

NOTES

PATENTING ISOLATED HUMAN ENHANCER ELEMENTS & THE UTILITY REQUIREMENT PROBLEM

*William B. McConnell**

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* B.A., Biology, University of Virginia, 2004; M.S., Biology-Genetics, University of Virginia, 2008; J.D. Candidate, 2013, Seton Hall University School of Law. The author is a former developmental genetics researcher who was supported primarily by NIH grants from 2005–2008.

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I. INTRODUCTION

The Human Genome Project was initiated in October 1990 with the goal of identifying all the roughly 25,000 genes in the human genome and sequencing the three billion nucleotide base pairs that comprise human deoxyribonucleic acid (DNA).¹ Hundreds of genes have been linked with specific clinical phenotypes since the Project was completed two years ahead of schedule in April 2003.² The vast majority of such phenotypes have been connected to mutations in DNA that code for a protein product.³ Other diseases have been linked with noncoding DNA, which was once commonly described as “junk DNA.”⁴ The study of noncoding DNA is now at the forefront of genetics studies because research has revealed that various noncoding regulatory elements, such as enhancers, repressors, and insulators, may

¹ Patricia Carson, PRACTICING LAW INSTITUTE–PHARMACEUTICAL AND BIOTECH PATENT LAW 7-171 (David K. Barr & Daniel L. Reisner eds., 2012).

² *Id.*; Dirk A. Kleinjan & Veronica van Heyningen, *Long-Range Control of Gene Expression: Emerging Mechanisms and Disruption in Disease*, 76 AM. J. HUM. GENETICS 8, 8 (2005).

³ Kleinjan, *supra* note 2, at 8.

⁴ Examination of the genome-wide association studies’ database suggests that mutations in noncoding DNA contribute to 40% of disease cases. Eric Splinter & Wouter de Laat, *The Complex Transcription Regulatory Landscape of Our Genome: Control in Three Dimensions*, 30 THE EUR. MOLECULAR BIOLOGY ORG. J. 21: 4345 (2011) (citing L.A. Hindorff et al., *A Catalog of Published Genome-Wide Association Studies*, available at <http://www.genome.gov/gwastudies> (2009); A. Visel et al., *Genomic Views of Distant-Acting Enhancers*, 461 NATURE 199–205 (2009)).

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alter gene expression in a tissue-specific manner.⁵

Despite tremendous advances in the biological sciences and the paradigm shift that “junk DNA” is not junk, the law has failed to evolve with science. With the Supreme Court’s recent reversal of the Federal Circuit’s decision in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*,⁶ the Court vacated and remanded *Ass’n for Molecular Pathology v. Myriad Genetics, Inc. (Myriad)*,⁷ the cornerstone case for whether isolated human DNA constitutes patentable subject matter.⁸ The result is that twenty-two years after the initiation of the Human Genome Project lawyers, scientists, and scholars still have no firm legal context with which to determine the patentability of DNA, ribonucleic acid (RNA), or other polynucleotides.⁹

This note presents novel arguments that the current legal framework for patenting polynucleotides is inadequate for patenting the majority of noncoding regulatory elements. Rather than address the patentability of all noncoding regulatory elements, this note will focus primarily on the patentability of isolated human enhancer elements. Part II introduces the basics of DNA, RNA, and polynucleotides and examines the science of enhancers. Part III discusses the current framework for patenting polynucleotides, which derives judicially from a combination of the *Myriad* and *In re Fisher*¹⁰ cases. Part IV identifies the inadequacies of the current framework, namely the utility requirement for patents set forth in the statute, case law, guidance documents, and training materials as it applies to noncoding regulatory elements. Part V then proposes an alternative test for the United States Patent and Trademark Office (USPTO) to assess whether isolated human enhancers satisfy the utility requirement for patenting. When applying the current legal framework for patenting polynucleotides to patenting enhancers, two routes to satisfy the utility requirement become evident. An inventor may satisfy the utility

⁵ Kleinjan, *supra* note 2, at 8–9.

⁶ 132 S. Ct. 1289 (2012).

⁷ 653 F.3d 1329 (Fed. Cir. 2011), *reh’g denied* (Sept. 13, 2011), *reh’g denied* (Sept. 16, 2011), *cert. granted, judgment vacated sub nom.* Ass’n for Molecular Pathology v. Myriad Genetics, Inc., 132 S. Ct. 1794 (2012).

⁸ David P. Miranda, *New York Intellectual Property Law Review*, 74. ALB. L. REV. 1091, 1111 (2012).

⁹ Eric J. Rogers, *Can You Patent Genes? Yes and No*, 93 J. PAT. & TRADEMARK OFF. SOC’Y 19, 55 (2011).

¹⁰ *In re Fisher*, 421 F.3d 1365 (Fed. Cir. 2005).

requirement by (1) linking his or her isolated human enhancer to a known human disease or (2) characterizing a gene the enhancer acts upon and that gene's corresponding protein product. This framework is sufficient for patenting enhancers that can immediately be linked to known human diseases; however, this framework is woefully inadequate for patenting enhancers studied through reverse genetics approaches and for enhancers not initially linked to known human diseases.

II. GENETICS & THE ROLE OF NONCODING DNA

To assess the current legal framework for patenting enhancers, it is necessary to understand the fundamentals of genetics, the differences between coding and noncoding DNA, and the functions and importance of noncoding enhancer elements. The inherent nature of enhancers is immensely complicated and does not lend itself to patenting them as isolated compositions of matter. Promoting the patentability of enhancers, however, is vital to advancing biotechnology and promoting medical research.

A. *Genetics Fundamentals*

Adenine, cytosine, guanine, thymine, and uracil are the individual nucleotides that form polynucleotides when joined.¹¹ The term polynucleotide encompasses DNA, RNA, and other man-made compounds composed of nucleotides, such as expressed sequence tags (ESTs).¹² The primary structural difference between DNA and RNA is that DNA is composed exclusively of adenine, cytosine, guanine, and thymine, while RNA substitutes uracil for thymine.¹³

In eukaryotes,¹⁴ DNA resides within the nucleus¹⁵ of the cell in either a coiled or uncoiled state. Human DNA is organized as twenty-three pairs of chromosomes¹⁶ that are tightly coiled by

¹¹ BRUCE ALBERTS ET AL., *MOLECULAR BIOLOGY OF THE CELL* 6 (Sarah Gibbs et al. eds., 4th ed. 2002).

¹² *Id.* at 366.

¹³ *Id.* at 6.

¹⁴ A eukaryote is an “[o]rganism composed of one or more cells with a distinct nucleus and cytoplasm.” *Id.* at G:13. Eukaryotes include all forms of life with the exception of viruses and prokaryotes (bacteria and archea). *Id.*

¹⁵ The nucleus is a membrane-bound organelle in a eukaryotic cell that contains DNA organized into chromosomes. *Id.* at G:25.

¹⁶ CECIE STARR & RALPH TAGGART, *BIOLOGY: THE UNITY AND DIVERSITY OF LIFE* 143 (Beverly McMillan & Kristin Milotich eds., 7th ed. 1995).

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proteins called histones within the nucleus.¹⁷ In the uncoiled state, DNA and proteins within the nucleus are referred to as chromatin.¹⁸

B. Coding vs. Noncoding DNA

The entirety of human DNA excluding the proteins associated with chromatin is referred to as the human genome,¹⁹ and the human genome is comprised of both coding and noncoding DNA.²⁰ Coding DNA specifically refers to the gene portions that are transcribed and ultimately produce a protein product.²¹ Noncoding DNA, by comparison, does not ultimately produce a protein product.²²

Genes within DNA may consist of both coding and noncoding segments.²³ The coding portions of genes are called exons, and the noncoding portions are called introns.²⁴ Transcription²⁵ of genes produces a complimentary RNA strand,²⁶ and translation of certain RNAs generates the protein products that are characteristic of coding DNA.²⁷

The process of eukaryotic transcription initiates when cellular machinery consisting of RNA polymerase and proteins called transcription factors bind a target gene.²⁸ The portion of the gene where this cellular machinery binds to initiate transcription is called the gene's promoter.²⁹ Upon the binding of RNA polymerase to a promoter, noncoding DNA regulatory elements

¹⁷ Histones are small abundant proteins that are particularly rich in arginine and lysine. The combination of four histones forms a nucleosome around which DNA is coiled in eukaryotic chromosomes. ALBERTS, *supra* note 11, at G:17.

¹⁸ Chromatin is a “[c]omplex of DNA, histones, and nonhistone proteins found in the nucleus of a eu[k]aryotic cell.” Chromosomes are composed of chromatin. *Id.* at G:7.

¹⁹ *Id.* at G:15.

²⁰ *Id.* at 33–34.

²¹ *Id.* at 8–10.

²² *Id.* at 33–34.

²³ ALBERTS, *supra* note 11, at 316–17.

²⁴ *Id.*

²⁵ Transcription is the process in a cell by which genetic material is copied from a strand of DNA to a complementary strand of messenger RNA (mRNA). *Id.* at 6–7.

²⁶ *Id.*

²⁷ *Id.* at 8–9.

²⁸ *Id.* at 310 (describing how general transcription factors aid in eukaryotic transcription).

²⁹ ALBERTS, *supra* note 11, at 311. A promoter is a “[n]ucleotide sequence in DNA to which RNA polymerase binds to begin transcription.” *Id.* At G:28.

may interact with the RNA polymerase and transcription factor complex to alter gene transcription.³⁰

As transcription proceeds, the RNA polymerase complex traverses the DNA template and produces an RNA strand by joining RNA nucleotides complimentary to the DNA nucleotide sequence being transcribed.³¹ The resultant RNA strand may be messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), or small nuclear RNA (snRNA).³² Only mRNAs, however, are translated to produce proteins.³³

Prior to translation, a process called splicing³⁴ modifies mRNA by excising intron-derived nucleotide stretches and joining the remaining exon-derived nucleotide stretches.³⁵ After splicing, the mature mRNA strand is transported from the cell's nucleus to a ribosome³⁶ in the cell's cytoplasm.³⁷ The ribosome then translates the mRNA into a corresponding amino acid chain, or polypeptide, that ultimately folds into an active protein product.³⁸

³⁰ Kleinjan, *supra* note 2, at 8, 9 (fig. 1).

³¹ ALBERTS, *supra* note 111, at 313–14.

³² *Id.* at 305.

³³ *Id.* at 7.

³⁴ Splicing is a process that involves the “[r]emoval of introns from mRNA precursors and the reattachment or annealing of exons.” STEDMAN’S MEDICAL DICTIONARY 1811 (27th ed. 2000).

³⁵ Kleinjan, *supra* note 2.

³⁶ Ribosomes are tiny organelles located within the cytoplasm of cells either freely or attached to the outer surfaces of the endoplasmic reticula and function as the site of protein production. ALBERTS, *supra* note 111, at 8–9.

³⁷ *Id.* at 7–9.

³⁸ *Id.* at 8–9.



Figure 1: DNA Transcription and Translation.

Abbreviations: Pr: Promoter; RNA pol: RNA polymerase; TF: Transcription Factor.

C. Noncoding DNA Regulatory Elements

Protein-coding genes are analogous to blueprints for constructing the human body, while noncoding regulatory elements, like enhancers, are more analogous to the construction workers that regulate and control the cellular machinery that execute the blueprints.³⁹ Cell-specific gene regulatory programs drive the differences between the over 200 cell types in the human body.⁴⁰ Each cell type is tremendously different, despite the fact that each cell contains the same genome.⁴¹ These programs rely on the interaction between noncoding regulatory elements and protein-coding DNA to activate and alter gene expression in a cell-specific manner.⁴² There are currently three known types of noncoding regulatory elements: (1) enhancers, (2) repressors,⁴³ and (3) insulators.⁴⁴ These noncoding regulatory elements may be identified through various methods, including screening for DNase I hypersensitive⁴⁵ sites and transgenic

³⁹ See generally Splinter, *supra* note 4 (explaining the “regulatory landscape” involving the interactions between co-activator protein genes and non-coding elements).

⁴⁰ *Id.* at 4345.

⁴¹ *Id.*; DNA is contained within both the nucleus and the mitochondria of a cell. Red blood cells are an exception to this generalization that each cell contains the same genome because red blood cells have neither a nucleus nor mitochondria such that they also lack DNA. Sveta. Kabanova et al., *Gene Expression Analysis of Human Red Blood Cells*, 6 INT’L J. MED. SCI. (4): 156, 157 (2009).

⁴² Splinter, *supra* note 4, at 4345.

⁴³ A repressor “combines directly with an operator gene to repress the operator and its structural genes, thus repressing protein synthesis . . .” STEDMAN’S, *supra* note 344, at 1550. The term ‘repressor’ is sometimes used synonymously with the term ‘silencer’ in the literature of the field. Splinter, *supra* note 4, at 4345.

⁴⁴ An insulator is a stretch of noncoding DNA that neutralizes the activation of transcription when located between an activator and a gene promoter. Splinter, *supra* note 4, at 4345.

⁴⁵ DNase I hypersensitive sites “are sites where the nucleosome fibre is locally disrupted, presumably through the action of DNA-binding proteins and associated factors.” *Id.*

“trapping” techniques, like enhancer traps.⁴⁶ Characterizing a noncoding regulatory element is done by determining the effect that the isolated noncoding regulatory element has upon a gene’s expression.⁴⁷ A rudimentary lab assay to characterize a noncoding regulatory element involves isolating the suspected regulatory element sequence and combining it with a reporter gene⁴⁸ in a plasmid⁴⁹ vector.⁵⁰ The vector construct is then transfected⁵¹ into cells using standard laboratory techniques, and the noncoding regulatory element is classified by its observed effect upon the reporter gene’s expression.⁵² The regulatory element is characterized as an enhancer if reporter expression is up-regulated.⁵³ The regulatory element is characterized as a repressor if reporter expression is down-regulated.⁵⁴ The regulatory element is characterized as an insulator if reporter expression is neutralized when the putative regulatory element is placed between an activator and a promoter.⁵⁵ This note focuses on enhancers.

Enhancers may be located within gene introns, upstream of a gene, or downstream of a gene.⁵⁶ Enhancers need not be adjacent to or even near a gene to regulate it.⁵⁷ Studies indicate that an enhancer may be as far as 1 one-million base pairs (1 Mb) upstream or downstream from a promoter and exert control over gene expression.⁵⁸ Other studies have indicated that enhancers may even ignore distal genes to act specifically on proximal

⁴⁶ Splinter, *supra* note 4, at 4345–46.

⁴⁷ *Id.* at 4345–46.

⁴⁸ A reporter gene is a gene whose protein product is detectable either visually or through some other assay. ALBERTS, *supra* note 11, at 532–33.

⁴⁹ A plasmid is “a genetic particle physically separate from the chromosome of the host cell (chiefly bacterial) that can stably function and replicate and usually confer some advantage to the host cell . . .” STEDMAN’S, *supra* note 344, at 1394.

⁵⁰ Splinter, *supra* note 4, at 4345.

⁵¹ Transfection is “a method of gene transfer utilizing infection of a cell with nucleic acid (as from a retrovirus) resulting in subsequent viral replication in the transfected cell.” STEDMAN’S, *supra* note 344, at 1860.

⁵² Splinter, *supra* note 4, at 4345.

⁵³ *See id.* (explaining the term “up-regulated” as when the reporter protein is produced in greater amounts).

⁵⁴ *See id.* (explaining “down-regulated” as when the reporter protein is produced in lesser amounts).

⁵⁵ *Id.*

⁵⁶ Kleinjan, *supra* note 2, at 8.

⁵⁷ *Id.* at 8–9 (fig. 1).

⁵⁸ *Id.*

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genes.⁵⁹ Enhancers may act on multiple gene promoters and they may do so in different ways.⁶⁰ One study of two human cell types suggested that there are approximately 55,000 potential enhancer elements, nearly 80% of which were specific to one cell or the other, despite sharing 85% of the same active genes.⁶¹ “This underscores the idea that enhancers are tissue-specific elements acting on tissue-specific genes.”⁶²

The data on enhancers and their operation within the mammalian genome suggests that gene function is governed by a “regulatory landscape”⁶³ exponentially more complex than researchers envisioned when noncoding DNA was originally thought to be “junk.”⁶⁴ Collectively, research indicates that enhancers do not operate by any single mechanism and that enhancers’ only real commonality is that they up-regulate gene expression.⁶⁵ Enhancers may slightly up-regulate gene expression or greatly up-regulate gene expression.⁶⁶ They may act on a single gene or on multiple genes, and they do so in a cell-specific manner.⁶⁷ They may act on an adjacent gene or on a gene that is tremendously distant within the scope of the genome.⁶⁸ This extreme variability and complexity of action from one cell to another is the basis for why patenting isolated human enhancers

⁵⁹ Wouter de Laat & Frank Grosveld, *Spatial Organization of Gene Expression: The Active Chromatin Hub*, 11 CHROMOSOME RES. 447, 455 (2003).

⁶⁰ See Splinter, *supra* note 4, at 4348–49 (describing that enhancers interacting with only select nearby promoters, and offer promoter competition, as an explanation for enhancer activity).

⁶¹ Nathaniel D. Heintzman et al., *Histone Modifications at Human Enhancers Reflect Global Cell-Type-Specific Gene Expression*, 459 NATURE 108, 109–12 (2009).

⁶² Splinter, *supra* note 4, at 4346.

⁶³ The term “regulatory landscape” was originally used to describe the complex organization of regulatory elements around the Hox gene loci. Francois Spitz et al., *A Global Control Region Defines a Chromosomal Regulatory Landscape Containing the HoxD Cluster*, 113 CELL 405, 414 (2003).

⁶⁴ Nat’l Inst. of Health U.S. Dep’t of Health and Human Servs., *ENCODE Data Describes Function of Human Genome*, NIH NEWS 1 (Sept. 5, 2012), <http://www.genome.gov/pfv.cfm?pageID=27549810>.

⁶⁵ GENE REGULATORY SEQUENCES AND HUMAN DISEASE 74 (Nadav Ahituv ed., 2012).

⁶⁶ Splinter, note 4, at 4346; *see also* Junichi Ohara & William E. Paul, *Up-Regulation of Interleukin 4/B-cell Stimulatory Factor 1 Receptor Expression*, 85 PROC. NAT’L ACAD. SCI. U.S. AM., 8221, 8224 (1988) (noting the varying degrees of up-regulation of two receptor sites).

⁶⁷ Chin-Tong Ong & Victor G. Corces, *Enhancer Function: New Insights into the Regulation of Tissue-Specific Gene Expression*, 12(4) NATURE REVIEWS GENETICS 283, 285 (2011).

⁶⁸ GENE REGULATORY SEQUENCES AND HUMAN DISEASE, *supra* note 65, at 4.

is incredibly difficult. This complex nature is particularly problematic when attempting to satisfy the utility requirement for patents.

III. THE CURRENT FRAMEWORK FOR PATENTING DNA

Patent law draws its functional rationale from Jeremy Bentham's theory of Utilitarianism, the objective of which is to promote "the greatest happiness" for the greatest number of people.⁶⁹ Pursuit of that objective in patent law requires lawmakers to strike an optimal balance between granting exclusive rights to stimulate innovation and disseminating the benefits of such innovation for the public benefit.⁷⁰ In patent law this is accomplished by granting inventors certain exclusive rights over their inventions as an incentive for future innovation.⁷¹ These rights are exclusionary and are commonly referred to as a "patent monopoly."⁷² An inventor granted these exclusive rights may exclude others from making, using, or selling his invention.⁷³ These exclusive rights also allow inventors to recoup the costs that come with innovating and to profit in many cases.⁷⁴ In exchange for the grant of a patent monopoly, society receives the benefit of the innovation and the knowledge of how to make and use the invention after the expiration of the patent.⁷⁵

To obtain exclusive rights over his claimed invention, an inventor's patent claim application must satisfy five general requirements. First, the patent must claim patentable subject matter.⁷⁶ "[L]aws of nature, natural phenomena, and abstract

⁶⁹ DEATH OF PATENTS 193 (Peter Drahos ed. 2005).

⁷⁰ See Jonathan R. Chally, *The Law of Trade Secrets: Toward a More Efficient Approach*, 57 VAND. L. REV. 1269, 1277-78 (2004) (stating that too much exclusivity in patent law "restricts competition and the efficient allocation of resources").

⁷¹ 35 U.S.C.A. § 101 (West, Westlaw through P.L. 112-283 approved 1/15/13).

⁷² Giles S. Rich, *Are Letters Patent Grants of Monopoly?*, 15 W. NEW ENG. L. REV. 239, 239 (1993).

⁷³ 35 U.S.C.A. § 271(a) (West, Westlaw through P.L. 112-283 approved 1/15/13).

⁷⁴ Chally, *supra* note 70, at 1274.

⁷⁵ See generally, William F. Baxter, *Legal Restrictions on Exploitation of the Patent Monopoly: An Economic Analysis*, 76 YALE L.J. 267, 268 (1966) (discussing the social value of innovation).

⁷⁶ 35 U.S.C.A. § 101 (West, Westlaw through P.L. 112-283 approved 1/15/13); see also *Brenner v. Manson*, 383 U.S. 519, 534 (1966) ("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

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ideas” are not patentable subject matter.⁷⁷ Second, the invention must satisfy the novelty requirement.⁷⁸ The invention must not have been disclosed in a single reference in the prior art, meaning that the invention must not already have been patented, published, or already known and used by others.⁷⁹ Third, the invention must be nonobvious.⁸⁰ In other words, the invention must not be based on an obvious addition to an existing invention and must not consist of an obvious combination of elements.⁸¹ Fourth, the invention must possess at least one “specific,” “substantial,” and “credible” use.⁸² A “specific” use is one that is specific to the claimed subject matter, not a general use applicable to a broad class of the invention.⁸³ A “substantial” use is one that is significant and presently available to the public; it must be a “real world” use and not merely serve as a research intermediary.⁸⁴ A “credible” use is one that a person of ordinary skill in the art would find believable “based on the totality of evidence and reasoning provided.”⁸⁵ Fifth, the written description in the patent application for the invention must enable a person of ordinary skill in the art of the patentable subject matter to construct and use the invention without undue experimentation.⁸⁶

The largest legal hurdles for patenting isolated human polynucleotides, whether DNA or RNA-based, are the subject matter requirement and the utility requirement. Nevertheless, researchers have filed more than three million patent applications relating to genes,⁸⁷ and over 40,000 DNA-related patents have been granted.⁸⁸ The USPTO “has issued 2,645

substantial utility.”)

⁷⁷ *Diamond v. Diehr*, 450 U.S. 175, 185 (1981).

⁷⁸ 35 U.S.C.A. § 102(a) (West, Westlaw through P.L. 112-283 approved 1/15/13).

⁷⁹ *Id.*

⁸⁰ 35 U.S.C.A. § 103 (West, Westlaw through P.L. 112-283 approved 1/15/13).

⁸¹ *See id.*

⁸² U.S. PATENT & TRADEMARK OFFICE, REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS 3 (1999) [hereinafter TRAINING MATERIALS], available at <http://www.uspto.gov/web/menu/utility.pdf>.

⁸³ Carson, *supra* note 1, at 186.

⁸⁴ *In re Fisher*, 421 F.3d 1365, 1372 (Fed. Cir. 2005).

⁸⁵ TRAINING MATERIALS, *supra* note 82, at 5.

⁸⁶ 35 U.S.C.A. § 112(a) (West, Westlaw through P.L. 112-283 approved 1/15/13).

⁸⁷ CARSON, *supra* note 1, at 7-171.

⁸⁸ *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329, 1355 (Fed. Cir. 2011).

patents claiming “isolated DNA.”⁸⁹

A. Patentable Subject Matter

Gene patents have generated quite a bit of controversy, culminating in the initiation of litigation against Myriad Genetics, Inc. in November 2009.⁹⁰ Plaintiffs challenged the validity of Myriad’s composition of matter and method claims over two “isolated”⁹¹ human genes, *BRCA1* and *BRCA2*.⁹² The lawsuit implicates the controversy over whether DNA constitutes patentable subject matter.⁹³ Section 101 of the Patent Act, 35 U.S.C. § 1 *et seq.*, states that a patent may only be obtained for “any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof”⁹⁴ However, patents may not be obtained for “products of nature.”⁹⁵ Therein lies the controversy of patenting human DNA, the natural biochemical blueprints at the core of all human development.

There are generally two competing rationales governing the patentability of genes. The first rationale against the patenting of genes is that isolated human genes do not constitute patentable subject matter because they are products of nature containing the same genetic information as native genes.⁹⁶ The second, competing rationale is that isolated human DNA possesses a distinctive chemical identity that is different from that of native DNA, such that the isolated human DNA constitutes patentable subject matter.⁹⁷

When Congress enacted § 101 of the Patent Act, it indicated

⁸⁹ *Id.*

⁹⁰ *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office*, 669 F. Supp.2d 365 (2009).

⁹¹ “Isolated” in the context of genes means that a gene is separated from the other natural elements contained in DNA within the body. *See id.* at 378 (discussing what constitutes an “isolated and purified” gene according to USPTO policy).

⁹² *Ass’n for Molecular Pathology*, 653 F.3d at 1334.

⁹³ *Id.* at 1348–57.

⁹⁴ 35 U.S.C.A. § 101 (West, Westlaw through P.L. 112-283 approved 1/15/13).

⁹⁵ *See Diamond v. Chakrabarty* 447 U.S. 303, 306, 309 (1980) (discussing the patent examiner’s rejection of patent claims of bacteria because they were “products of nature,” and that as living things they are not patentable” under the Patent Act because “[t]he laws of nature, physical phenomena, and abstract ideas have been held not patentable.”).

⁹⁶ *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329, 1375 (Fed. Cir. 2011) (Bryson, C.J., dissenting).

⁹⁷ *Id.* at 1351 (majority opinion).

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that “anything under the sun that is made by man” is subject matter for a patent.⁹⁸ The Supreme Court has interpreted § 101 several times and has yet to overturn it.⁹⁹ While the Supreme Court has never ruled on the patentability of DNA, the Court of Appeals for the Federal Circuit in July 2011 followed the latter rationale in holding that isolated human DNA is patentable as a composition of matter, because the chemical nature of isolated DNA has a distinctive chemical identity different from that of native DNA.¹⁰⁰ In doing so, the Federal Circuit rejected the District Court’s holding that DNA did not constitute patentable subject matter because isolated DNA contains the same sequence information as native DNA.¹⁰¹

The legal landscape for patenting DNA is uncertain given the Supreme Court’s recent holding in *Prometheus*¹⁰² in March 2012.¹⁰³ The Court in *Prometheus* denied patenting a method claim for a medical diagnostic procedure.¹⁰⁴ After granting *certiorari* to the *Myriad* case, the Court vacated and remanded *Myriad* to the Federal Circuit so that it is consistent with *Prometheus*.¹⁰⁵ While the rationale governing the rejection of the method claims in *Myriad* might be affected, the *Prometheus* holding is expected to have no effect on the Federal Circuit’s previous holdings in *Myriad* concerning the patentability of isolated DNA as a composition of matter.¹⁰⁶

On the other hand, Justice Breyer in his dicta in *Prometheus* was critical of claims over “laws of nature” and minimal extensions thereof, such that claims to isolated DNA as patentable subject matter might be scrutinized by the Federal Circuit on remand.¹⁰⁷ As if the patentability of isolated DNA were not already uncertain, the current framework is further

⁹⁸ S. Rep. No. 82-1979, at 2399 (1952).

⁹⁹ See, e.g., *Diamond v. Diehr*, 450 U.S. 175, 183–85, 87 (1981) (discussing cases in which the court interpreted § 101, and declined to overrule it).

¹⁰⁰ *Ass’n for Molecular Pathology*, 653 F.3d at 1353–54.

¹⁰¹ *Id.* at 1353.

¹⁰² *Mayo Collaborative Servs. v. Prometheus Labs.*, 132 S. Ct. 1289, 1294 (2012).

¹⁰³ *Id.* at 1289.

¹⁰⁴ *Id.* at 1295, 1297–98.

¹⁰⁵ *Ass’n for Molecular Pathology v. Myriad Genetics*, 132 S. Ct. 1794.

¹⁰⁶ See *Mayo Collaborative Servs.*, 132 S. Ct. at 1303–04 (declaring the government’s argument that other sections of 35 U.S.C. could be used to declare matter patentable under §101 would be inconsistent with prior law).

¹⁰⁷ See *id.* at 1294 (discussing the various “warnings” precedent that involved laws of nature as patentable subject matter provided for the Court in determining the present case).

complicated by the fact that the previous *Myriad* decision failed to address other important issues regarding the patentability of DNA, like how isolated human DNA may possess utility.¹⁰⁸

B. The Utility Requirement

Section 101 of the Patent Act states: “Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.”¹⁰⁹ The utility requirement derives from the term *useful* in § 101, and the current standard for satisfying the utility requirement is largely derived from the courts and from the guidelines and training materials issued by the USPTO.¹¹⁰ In analyzing the utility requirement for patents, the Supreme Court in *Brenner v. Manson* determined that an invention must have “specific” utility and described an invention with specific utility as having “practical” and “real world” utility.¹¹¹

1. 2001 Utility Guidelines

While not binding upon the courts, the USPTO issued its latest version of the Utility Guidelines (Guidelines) as a complement to the 2000 Revised Interim Utility Guidelines Training Materials (Training Materials) in January 2001 to educate and assist inventors in assessing the utility of their inventions.¹¹² The Guidelines were issued largely in response to growing questions about the patentability of polynucleotides, namely ESTs.¹¹³ In contrast to the 1995 Utility Guidelines, the 2001 Guidelines state an invention has well-established utility when (1) a person with ordinary skill in the art immediately appreciates the invention’s utility based on the invention’s characteristics (e.g., properties or applications of a product or process), and when (2) the “utility is

¹⁰⁸ See *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office*, 653 F.3d 1329, 1329 (Fed. Cir. 2011) (failing to mention other issues in this case).

¹⁰⁹ 35 U.S.C.A. § 101 (2012) (West, Westlaw through P.L. 112-283 approved 1/15/13) (emphasis added).

¹¹⁰ Utility Examination Guidelines, 66 Fed. Reg. 1092–02, 1093 (Jan. 5, 2001).

¹¹¹ *Brenner v. Manson*, 383 U.S. 519, 534–35 (1966).

¹¹² Utility Examination Guidelines, 66 Fed. Reg. at 1092.

¹¹³ *Id.*

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specific, substantial, and credible.”¹¹⁴ The “specific” and “substantial” utility requirement excludes “throw-away,” “insubstantial,” or “non-specific” utilities, such as the use of a complex invention as a paperweight in order to satisfy the utility requirement.¹¹⁵ A claimed invention need only have one credible assertion of specific and substantial utility.¹¹⁶ “Credibility is assessed from the perspective of one [with] ordinary skill in the art in view of the disclosure and any other evidence of record (*e.g.*, test data, affidavits or declarations from experts in the art, patents or printed publications) that is probative of the applicant’s assertions.”¹¹⁷

2. 2000 Utility Guidelines Training Materials

To provide guidance to patent examiners in assessing utility under the Patent Act, the USPTO published the Training Materials (Materials) in 1999.¹¹⁸ The Materials state: “For method claims that recite more than one utility, if at least one utility is credible, specific, and substantial, a rejection under 35 U.S.C. § 101 should not be made . . . [f]or product claims that do not recite any utilities, disclosure or assertion of one specific, substantial and credible utility meets the criteria of 35 U.S.C. § 101.”¹¹⁹

The Materials elucidate the meanings of “specific,” “substantial,” “credible,” and “well-established,” and provide examples of applying the utility requirement to DNA-based claims.¹²⁰ The Materials define a “specific utility” as one “that is specific to the subject matter claimed” in contrast with general utility “that would be applicable to the broad class of the invention.”¹²¹ As applied to a polynucleotide by example, “a claim to a polynucleotide whose use is disclosed simply as a ‘gene probe’ or ‘chromosome marker’ would not be considered to be specific in

¹¹⁴ *Id.* at 1098.

¹¹⁵ *Id.*

¹¹⁶ *Id.*

¹¹⁷ *Id.*

¹¹⁸ Press Release, U.S. PATENT & TRADEMARK OFFICE, USPTO OFFERS TRAINING MATERIALS FOR INTERIM WRITTEN DESCRIPTION AND UTILITY GUIDELINES (March 1, 2000), <http://www.uspto.gov/news/pr/2000/00-15.jsp>. See TRAINING MATERIALS, *supra* note 82.

¹¹⁹ TRAINING MATERIALS, *supra* note 82, at 3–4.

¹²⁰ *Id.* at 5–8.

¹²¹ *Id.* at 5; see also, CARSON, *supra* note 1, at 7–10.

the absence of a disclosure of a specific DNA target.”¹²² Further, a claimed diagnostic utility “such as diagnosing an unspecified disease” is ordinarily insufficient to satisfy the utility requirement due to lack of specificity.¹²³

The Materials define a “substantial utility” as one that describes a “real world” use. Utilities “that require . . . further research to identify or reasonably confirm a real world . . . use are not considered to be substantial utilities.”¹²⁴ A claimed utility is not substantial if the applicant’s invention is “merely useful for further research, or a method . . . or intermediate for making a final product that has no known specific, substantial utility . . .”¹²⁵ Examples that do not meet substantial utility include:

- A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.
- B. A method of treating an unspecified disease or condition
- C. A method of assaying for or identifying a material that itself has no “specific and/or substantial utility”.
- D. A method of making a material that itself has no specific, substantial and credible utility.
- E. A claim to an intermediate product for use in making a final product that has no specific, substantial and credible utility.¹²⁶

“Credible utility” under the Training Materials hinges on “whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of evidence and reasoning provided.”¹²⁷ If “the logic underlying the assertion is seriously flawed . . .” or the factual basis of the assertion is “inconsistent with the logic underlying the assertion,” then the

¹²² TRAINING MATERIALS, *supra* note 82, at 5; *see also*, CARSON, *supra* note 1, at 10.

¹²³ TRAINING MATERIALS, *supra* note 82, at 5–6; CARSON, *supra* note 1, at 7–186.

¹²⁴ *In re Fisher*, 421 F.3d 1365, 1372 (Fed. Cir. 2005); TRAINING MATERIALS, *supra* note 82, at 4, 6.

¹²⁵ CARSON, *supra* note 1, at 7–186; *see also* TRAINING MATERIALS, *supra* note 82, at 6–7 (identifying examples of situations that require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use).

¹²⁶ TRAINING MATERIALS, *supra* note 82, at 6–7; *see also* CARSON, *supra* note 1, at 7–186 (listing the examples that do not define “substantial utilities”).

¹²⁷ TRAINING MATERIALS, *supra* note 82, at 5; *see also*, CARSON, *supra* note 1, at 7–10 (noting that the benefit of the invention must be “in currently available form” and must have “immediate value” in the sense that further research is not required to ascertain its usefulness).

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claimed utility is not credible.¹²⁸ The Materials define a “well-established utility” as a “specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification’s disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.”¹²⁹

The Materials provide two examples examining satisfaction of the utility requirement by claims to DNA sequences.¹³⁰ These examples elucidate how satisfying the utility requirement for a claim over a DNA sequence is quite difficult unless the claimed DNA sequence possesses well-established utility.¹³¹ Example 9, designated as “DNA Fragments,” concerns a specification that discloses DNA fragments that are claimed as useful for probes to isolate the full-length genes corresponding to the sequences.¹³² However, no “use is disclosed for any of the putative proteins other than the possibility of using them to identify and study the cellular mechanisms and activities in which the proteins are involved.”¹³³ The Training Materials conclude that the claimed invention does not have a well-established utility, noting that there is no prior art that points to the activity of the complementary DNA (cDNA)¹³⁴ or proteins that can be obtained using the cDNA.¹³⁵ The claimed invention also lacks specific and substantial utility based on the lack of knowledge regarding the full-length gene.¹³⁶ In particular, the Training Materials state that there is no specific utility because the asserted utility for use as a probe “is not particular to the sequence being claimed because it would be applicable to the general class of cDNAs. Any partial nucleic acid prepared from any cDNA may be used as a probe in the preparation and or identification of a full-length cDNA.”¹³⁷ Moreover, there is no “substantial” utility because

¹²⁸ TRAINING MATERIALS, *supra* note 82, at 5; *see also*, CARSON, *supra* note 1, at 7-10.

¹²⁹ TRAINING MATERIALS, *supra* note 82, at 7; *see also*, CARSON, *supra* note 1, at 7-10 (using the example of a microscope to demonstrate the “immediate, real world benefit” requirement).

¹³⁰ TRAINING MATERIALS, *supra* note 82, at 13-26.

¹³¹ *See id.* (presenting examples of rejected claims).

¹³² *Id.* at 50.

¹³³ *Id.*

¹³⁴ Complementary DNA (cDNA) refers to either “single-stranded DNA that is complementary to messenger RNA . . . [or] dDNA that has been synthesized from mRNA by the action of reverse transcriptase.” STEDMAN’S MEDICAL DICTIONARY, *supra* note 34, at 106770.

¹³⁵ TRAINING MATERIALS, *supra* note 82, at 51.

¹³⁶ *Id.* at 51-52.

¹³⁷ *Id.* at 51.

where “the only utility asserted for the protein is for identifying and studying the properties of the protein itself or the mechanisms in which the protein is involved” the invention does not define a “real world” use.¹³⁸

The second example, Example 10, is entitled “DNA Fragment Encoding a Full Open Reading Frame (ORF).”¹³⁹ There, “the specification discloses a nucleic acid sequence that has a high degree of homology to a DNA ligase.”¹⁴⁰ The sequence encodes an amino acid sequence that has 95% homology to the consensus sequence of the known DNA ligases, where there is high sequence conservation among DNA ligases.¹⁴¹ Moreover, the USPTO’s prior art search reveals that the next highest level of homology among sequences disclosed in the prior art is 50%.¹⁴² “Under these facts, the [US]PTO concluded that a ‘well-established’ utility is shown.”¹⁴³ “Based upon applicant’s disclosure and the results of the [US]PTO search, there is no reason to doubt the assertion that [the claimed polynucleotide sequence] encodes a DNA ligase . . . [and] DNA ligases have a well-established use in the molecular biology art based on this class of protein’s ability to ligate DNA.”¹⁴⁴

This example is consistent with the USPTO’s responses to comments concerning the 2001 Utility Guidelines.¹⁴⁵ The Guidelines state,

[W]hen a patent application claiming a nucleic acid asserts a specific, substantial, and credible utility, and bases the assertion upon homology to existing nucleic acids or proteins having an accepted utility, the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion.¹⁴⁶

Moreover, the USPTO stated that “[w]hen a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to

¹³⁸ CARSON, *supra* note 1, at 7-187 to 7-188; *Id.* at 51-52.

¹³⁹ TRAINING MATERIALS, *supra* note 82, at 53; CARSON, *supra* note 1, at 7-188.

¹⁴⁰ CARSON, *supra* note 1, at 7-188; TRAINING MATERIALS, *supra* note 82, at 53-54.

¹⁴¹ TRAINING MATERIALS, *supra* note 82, at 53-54; CARSON, *supra* note 1, at 7-188.

¹⁴² CARSON, *supra* note 1, at 7-188; TRAINING MATERIALS, *supra* note 82, at 54.

¹⁴³ TRAINING MATERIALS, *supra* note 82, at 54; CARSON, *supra* note 1, at 7-188.

¹⁴⁴ TRAINING MATERIALS, *supra* note 82, at 54; CARSON, *supra* note 1, at 7-188.

¹⁴⁵ CARSON, *supra* note 1, at 7-188.

¹⁴⁶ Utility Examination Guidelines, 66 Fed. Reg. 1092-02, 1096 (Jan. 5, 2001); CARSON, *supra* note 1, at 7-188.

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the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein.”¹⁴⁷ The USPTO has cautioned, however, that there “is no *per se* rule regarding homology, and each application must be judged on its own merits.”¹⁴⁸

3. *In re Fisher*

The Federal Circuit in *In re Fisher* addressed the utility requirement for the patentability of short man-made DNA fragments called ESTs in 2005.¹⁴⁹ ESTs are “short nucleotide sequence[s] that represent[] a fragment of a cDNA clone.”¹⁵⁰ ESTs are particularly useful in assays for determining which genes are expressed in specific tissues at specific times.¹⁵¹ *Fisher* involved claims for five ESTs “corresponding to genes expressed from the maize pooled leaf tissue at the time of anthesis.”¹⁵² The applicant, however, did not know the structure or function of the genes or their corresponding proteins.¹⁵³

Ultimately, the Federal Circuit determined that a claim to an EST fails to satisfy the utility requirement when the EST codes for part of a gene whose function is unknown.¹⁵⁴ The Federal Circuit agreed with the position supported by the Government and numerous amici that until the corresponding genes have a known function and known protein products, the claimed ESTs lack utility and are unpatentable.¹⁵⁵ In doing so, the Federal Circuit elaborated on what constitutes substantial utility, finding that an invention with substantial utility provides a “significant” and “immediate benefit to the public,” not merely use as a “research intermediate.”¹⁵⁶ Further, the Federal Circuit described

¹⁴⁷ Utility Examination Guidelines, 66 Fed. Reg. at 1096; CARSON, *supra* note 1, at 7-188 to 7-189.

¹⁴⁸ Utility Examination Guidelines, 66 Fed. Reg. at 1096 (emphasis added); CARSON, *supra* note 1, at 7-189.

¹⁴⁹ *In re Fisher*, 421 F.3d 1365, 1369–70 (Fed. Cir. 2005).

¹⁵⁰ *Id.* at 1367.

¹⁵¹ *See id.* (“Scientists routinely compile cDNA into libraries to study the kinds of genes expressed in a certain tissue at a particular point in time.”).

¹⁵² *Id.* at 1368. Anthesis is the period during which flower expansion occurs. THE RANDOM HOUSE COLLEGE DICTIONARY 57 (JESS STEIN & LEONORE HAUCK eds., rev. ed. 1984).

¹⁵³ *In re Fisher*, 421 F.3d 1365, 1368 (Fed. Cir. 2005).

¹⁵⁴ *Id.* at 1370.

¹⁵⁵ *Id.*

¹⁵⁶ *Id.* at 1371, 1373 (quoting *Nelson v. Bowler*, 626 F.2d 853, 856 (C.C.P.A. 1980)).

“specific” utility as being “not so vague as to be meaningless.”¹⁵⁷

The *Fisher* holding is significant because it applies to the patentability of all isolated noncoding DNA.¹⁵⁸ While this framework might be appropriate for patenting ESTs, it is inappropriate for patenting other functional, noncoding DNA not immediately linked to a known human disease.¹⁵⁹ Noncoding regulatory elements, such as enhancers, have been implicated in numerous human diseases discussed below.¹⁶⁰ Having appropriate tests for their patentability is crucial to promote meaningful advances in biotechnology and medicine.

IV. SATISFYING THE UTILITY REQUIREMENT FOR NONCODING DNA ELEMENTS IS DIFFICULT

Recent research has definitively shown the value of enhancers in understanding gene function and human disease.¹⁶¹ Nevertheless, the existing legal framework for assessing the utility of noncoding DNA is grossly inadequate, particularly where that utility is not an industrial application. Few patents claiming enhancers have been issued, and the majority of them are contained in plant patents and process patents.¹⁶²

A. *The Importance of Patenting Enhancers*

The patenting of biotechnological innovation has tremendously benefitted modern society, from Andrew Moyer’s patented method for industrial production of penicillin in 1948¹⁶³ to today’s numerous patented drugs for cancer treatment.¹⁶⁴ For this reason, the law should encourage the study of enhancers. The immense importance of enhancers to understanding gene function and a growing body of research that has implicated

¹⁵⁷ *Id.* at 1371.

¹⁵⁸ *See id.* at 1375–76 (noting the decision’s application to chemical and biological compounds and entities).

¹⁵⁹ *In re Fisher*, 421 F.3d 1365, 1368–71 (Fed. Cir. 2005) (outlining the framework).

¹⁶⁰ *See infra* Part IV.A.

¹⁶¹ *See Splinter*, *supra* note 4, at 4345–46 (illustrating the use of enhancers for identifying and classifying regulatory DNA sites in the genome).

¹⁶² *See infra* Parts IV.A–D (exploring the few patents issued).

¹⁶³ Method for Prod. of Penicillin, U.S. Patent No. 2,442,141 (filed May 11, 1945) (issued May 5, 1948).

¹⁶⁴ *Cancer Drug Information*, NAT’L CANCER INST., <http://www.cancer.gov/cancertopics/druginfo/alphalist> (last updated April 5, 2013).

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noncoding DNA mutations in human diseases require a legal foundation that allows for their full exploration. This growing body of research shows that sequence alterations in noncoding DNA, like enhancers, may alter the regulation of critical genes, causing congenital¹⁶⁵ and somatically acquired¹⁶⁶ diseases.¹⁶⁷ This was first medically recognized in a thalassaemia¹⁶⁸ patient when it was determined that a deletion outside the patient's intact β -globin gene effectively altered expression of that gene.¹⁶⁹

Several known human diseases have since been linked with mutations in noncoding DNA. Preaxial polydactyly,¹⁷⁰ for example, has been linked with a point mutation¹⁷¹ in noncoding DNA that interferes with regulation of the *sonic hedgehog* gene,¹⁷² despite being located approximately 1 Mb from the gene.¹⁷³ Alterations in noncoding DNA are also implicated in B-cell lymphomas and T-cell leukaemias where chromosomal

¹⁶⁵ A congenital disease “[e]xist[s] at birth, . . . [that is] either hereditary or due to an influence occurring during gestation up to the moment of birth.” STEDMAN’S MEDICAL DICTIONARY, *supra* note 4, at 88610.

¹⁶⁶ A somatically-acquired disease results from a mutation in any cell in the body other than germ line cells, such that the mutation is not passed to children. *Mutations: Somatic and Germline*, NAT’L CANCER INST., <http://www.cancer.gov/cancertopics/understandingcancer/cancer/genomics/page10> (last reviewed Sept. 1, 2006). Cancers are caused by somatic cell mutations. *Id.*

¹⁶⁷ Splinter, *supra* note 4, at 4345 (citing Kleinjan, *supra* note 2, at 8).

¹⁶⁸ Thalassaemia, also known as Cooley’s anemia, is a hereditary disease that results from defects in the synthesis of hemoglobin, the protein responsible for binding oxygen from the lungs and transporting it to tissues throughout the human body. *Thalassemia*, MEDLINEPLUS MEDICAL ENCYCLOPEDIA, <http://www.nlm.nih.gov/medlineplus/ency/article/000587.htm> (last updated March 22, 2013).

¹⁶⁹ L.H.T. Van der Ploeg et al., *γ - β -Thalassaemia Studies Showing that Deletion of the γ - and δ -Genes Influences β -Globin Gene Expression in Man*, 283 NATURE 637, 637 (1980).

¹⁷⁰ Preaxial polydactyly is a disease characterized by the “[p]resence of more than five digits on [the] hand or foot.” STEDMAN’S MEDICAL DICTIONARY, *supra* note 34, at 325060.

¹⁷¹ A point mutation is one “that involves a single nucleotide; it may consist of loss of a nucleotide, substitution of one nucleotide for another, or the insertion of an additional nucleotide.” *Id.* at 263650.

¹⁷² The *sonic hedgehog* (*shh*) gene produces a protein that has been found to be expressed at the posterior end of the limb bud in a region called the zone of polarizing activity. HARVEY LODISH, ET AL., MOLECULAR CELL BIOLOGY 1014–16 (Sara Tenney, et al. eds., 4th ed. 2001). Misexpression of *shh* has been implicated in defects in digit formation and limb development in addition to other developmental abnormalities. *Id.*

¹⁷³ Laura A. Lettice et al., *A Long-Range Shh Enhancer Regulates Expression in the Developing Limb and Fin and is Associated with Preaxial Polydactyly*, 12 HUM. MOLECULAR GENETICS 1725–26 (2003).

rearrangements “juxtapose strong regulatory sequences of antigen receptor loci to proto-oncogenes.”¹⁷⁴ Various eye diseases (e.g. aniridia¹⁷⁵ and glaucoma¹⁷⁶), X-linked deafness,¹⁷⁷ Rieger syndrome,¹⁷⁸ and numerous other human diseases may be linked to alterations in noncoding DNA that interfere with gene regulation.¹⁷⁹ Startlingly, the genome-wide association studies’ database suggests that “mutations in non-coding [DNA] contribute to . . . 40% of disease cases.”¹⁸⁰

The medical and scientific importance of enhancers is unquestioned. Their importance does, however, raise questions about how to better promote and encourage research of enhancers through patent law. As discussed below, there are currently two routes for an isolated human enhancer to satisfy the utility requirement, and neither route is entirely appropriate.¹⁸¹

¹⁷⁴ Splinter, *supra* note 4, at 4345.

¹⁷⁵ Aniridia is characterized by the “[a]bsence of the iris; when congenital, a rudimentary iris root is usually present. About 60% of cases are inherited as autosomal dominant, although somewhat irregularly manifested.” STEDMAN’S MEDICAL DICTIONARY, *supra* note 34, at 23480.

¹⁷⁶ Glaucoma is “[a] disease of the eye characterized by increased intraocular pressure, excavation, and atrophy of the optic nerve; produces defects in the field of vision.” *Id.* at 163290.

¹⁷⁷ X-linked deafness is the inability to hear caused by a mutation in the X chromosome. *See id.* at 103100 (defining “deafness” as the “inability to hear”); William Reardon, *Sex Linked Deafness: Wilde Revisited*, 27 J. MED. GENETICS 376, 376, 378–79 (1990). The disease generally affects only males, accounting for approximately 6.2% of deafness in men, and is carried by females as a recessive trait. *Id.*

¹⁷⁸ Rieger syndrome is an autosomal dominant disease characterized by malformations of the teeth, underdevelopment of the anterior eye, and malformations of the abdominal region. *See* STEDMAN’S, *supra* note 34, at 121670, 196070, 241890, 397030. Rieger syndrome is often associated with glaucoma. *See Genetic and Rare Diseases Information Center (GARD): Axenfeld-Rieger Syndrome* OFF. RARE DISEASES RES., <http://rarediseases.info.nih.gov/GARD/QnASelected.aspx?diseaseID=5701> (last visited April 15, 2013) (linking Rieger syndrome to glaucoma).

¹⁷⁹ Kleinjan, *supra* note 2, at 9–11 (tbl. 1). Table 1 summarizes various human diseases linked to altered gene regulation caused by “position effects” from chromosome rearrangements. *Id.*

¹⁸⁰ Splinter, *supra* note 4, at 4345 (citing L.A. Hindorff et al., *A Catalog of Published Genome-Wide Association Studies*, NAT’L HUM. GENOME RES. INST., <http://www.genome.gov/gwastudies> (last visited April 15, 2013); Axel Visel et al., *Genomic Views of Distant-Acting Enhancers*, 461 NATURE 199, 204 (2009)).

¹⁸¹ *See infra* Part IV.D.

*B. Plant Patents & Industrial Process Patents
that Claim Enhancers*

Enhancers have been patented in plants as elements in a transgenic vector for conferring “greater tolerance to sucrose, greater tolerance to dehydration, or greater tolerance to osmotic stress.”¹⁸² Production of transgenic seeds developed from such a vector may be quite lucrative in the agricultural industry. Monsanto, for example, is a Fortune 500 company that produces and distributes genetically-modified seeds for enhanced crop resistance and production.¹⁸³ Similarly, mammalian enhancers have been patented as an element of a process for mass-producing antibodies.¹⁸⁴ In sum, non-human enhancers have been patented in industrial applications where utility may be linked to a manufacturing process, but a search of the USPTO’s database reveals little when it comes to patents for isolated human enhancer elements.¹⁸⁵

C. Patent 8,084,229: A Single Human Enhancer Patent

As recent as April 2013, a search of the USPTO Patent Full-Text and Image Database¹⁸⁶ for issued patents database revealed that only one isolated human enhancer has been patented as a composition of matter.¹⁸⁷ This search utilized “human” and “enhancer” as search terms to produce 675 results.¹⁸⁸ Review of each individual search result found that only Patent 8,084,229 (“229 Patent”) claimed an isolated human enhancer element in

¹⁸² Polynucleotides & Polypeptides in Plants, U.S. Patent No. 7,825,296 (filed Dec. 20, 2006).

¹⁸³ *Monsanto at a Glance*, MONSANTO, <http://www.monsanto.com/whoweare/Pages/default.aspx> (last visited April 15, 2013).

¹⁸⁴ Enhanced Prod. of Proteinaceous Materials in Eucaryotic Cells, U.S. Patent No. 4,663,281 (filed Mar. 22, 1988); see *Mass. Inst. of Tech. v. ImClone Sys., Inc.*, 498 F. Supp. 2d 435, 436–37 (D. Mass. 2007) (stating that mammalian enhancers are utilized to “express protein antibodies in commercial quantities”).

¹⁸⁵ USPTO PAT. FULL-TEXT & IMAGE DATABASE, <http://patft.uspto.gov/netahtml/PTO/search-adv.htm> (last visited April 15, 2013) (follow “Advanced” hyperlink; then search “Query” using “acm/(human and enhancer)”).

¹⁸⁶ *Id.*

¹⁸⁷ ‘229 Patent, GDEP Enhancer Element & Use Thereof to Confer Retinal Specific Gene Expression, U.S. Patent No. 8,084,229 (filed Dec. 29, 2008).

¹⁸⁸ USPTO PAT. FULL-TEXT & IMAGE DATABASE, *supra* note 185.

the substantive, enumerated claims.¹⁸⁹

Entitled “GDEP enhancer element and use thereof to confer retinal specific gene expression,” the ‘229 Patent makes eleven claims and was issued on December 27, 2011 and claims a human enhancer linked to the Gene Differentially Expressed in the Prostate (GDEP) gene that confines gene expression specifically to the retina and prostate.¹⁹⁰ The patent’s claimed utility is that the *GDEP* enhancer may be utilized in conjunction with gene therapy techniques to direct expression of a “heterologous eukaryotic gene promoter and confer[] retinal specific expression on the therapeutic gene.”¹⁹¹

Courts have not yet addressed the issue of the patentability of isolated human enhancers and the utility requirement, and it remains to be seen whether the ‘229 Patent would remain valid if challenged.¹⁹² Nevertheless, when a search of the USPTO’s patents database reveals only one isolated enhancer sequence compared to at least 2,645 patents claiming “isolated DNA,” the disparity certainly raises eyebrows.¹⁹³ This note suggests that the existing tests for satisfying the utility requirement are inadequate and overly stringent for claims covering enhancers that are not implicated in a known human disease.

D. The Current Law, Materials, & Guidelines Discourage Research of Enhancers

Combining all of the references for examining utility under § 101 of the Patent Act reveals that a claim for an enhancer under the current framework may generally satisfy the requirement through two routes. Through the first route, a claim over an enhancer may satisfy the utility requirement if the enhancer is linked to a known human disease and if it provides a credible basis for diagnosis or treatment of the disease.¹⁹⁴ The single act of linking an enhancer to a known human disease generally satisfies specific and substantial utility.¹⁹⁵ Through the second route, a claim over an enhancer not linked to a human

¹⁸⁹ ‘229 Patent, *supra* note 187.

¹⁹⁰ *Id.*

¹⁹¹ *Id.*

¹⁹² *See* notes 94–110 and accompanying text.

¹⁹³ *See* notes 188–91 and accompanying text.

¹⁹⁴ TRAINING MATERIALS, *supra* note 82 at 4–6.

¹⁹⁵ *Id.* The disease must be known. *See id.* at 46 (noting that the disease cannot be “unspecified” or “undisclosed”). \

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disease may satisfy the utility requirement if (a) the enhancer corresponds to a known gene and (b) the protein product of the corresponding gene is known and characterized.¹⁹⁶ Neither test is completely appropriate for patenting isolated human enhancers, as will be explained below.

1. Forward Genetics Approaches vs. Reverse Genetics Approaches to Linking Enhancer with Human Diseases

The first route to satisfying utility derives from the USPTO's 2001 Examination Guidelines and 1999 Training Materials.¹⁹⁷ This route is problematic whether a researcher seeks to patent genes, enhancers, or any other polynucleotide, because it discourages using one of the fundamental approaches to linking DNA mutations with human diseases. Linking human disease and DNA mutations may be accomplished using either a forward genetics approach or a reverse genetics approach.¹⁹⁸ The fundamental difference between these two approaches is the starting point of the research.¹⁹⁹ Forward genetics approaches start with a disease phenotype, while reverse genetics approaches start with DNA.²⁰⁰ This starting point may have tremendous consequences on the patentability of genes and noncoding regulatory elements under study, particularly in light of the patent law changes that took effect on March 16, 2013, under the America Invents Act.²⁰¹

Forward genetics isolates a disease phenotype and then seeks to connect that phenotype to its underlying DNA mutation.²⁰² As an example, researchers might utilize a forward genetics approach using mice as a model organism by isolating DNA from

¹⁹⁶ See *In re Fisher*, 421 F.3d 1365, 1368, 1370, 1373–74 (Fed. Cir. 2005) (rejecting a patent application for ESTs on the ground that they “do not correlate to an underlying gene of known function”).

¹⁹⁷ Utility Examination Guidelines, 66 Fed. Reg. 1092–02 (Jan. 5, 2001); see TRAINING MATERIALS, *supra* note 82.

¹⁹⁸ See Melissa D. Adams & Jeff J. Sekelsky, *From Sequence to Phenotype: Reverse Genetics in Drosophila Melanogaster*, 3 NATURE REVS.: GENETICS 189, 189 (2002) (discussing the forward and reverse genetics approaches).

¹⁹⁹ *Id.*

²⁰⁰ *Id.*

²⁰¹ Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat 284 (2011) (codified at 35 U.S.C. §§ 1–375); The United States converted from a “first-to-invent” to a “first-to-file” system on March 16, 2013. *Id.* The “first-to-invent” system benefits reverse genetics researchers by establishing priority for patenting an isolated enhancer at the point the enhancer is isolated.

²⁰² Adams & Sekelsky, *supra* note 197, at 189.

a mouse exhibiting a disease phenotype and comparing it with wild-type DNA. Researchers may then identify sequence differences in the DNA samples to isolate any putative DNA mutation underlying the disease phenotype.

Reverse genetics, in contrast, identifies a DNA region of interest and selectively mutates it to create disease phenotypes.²⁰³ For example, a reverse genetics approach using mice as a model organism might identify a chromosome arm that contains several candidate genes and regulatory elements suspected to be involved with albinism,²⁰⁴ which is characterized by lack of pigment. Researchers using this reverse approach would then selectively mutate each of the genes and regulatory elements and seek to recreate the lack of pigment phenotype in mice and identify the putative gene(s) or regulatory element(s) whose mutation causes the disease.

While forward genetics approaches to studying human disease have been highly successful, those approaches rely on a disease phenotype being visible or easy to detect.²⁰⁵ Reverse genetics approaches are not limited to visible or easy-to-detect phenotypes.²⁰⁶ Reverse genetics approaches are also particularly useful in analyzing diseases that may be caused by multiple DNA mutations.²⁰⁷ With regard to human diseases, reverse genetics approaches have been used successfully to link many diseases with DNA mutations, including Duchenne muscular dystrophy,²⁰⁸ chronic granulomatous disease,²⁰⁹ and retinoblastoma.²¹⁰

The existing legal framework for patenting polynucleotides, however, discourages reverse genetics approaches to studying

²⁰³ *Id.*

²⁰⁴ Albinism refers to “[a] group of inherited (usually autosomal recessive) disorders with deficiency or absence of pigment in the skin, hair, and eyes, or eyes only, due to an abnormality in production of melanin.” STEDMAN’S, *supra* note 34, at 11550.

²⁰⁵ See Adams & Sekelsky, *supra* note 197, at 189 (describing the long use of forward genetics to discover disease phenotypes through mutations on already recognized genes).

²⁰⁶ *Id.*

²⁰⁷ *Id.*

²⁰⁸ Duchenne muscular dystrophy (DMD) is “an X-linked disorder of unknown etiology affecting about 1 in 3000 males . . . characterized by progressive muscle wasting.” Stuart H. Orkin, *Reverse Genetics and Human Disease*, 47 CELL. 845, 845 (1986).

²⁰⁹ Chronic granulomatous disease (CGD) is an inherited disorder that impairs the immune system because “phagocytes from affected patients fail to generate superoxide on ingestion of microbes.” *Id.* at 846.

²¹⁰ Retinoblastoma (Rb) is a malignant cancer of the retina. *Id.* at 846–47.

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human disease because satisfying the utility requirement using a forward genetics approach requires less effort. As discussed above, linking a gene or noncoding regulatory element to a known human disease generally satisfies the test for specific and substantial utility, such that the researcher need only assert a single credible utility, like using the DNA sequence for diagnosis or treatment of the underlying disease.²¹¹ Asserting a credible diagnosis is a particularly low hurdle in that the researcher need only describe how to compare a hypothetical patient's DNA sequence to the claimed wild-type²¹² sequence and determine whether the patient has a mutation in the claimed DNA sequence.²¹³ Under this framework, it is far easier for a researcher to patent forward genetics approaches because the starting point is a human disease; the researcher may quickly patent a candidate DNA sequence without having to expend the extra time and effort to characterize it.

By contrast, it is more difficult for researchers to patent isolated DNA studies using reverse genetics approaches because the end point is a disease phenotype and assessment of whether it correlates to a known disease.²¹⁴ Under this first route, a researcher who employs a reverse genetics approach would have to spend considerable time and effort mutating the DNA sequence of interest in order to link it to a human disease, if at all. With regard to obtaining patents over enhancers, the added effort required to patent discourages researchers from using reverse genetics approaches. Discouraging a fundamental approach to medical research is bad policy. The purpose of patent law pursuant to Article I, Section 8, Clause 8 of the U.S. Constitution is to “[t]o promote the [p]rogress of [s]cience.”²¹⁵

²¹¹ See *supra* notes 193–95 and accompanying text.

²¹² Wild-type refers to “a gene, phenotype, or genotype that is overwhelmingly common among those possible at a locus of interest that it represents the standard characteristic . . .” STEDMAN’S, *supra* note 34, at 423280.

²¹³ See Nathan D. Lawson & Scot A. Wolfe, *Forward and Reverse Genetic Approaches for the Analysis of Vertebrate Development in the Zebrafish*, 21 *Dev. Cell*, 48, 48 (2011) (“Carriers of interesting modified alleles are identified by the observation of particular displayed phenotypes, and subsequent mapping of the allele within the genome reveals genes that are associated with the observed biological process.”).

²¹⁴ See Adams & Sekelsky, *supra* note 197, at 189 (explaining that “only the sequence and position in the genome” are known at the inception of the reverse genetics approach).

²¹⁵ U.S. CONST. art. I, § 8, cl. 8.

Discouraging reverse genetics approaches to scientific research directly contradicts that purpose.

This observation is compounded by the fact that researchers employing reverse genetics approaches are now no longer be able to rely on the advantages of the “first-to-invent” standard of traditional American patent law.²¹⁶ The old standard affords some protection to a researcher who uses the reverse genetics approaches that may take longer to satisfy the utility requirement because that researcher could establish priority in a patent dispute by having conceived the invention first. For claims over isolated DNA, the date of conception *per se* occurs at the point the DNA is isolated,²¹⁷ which provided researchers who use reverse genetics approaches an advantage because the starting point of their research is DNA.²¹⁸ Pursuant to the America Invents Act, wherein the “first-to-file” provision became effective on March 16, 2013, the researcher who first files with the USPTO is awarded the patent in a dispute between two inventors.²¹⁹ This transition from the “first-to-invent” standard to a “first-to-file” standard will effectively remove any advantage that reverse genetics researchers may have had in a patent dispute by establishing priority through isolation of the subject DNA. With regard to obtaining patents over enhancers and protecting research work product from being scooped, this provides forward genetics researchers a decided advantage over reverse genetics researchers.

The net effect is that the current legal framework of the first route to satisfying utility discourages researchers from using reverse genetics approaches to study noncoding regulatory elements, like enhancers. The Utilitarian Theory at the foundation of American patent law is premised on encouraging innovation, and the current legal framework does precisely the opposite by discouraging reverse genetics approaches in an

²¹⁶ Under the former law, the inventor who is first to conceive an invention is awarded the patent in a dispute between two inventors. Under the new law, the inventor who is first to file will be awarded the patent in a dispute between two inventors. See Alexa L. Ashworth, *Race You to the Patent Office! How the New Patent Reform Act will Affect Technology Transfer at Universities*, 23 Alb. L.J. Sci. & Tech. 383 (2013) (discussing the America Invents Act and how it has changed the patent law regime in the United States).

²¹⁷ *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1205–06 (Fed. Cir. 1991).

²¹⁸ Adams & Sekelsky, *supra* note 197, at 189.

²¹⁹ Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 3(b)(1)(n), 125 Stat 284 (2011) (codified at 35 U.S.C. § 102).

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emerging field of biotechnology with tremendous potential to cure various human diseases.²²⁰

2. The *In re Fisher* Test for Utility is too Stringent when Applied to Enhancers

To review, an enhancer may act on a single gene or multiple genes, and it may trigger varying degrees of up-regulation in those genes.²²¹ Enhancers are promoter-specific and “tissue-specific” such that they regulate different genes in different tissues.²²² An enhancer may be located within the intron of the gene upon which it acts, or it may be located as far as 1 Mb from the gene it up-regulates.²²³ Because of these variable qualities, determining the gene or genes that an enhancer acts upon is a daunting task that often involves timely experimentation by “trial and error.”²²⁴

Satisfying the utility requirement through the second route is a similarly daunting task for inventors. The second route to satisfying utility derives from *In re Fisher* and the analysis of how an EST may satisfy utility.²²⁵ The process of isolating a human gene and characterizing the function of the gene’s corresponding protein product is a process that, by itself, may take several years.²²⁶ Isolating an enhancer, characterizing a corresponding gene, and determining the function of the gene’s corresponding protein may take decades to accomplish, particularly because of the immensely complex and unpredictable nature of enhancer elements. Holding researchers to this

²²⁰ See David S. Olson, *Taking the Utilitarian Basis of Patent Law Seriously: The Case for Restricting Patentable Subject Matter*, 82 TEMP. L. REV. 181, 182–84 (2009–10) (outlining the criteria for determining whether patents should be granted for certain types of innovation).

²²¹ Splinter, *supra* note 4, at 4348–49.

²²² *Id.* at 4346.

²²³ Kleinjan, *supra* note 2, at 8.

²²⁴ Having personally created and implemented an “enhancer trap” transgenic vector for use in *Xenopus tropicalis*, I was successfully able to demonstrate the “capture” of several putative enhancers but after over two years of effort was never able to locate successfully the genes upon which any of the putative enhancers were exerting control. McConnell, W.B., Nakayama, T., Ogino, H., & Grainger, R. M., *Transgenic Methods for Studying Gene Function in Xenopus tropicalis* (Jan. 2009) (unpublished M.S. thesis, University of Virginia) (on file with the Biology & Psychology Library, University of Virginia).

²²⁵ *In re Fisher*, 421 F.3d 1365, 1370–71 (Fed. Cir. 2005) (requiring a specific use be disclosed).

²²⁶ See *generally id.* at 1380 (Radar, J., dissenting) (describing the lengthy process of discovering the particular use for an EST invention).

standard for utility when seeking to patent an isolated enhancer is unreasonable. It runs contrary to the notion of a “patent bargain,” discourages innovation, and might explain the lack of existing patents for isolated human enhancers.²²⁷

The Utilitarian foundation of patent law is premised on rewarding inventors for disclosing and disseminating new innovations for the public benefit. “The federal patent system thus embodies a carefully crafted bargain for encouraging the creation and disclosure of new, useful, and nonobvious advances in technology and design in return for the exclusive right to practice the invention for a period of years.”²²⁸ Congress, however, certainly did not contemplate that the Patent Act’s utility requirement may require some inventors to expend twenty years of labor and financial resources for twenty years of the exclusive rights granted by a patent. The extra costs of determining and locating a gene on which a given enhancer acts and the extra costs of characterizing that gene’s corresponding protein product are tremendous. The likelihood is slim that an inventor will patent a human enhancer with a sufficiently lucrative application to counterbalance such costs. That is hardly a “patent bargain.”²²⁹

When applied to patenting enhancers not linked to a known human disease, the test for utility derived from *Fisher* is overly stringent and discourages researchers from studying enhancers not linked to disease. Moreover, enhancer researchers are dissuaded from seeking patent protection for their discoveries because protecting the fruits of their labor is more easily accomplished through trade secrecy.²³⁰ While trade secrecy certainly has its place in protecting innovation from infringement, society is deprived of the benefit of new and useful inventions when they are not disclosed because researchers are discouraged from seeking patent protection. In the event a researcher protects his discovery of an enhancer through trade secrecy, there is substantial risk that his discovery never be developed or disclosed to the public. This consequently prevents

²²⁷ See *Bonito Boats, Inc. v. Thunder Craft Boats, Inc.*, 489 U.S. 141, 150–51 (1989) (explaining the notion of “patent bargain”).

²²⁸ *Id.*

²²⁹ See *id.* at 146, 150–51 (allowing the inventor to benefit from his or her invention whether it is disclosed or not).

²³⁰ UNIF. TRADE SECRETS ACT § 1, 14 U.L.A. 542 (1979) (amended 1985) (providing a broad definition of “trade secret” and allowing for extensive protection of trade secrets).

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other inventors from utilizing such knowledge to develop other useful inventions or derivative therapies. From such a Utilitarian perspective, society is deprived of the innovations and corresponding industrial and medical applications that would otherwise result if patent law encouraged researchers to study enhancers and seek patent protection of their inventions. For this reason, a separate test for utility specific to enhancers should be developed and implemented by the USPTO.

3. A Solution to the Utility Requirement Problem For Enhancers

Coding DNA, noncoding regulatory elements, and ESTs are all polynucleotides, but their properties and functions are completely different.²³¹ The USPTO, as such, should recognize them differently by adding new utility tests for enhancers and other functional noncoding DNA elements when the existing legal framework does not adequately apply to such elements. Researchers have only just “scratched the surface” of understanding the mechanisms by which DNA functions in human development and disease. New, crucial noncoding elements and mechanisms are bound to be discovered. For instance, the role of histone coding²³² in DNA transcription is certain to generate new patentable discoveries with important biotechnological and medical applications. In this regard, addressing the patentability of future discoveries is best accomplished through the USPTO because it may respond to new issues more efficiently than Congress and because scientists who work at the USPTO are better equipped to respond to advances in biotechnological sciences as they arise.²³³

This note posits that the utility of isolated enhancers is innate in their ability to activate, enhance, and regulate gene expression and that the totality of research on enhancer elements is

²³¹ See *supra* Part II.A.

²³² Thomas Jenuwein & C. David Allis, *Translating the Histone Code*, 293 *SCI.* 1074, 1074 (Aug. 10 2001). The “histone code” is a hypothesis that the transcription of DNA is partially regulated by chemical modifications to histone proteins. *Id.* at 1074–75.

²³³ See USPTO, GENERAL REQUIREMENTS BULLETIN FOR ADMISSION TO THE EXAMINATION FOR REGISTRATION TO PRACTICE IN PATENT CASES BEFORE THE UNITED STATES PATENT AND TRADEMARK OFFICE, *available at* http://www.uspto.gov/ip/boards/oed/GRB_March_2012.pdf (last visited April 15, 2013) (demonstrating the numerous technical requirements to practice Patent Law).

sufficient to support an assertion that enhancers possess well-established utility. Thus, this note proposes a new utility test specific to isolated human enhancers: so long as a claimed enhancer's innately useful, well-established biological properties can be affirmatively recapitulated *in vivo* in a human cell line, the claim over the isolated human enhancer satisfies the utility requirement.²³⁴

The USPTO defined the term *well-established utility* in the 2000 Training Materials as one that is "a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art."²³⁵ Enhancers possess specific utility because enhancers may act in a promoter-specific, tissue-specific manner.²³⁶ Enhancers possess substantial utility because they have "gene-regulating activity," which is described in the comments section of the 2001 Utility Guidelines as being a "specific and substantial" use.²³⁷ This gene-regulating activity is particularly beneficial for elucidating the function and structure of the genes upon which the isolated enhancers may act.²³⁸ Moreover, the specific and substantial utility of enhancers is credible because a person of ordinary skill in the art would find enhancers' innate utility believable due to the totality of published research that supports the assertion.²³⁹ The totality of research on enhancers strongly supports that they possess innate, well-established utility similar to DNA ligases, as described in Example 10 of the 2000 Training Materials.²⁴⁰ Given this well-established utility, the proposed

²³⁴ See, e.g., TRAINING MATERIALS, *supra* note 82, at 53–55 (finding that DNA ligases possess "well-established utility" because as a class of proteins they are innately useful due to their ability to ligate DNA; researchers took cDNA from human kidney cells and sequenced them with the resulting homologies indicating that a DNA ligase had been encoded).

²³⁵ *Id.* at 7.

²³⁶ See *id.* at 5–6 (giving an example of nucleotide sequences that may have specific utility if they act specifically on a target); Splinter, *supra* note 4, at 4348–49 (describing enhancers as "tissue-specific").

²³⁷ See Utility Examination Guidelines, 66 Fed. Reg. 1092–02, 1095 (Jan. 5, 2001) (claiming "DNA may have a specific and substantial utility because [for example] . . . it has a gene-regulating activity.").

²³⁸ See Kleinjan, *supra* note 2, at 8.

²³⁹ See *id.* at 8–10 (discussing multiple research papers regarding enhancers); see also TRAINING MATERIALS, *supra* note 82, at 7, 53–55 (asserting that if the utility is known, then the utility need not be asserted).

²⁴⁰ See TRAINING MATERIALS, *supra* note 82, at 53–55 (finding that DNA ligases possess well-established utility because as a class of proteins they are

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“recapitulation test” for isolated human enhancers is appropriate because it hinges on demonstrating such well-established utility.²⁴¹

Recapitulating enhancer activity *in vivo* may be performed in numerous ways.²⁴² One potential assay to demonstrate the recapitulation of enhancer activity is to transfect human cells with a modified “enhancer trap” vector comprised of the putative enhancer sequence adjacent to a basal promoter driving a reporter gene (*e.g.* green fluorescent protein (GFP) gene).²⁴³

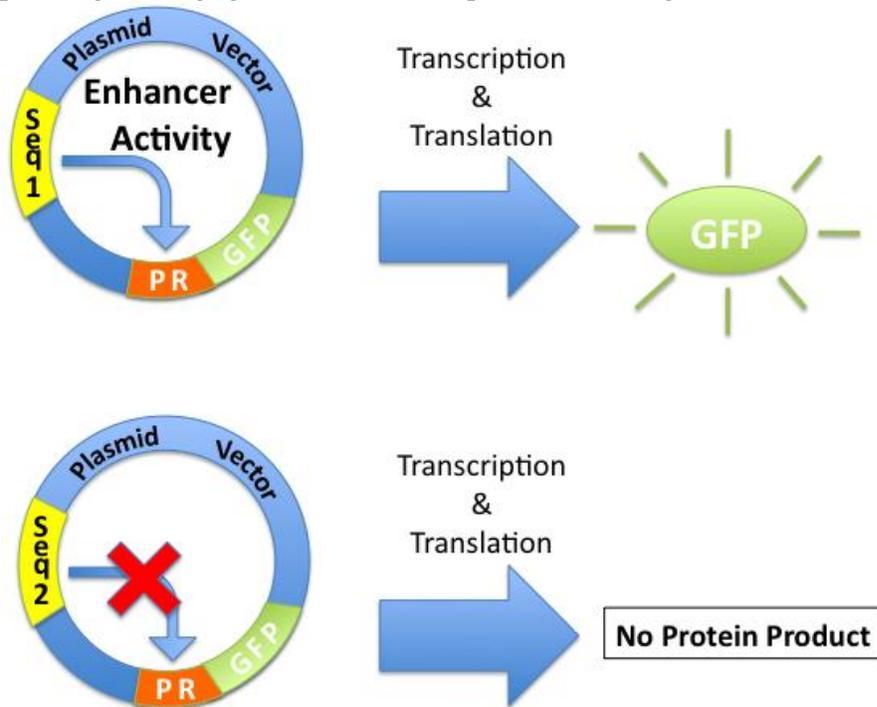


Figure 2: “Recapitulation Test” Concept

The plasmid vector consists of a basal promoter driving expression of green fluorescent protein (GFP).²⁴⁴ Alone, the basal

innately useful due to their ability to ligate DNA).

²⁴¹ *Id.* at 55 (“In order to determine whether the claimed invention has a well-established utility the examiner must determine that the invention has a specific, substantial and credible utility that would have been readily apparent to one of skill in the art.”).

²⁴² *See infra* Figure 2.

²⁴³ *Id.*

²⁴⁴ *Id.*

promoter is unable to drive detectable expression of GFP.²⁴⁵ However, when the inserted DNA sequence contains an enhancer element the basal promoter may drive expression of GFP under control of the enhancer.²⁴⁶ Expression of GFP sufficient enough to be visualized indicates that the DNA sequence inserted in the plasmid vector contains an enhancer element.²⁴⁷ Abbreviations: PR: basal promoter; GFP: green fluorescent protein; Seq1: DNA sequence containing an enhancer; Seq2: noncoding DNA sequence devoid of any functional element.

Data indicates that even though enhancers may act in a promoter-specific, tissue-specific

manner, “enhancers and promoters show little specificity and will always act on each other [in] artificial constructs where the enhancer and minimal promoter are close together”²⁴⁸ Expression of the reporter protein (*e.g.* GFP) *in vivo* would strongly indicate that the inserted sequence contains an enhancer element because the basal promoter alone would not drive detectable expression of the reporter.²⁴⁹

The future of genetics research lies less with the genes themselves and more with ways to manipulate and control them, like using enhancers to up-regulate gene activity. The USPTO should act accordingly by issuing new guidelines for patent applicants and training materials for examiners that specifically recognize assessing the utility of noncoding DNA regulatory elements. For enhancers, the USPTO should include the “recapitulation test” so that researchers need only demonstrate the enhancer activity of an isolated enhancer element to satisfy the utility requirement for patenting.

While new guidelines and training materials issued by the USPTO are not legally binding, the Federal Circuit typically looks to the tests set forth by the USPTO when reviewing patent law issues.²⁵⁰ Congress need not amend the Patent Act to make

²⁴⁵ *Id.*

²⁴⁶ *Id.*

²⁴⁷ *Id.*

²⁴⁸ Splinter, *supra* note 4, at 4348.

²⁴⁹ *Id.* at 4345-46 (indicating that an experiment may choose to use a reporter to gauge gene expression which would not be expressed at the basal transcription level promoter as the promoter alone would be insufficient, requiring an enhancer to express the gene reporter).

²⁵⁰ See *Information Quality Guidelines*, USPTO.GOV, <http://www.uspto.gov/products/catalog/infoqualityguide.jsp> (last modified Jan. 7, 2013) (explaining that the guidelines of the USPTO are meant to improve the quality of information disseminated by the USPTO, but are not meant to be

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new tests for assessing utility legally binding. If and when the USPTO issues new guidelines and training materials, the judicial branch needs to take the initiative in specific litigation to make the “recapitulation test” and any other utility tests for noncoding regulatory elements legally binding through case law. This action on the part of the judicial branch, however, seems unlikely unless the USPTO acts first. Therefore, it is imperative that the USPTO act to issue updated guidelines and training materials that specifically recognize the patentability of noncoding regulatory elements and incorporate the “recapitulation test” for enhancers.

V. CONCLUSION

The noncoding DNA that was once considered “junk” is now recognized as being vital to proper gene regulation and is implicated in numerous human diseases.²⁵¹ Patentability of noncoding regulatory elements, like enhancers, is essential to promoting the advancement of biotechnology and medical research. The current legal landscape for patenting polynucleotides applies very poorly to patenting noncoding DNA sequences, like enhancers. The faults of the current legal framework for patenting enhancers is further compounded by the fact that twenty-two years after the initiation of the Human Genome Project, there is still no clear context with regard to whether DNA even constitutes patentable subject matter.

The USPTO should issue new, updated guidelines and training materials to address the utility of all isolated human noncoding DNA, including enhancers. The new guidelines and training materials should include a separate “recapitulation test” for enhancers to satisfy the utility requirement. For isolated human enhancers implicated in disease, the test for utility should remain the same as that currently applied to isolated genes implicated in disease; but it should be non-exclusive. For isolated human enhancers not implicated in disease, demonstrating

legally binding); *see also* Melissa F. Wasserman, *The PTO's Asymmetric Incentives: Pressure to Expand Substantive Patent Law*, 72 OHIO ST. L.J. 379, 421–22 (2011) (indicating that because the Federal Circuit sees such a small percentage of all patents disputed in need of review, it will often entrench a rule or rules made by the PTO that have already been relied on by thousands of patentees, so as to not upset the status quo). *See, e.g., In re Fisher*, 421 F.3d 1365, 1370–71 (Fed. Cir. 2005) (citing the USPTO guidelines).

²⁵¹ *See* Kleinjan, *supra* note 2, at 10 (tbl. 1) (showing human diseases that have been linked to certain genes).

utility should require recapitulation of the putative enhancer element's enhancer activity in an *in vitro* human cell assay.

These proposed changes will encourage reverse genetics research by providing a less burdensome route to patenting enhancers whether the enhancer is linked to a disease or not. Further, the addition of the "recapitulation test" for enhancers will further the objectives of patent law and help promote the optimal Utilitarian balance between rewarding innovation and providing public benefit.