the realm of philosophy."[151] For that reason, "[p]roof of . . . utility is further supported when . . . the inventions . . . have on their merits been met with commercial success."[152] This nexus between utility and commercial success exists because "[p]eople rarely, if ever, appropriate useless inventions."[153]

The utility of ESTs is not merely an abstract exercise in "the realm of philosophy." Rather, a vast industry has developed in the commercial marketplace for ESTs, including for ESTs that code

146 *See supra* Section II(C)(3).
147 *See supra* Section II(C)(5).
148 *See supra* Section II(C)(6).
149 *See supra* Section II(C)(7). The Federal Circuit has recognized that each of these disclosed uses must be presumed to be specific and substantial in the absence of evidence to the contrary. *See In re* Brana, 51 F.3d 1560, 1566 (Fed. Cir. 1995).
150 *See, e.g., Juicy Whip, Inc. v. Orange Bang, Inc.,* 185 F.3d 1364, 1366 (Fed. Cir. 1999) (holding that "substantial utility" standard is met by an invention that "is capable of providing *some identifiable benefit*.") (emphasis added); *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980) (holding that substantial utility merely requires that "one skilled in the art can use a claimed discovery in a manner which provides *some immediate benefit* to the public") (emphasis added).
151 *See Brenner v. Manson*, 383 U.S. 519, 536 (1966) (quoting *In re* Rushing, 343 F.2d 965, 970 (C.C.P.A. 1965)).
152 *Raytheon Co. v. Roper Corp.,* 724 F.2d 951, 959 (Fed. Cir. 1983). Nevertheless, commercial success is not a necessary element of utility: "development of a product to the extent that it is presently commercially salable in the market place is not required to establish 'usefulness' within the meaning of Section 101." *In re* Langer, 503 F.2d 1380, 1393 (C.C.P.A. 1974).
153 *Raytheon*, 724 F.2d at 959. *Accord In re Langer*, 503 F.2d at 1393.

genes of unknown function. Numerous well-known biotechnology and genomics companies have dedicated substantial time, effort, and financial resources to research, discover, and utilize ESTs with respect to a variety of organisms. Many of these same companies have collectively derived hundreds of millions of dollars in revenues from licensing databases of ESTs that correspond to genes both of known ***and*** unknown function. For example:

- By 2000, Human Genome Sciences had obtained more than $265 million in licensing fees and royalty payments from a number of large pharmaceutical companies for access to its proprietary EST databases;[154]

- Incyte Pharmaceuticals reported 1998 revenues from subscriptions to its EST databases at $105.6 million,[155] and by 2000 had "signed up eleven companies for amounts ranging from $20 million to $25 million per client plus royalties";[156]

- DuPont signed a five-year deal with Lynx Therapeutics to use Lynx's technology to organize Dupont's extensive crop EST databases and to provide genomic maps for crops in an effort to improve yield and agronomic traits such as drought tolerance;[157]

- Celera Genomics has licensed its "Human Gene Index" EST database to companies such as Amgen, Inc.,[158] Novartis,[159] and Pharmacia & Upjohn[160] to, among other things, "enable and accelerate … [the] identification of novel genes and factors that regulate and control gene expression";[161]

- Gene Logic, Inc. licenses its EST databases to numerous companies such as Procter & Gamble Pharmaceuticals[162] and Organin, N.V.,[163] and in 1999 entered into an agreement with Affymetrix, Inc. to build a large commercial EST database for drug development;[164] and

- Exelixis Pharmaceuticals Inc. and Bayer AG entered into a collaboration agreement in 1998 that gives Bayer a license to Exelixis's "FlyTag" Drosophila EST database and obligates Exelixis to develop new pest species EST databases for Bayer.[165]

ESTs also are used for the study of gene expression in the burgeoning field of microarray analysis.[166] According to recent reports, the global microarray market is poised to grow to nearly $1 billion in annual revenues by 2010.[167]

It runs contrary to common sense to think that sophisticated corporations and knowledgeable scientists would dedicate hundreds of millions of dollars to an industry based upon

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154 *See* Holman, *supra* note 10, at 754-55.
155 Press Release, Incyte Pharmaceuticals, Inc., Incyte Reports Year-end Results and 1999 Financial Targets, Announces Decision not to Pursue Tracking Stock Vehicle (Feb. 3, 1999), http://www.incite.com/news/1999/pharmacia.html.
156 *See* Holman, *supra* note 10, at 755.
157 Jim Shrine, *Lynx, Dupont Sign $60M Deal for Crop Genomics,* BIOWORLD TODAY, Nov. 6, 1998.
158 Press Release, Perkin-Elmer, Perkin-Elmer's Celera Genomics to Provide Amgen Access to New Database Products (Jan. 12, 1999), http://www.perkin-elmer.com/press/prc5506.html.
159 Press Release, Perkin-Elmer, Celera Genomics Enters into Five-Year Database Agreement with Novartis (Apr. 19, 1999), http://www.perkin-elmer.com/press/prc5544.html.
160 Press Release, Perkin-Elmer, Celera Genomics and Pharmacia & Upjohn Enter into Five-Year Subscription Agreement for Celera Database Products (Mar. 17, 1999), http://www.perkin-elmer.com/press/prc5539.html.
161 Press Release, *supra* note 159.
162 Press Release, Gene Logic, Gene Logic, Procter & Gamble Pharmaceuticals Expand Drug Discovery Collaboration (Dec. 14, 1998), http://www.genelogic.com/PR-PGExpansion.htm.
163 Press Release, Gene Logic, Gene Logic and Organon Enter Gene Expression Database Alliance (Jan. 8, 1997), http://www.genelogic.com/PR-Organon.htm.
164 Press Release, Gene Logic, Gene Logic to Use Affymetrix Genechip Arrays to Build Gene Expression Database Product (Jan. 11, 1999), http://www.genelogic.com/PR-GeneChip.htm.
165 Press Release, Exelixis Pharmaceuticals, Inc., Exelixis Pharmaceuticals Delivers Target for Screening to Bayer AG (Apr. 1, 1999), http://www.exelixis.com/text/news/releases/99news/04_01.htm.
166 Microarrays display ordered sets of data points that correspond to known DNA molecules. Scientists can use microarrays to detect thousands of genes in a small sample simultaneously, and to analyze the expression of those genes. *See* SNUSTAD & SIMMONS, *supra* note 15, at 536-38.
167 *See, e.g.,* Frost & Sullivan, *Strategic Analysis of World DNA Microarray Markets,* Report A776 (Mar. 2004).

useless items of commerce. Just as "[p]eople rarely, if ever, appropriate useless inventions,"[168] people rarely, if ever, invest hundreds of millions of dollars in industries built upon useless inventions. The undeniable existence of a significant industry directed to the usefulness of ESTs only further confirms that ESTs meet the minimal utility requirement of 35 U.S.C. Section 101.[169]

VII. CONCLUSION

In the last decade, ESTs have emerged as important and commercially valuable research tools in the field of genetics. For more than a decade, however, intense controversy has surrounded the patenting of ESTs. The PTO simply does not have the power to treat Congress' silence on the issue as a license to resolve the EST debate on its own by imposing a heightened utility requirement that all but precludes the patenting of ESTs. The PTO should apply the minimal standard of utility to ESTs, just as it does to all other inventions - a threshold that *all* ESTs satisfy given their inherent usefulness as research tools.

168 *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 959 (Fed. Cir. 1983).

169 In recent cases, the PTO has suggested that the success of the EST industry lacks probative value because the industry "is premised on . . . the potential usefulness of EST databases, clone sets or microarrays" and "the claims on appeal are not directed to EST databases, clone sets and/or microarrays." *Ex parte* Fisher, Patent and Trademark Office Board of Patent Appeals and Interferences Appeal No. 2002-2046, at 24 (Mar. 31, 2004). Of course, the databases, clone sets, and microarrays would be useless without each of the individual ESTs. Indeed, the PTO itself has recognized as much in other cases by allowing patents to issue for inventions directed to a single component that plainly must be used with other components to have any meaningful commercial value - for example, a patent on a single LEGO block. *See, e.g.*, U.S. Patent No. Des. 328,929 (issued Aug. 25, 1992).

Moreover, by general operation of the PTO's own rules applicants are precluded from claiming more than 10 ESTs in a single application. *See* MPEP Section 803.04. The PTO cannot have it both ways. Having precluded applicants from claiming all ESTs properly disclosed in a patent application, the PTO should not be permitted to ground a lack of utility finding on the fact that a claim is directed to only a handful of ESTs.