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After Myriad: Reconsidering the Incentives for Innovation in the Biotech Industry

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NOTE

AFTER MYRIAD: RECONSIDERING THE INCENTIVES FOR INNOVATION IN THE BIOTECH INDUSTRY

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ABSTRACT

35 U.S.C. § 101 allows a patent for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." Recently, the Supreme Court issued several key decisions affecting the doctrine of patentable subject matter under § 101. Starting with Bilski v. Kappos *(2011), and continuing with* Mayo Collaborative Services, Inc. v. Prometheus Laboratories *(2012),* Association for Molecular Pathology v. Myriad Genetics *(2013) and, most recently,* Alice Corporation Pty. Ltd. v. CLS Bank International *(2014), every year has brought another major change to the way in which the Court assesses patentability. In* Myriad*, the Court directly addressed the patentability of isolated genetic material. Due to the underlying biological phenomena involved, this decision split genetic material into two groups. Large, complex animal, plant, and fungal genes remain patentable under some limited circumstances, while viral, bacterial, and simple eukaryotic genes are categorically unpatentable. The biotechnology industry evolved in an era in which gene patents were freely granted. As a result, legal and regulatory pathways have emerged that allow existing biotechnology products to be protected in many of the same ways as traditional pharmaceutical products. However, entirely new areas of biotechnology, those emerging in the shadow of* Myriad*, may be threatened by a deprivation of the incentives and protection that the patent system offers. This Note discusses one such new area of biotechnology, non-coding RNA therapeutics and diagnostics, and the ways in which the categorical exclusion of some*

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genes threatens this promising area of innovation. In addressing this, I propose a re-ordering of the patentable subject matter analysis that would ameliorate many of these issues.

INTRODUCTION

In June of 2013, the Supreme Court handed down its decision in *Association of Molecular Pathology v. Myriad Genetics*.[1] The Court held that isolated, but otherwise "unmodified" genetic material is not patentable under 35 U.S.C. § 101, and therefore effectively barred the patenting of (most) human genes. This was seen as a victory by those who had long felt ethical discomfort with fundamental elements of our biology being "owned," and those who believed that gene patents inhibited access genetic diagnostics, a key aspect of modern healthcare.[2] However, The Biotechnology Industry Organization decried the loss of gene patents as an unjustified attack on the research enterprise which harmed the pursuit of novel drugs or diagnostic methods.[3]

1. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013).

2. Glen Hess, *High Court Nixes Gene Patents*, CHEM. AND ENGINEERING NEWS, June 17, 2013, at 7; Borsellino, M., *World Medical Association Tackling Health Database Issue*. 36 MED. POST. 40 (2000).

3. Press Release, Biotechnology Indus. Org., Statement On U.S. Supreme Court Review Of Isolated DNA Patents, Jun. 13, 2013), *available at* http://www.bio.org/media/press-release/statement-us-supreme-court-review-isolated-dna-patents; *see also* Brief for Biotechnology Industry Organization & the Association of University Technology Managers as Amici Curiae Supporting Reversal at 12–14, Ass'n for Mol. Pathol. v USPTO, 653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406), 2010 WL 4853322 at *27–33, for a more detailed account of BIO's long-standing argument.

Patent practitioners, however, had been awaiting a clarifying statement from the Court on the nature of patentable subject matter, one of the most difficult aspects of patentability to pin down.[4] The decision of the Court did little to clarify this area of law, and may have created more confusion than it alleviated. This confusion has to do with two underlying mismatches between the decision as it was written and the technology that it ultimately affects. First, the decision fails to meaningfully define what a "gene" is or to delimit what a "DNA Sequence" entails. Second, and more troubling, the decision creates a "categorical inclusion," defining cDNA[5] as *per se* patentable, so long as its sequence is different from that of the corresponding genomic sequence.[6] As the opinion notes in passing, this necessarily creates a categorical *exclusion* for cDNAs that have sequences identical to their corresponding genomic sequences.[7] Perhaps unbeknownst to the justices, this category includes a vast number of biologically relevant genes, including all viral genes, bacterial genes, and significant segments of mammalian (including human) genomes.[8]

This categorical divide has disparate impacts on innovation in biotechnology research sectors depending on the maturity of the sector. In the more mature areas of protein biologics (including antibodies), there are enough well-understood areas of patentable novelty outside the basic genetic sequences that underlie these products such that biologics can be well-protected in the absence of a gene patent.[9] Genetic diagnostics, as a less mature part of the industry, are at a greater risk. But, as will be described below, the combination of market forces and FDA exclusivities along with the relatively low cost of diagnostics development is likely to ensure that adequate incentives to innovate remain post-*Myriad*.[10] As will be discussed below, a

4. *See, e.g.*, Eileen M. Kane, *Patenting Genes and Genetic Methods: What's at Stake?*, 6 J. BUS. TECH. L. 1, 5 (2011) ("Volatility in the judicially-created tests for patentable subject matter has been a feature of this area of patent law. The unstable nature of the patent eligibility doctrine is evident from patent law jurisprudence, as legal tests have been developed at one juncture, only to fall out of use or into explicit disregard or repudiation.").

5. cDNA, or complementary DNA, consists of genomic sequences that have been transcribed into their corresponding RNA molecules and then reverse-transcribed, using viral enzymes, back into DNA. The RNA sequence may be subject to chemical "editing" processes within the cell that cause its sequence to be different than that of the corresponding genomic sequence. *See* BENJAMIN LEWIN, GENES V, 149–51, 640–42 (1994).

6. *Myriad*, 133 S. Ct. at 2119.

7. *Id*.

8. cDNAs, *supra* note 5, have different sequences from genomic DNA in the case of genes from animals, plants, fungi, and protists that are intended to be translated into proteins, since the intervening non-coding sequences or "introns" are removed through an intracellular process known as splicing. Regions of the genome that do not encode proteins, as well as all genes from bacteria and viruses, do not contain introns, and therefore cDNAs derived from these would be identical to the genomic sequence.

9. *See* discussion *infra*, Part I.A.

10. *See Mystery Solved! What is the Cost to Develop and Launch a Diagnostic?*, DIACEUTICS, INC., http://www.diaceutics.com/mystery-solved-what-cost-develop-and-launch-

greater threat to diagnostic development comes from the Supreme Court's decision in *Mayo v. Prometheus*. *Prometheus*, in holding that the relationship between information (in the form of serum metabolite levels) and a disease state is an unpatentable "law of nature," casts doubt on the patentability of diagnostic methods *per se*.[11] Though this Note focuses on the impacts of *Myriad* on a distinct class of emerging genetic technologies, I will also argue that reining in the uncertainty in patentable subject matter doctrine that led to *Myriad* will also keep the diagnostics industry safe from the excesses of *Prometheus*.

While changes in patentable subject matter doctrine may largely spare traditional therapeutics and diagnostics, newly emerging genomic technologies remain deeply vulnerable. Advances in drug delivery technology have made RNA-based therapeutics plausible, and research into the vast non-coding regions of the genome—not included in the early versions of the human genome, which focused on coding sequences only[12]—has revealed large numbers of expressed sequences that do not lead to the production of proteins, but have profound effects on physiology.[13] Because these sequences are generally not subject to splicing or editing, their cDNAs will be identical to the genomic sequence, and thus, fall into *Myriad*'s categorical exclusion. Consequently, these potentially groundbreaking sources of novel therapies and diagnostic methods are not patentable at the level of their most fundamental attributes.

This brief review of the unintended consequences of *Myriad* is not a call to panic. The past is littered with decisions that caused patent practitioners, the PTO, and the courts to change the ways they spar over attempts to gain or deny protection for inventions. Rather, this review is intended to illustrate the impacts of *Myriad* and *Prometheus* on an especially promising area of biomedical innovation and how the patent system can cope with these adjustments to patentable subject matter doctrine.

In Part I, I will briefly discuss the development of the biotechnology industry and the role of patent incentives in its successes. Using the general cases of more traditional biotherapeutics and molecular diagnostics, I will examine several of the ways in which patent and non-patent incentives work to foster the development of various types of biotechnology products. In Part II, I will discuss the ways in which *Myriad* alters these incentives in the case

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diagnostic (last visited Nov. 7, 2014) (giving a dollar range of $20–106M for the full development path of novel diagnostic tests). *Compare* Christopher P. Adams and Van V. Brantner, *Estimating The Cost Of New Drug Development: Is It Really $802 Million?*, 25 HEALTH AFF. 420, 420 (2006) (giving a range of $500M–2B for the total cost of developing a therapeutic drug).

11. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S.Ct. 1289 (2012)

12. *See* The Encode Project Consortium, *An Integrated Encyclopedia of DNA Elements in the Human Genome*, 489 NATURE 57 (2012).

13. Claes Wahlestedt, *Targeting Long Non-Coding RNA to Therapeutically Upregulate Gene Expression*, 12 NATURE REV. DRUG DISCOVERY 433,434 (2013).

of products derived from non-coding RNAs. Finally, in Part III, I will compare a number of proposed alternative approaches to the patentable subject matter conundrum with respect to their ability to meet the needs of both the patent system and the biotechnology industry. The conclusion of this Note suggests a relatively minor tweak to existing patentable subject matter analysis that may, at long last, bring stability to the doctrine while at the same time offer a legal test that does not require judges to be technical subject-matter experts.

I. Gene Patents as Incentives in Biotechnology:

The law surrounding gene patents has long centered on the so-called "central dogma" of molecular biology: the idea that genes consist of regions of DNA, which are transcribed into messenger RNA molecules, which are then translated according to their sequences into their corresponding polypeptides, which then fold into the proteins that carry out the functions of the cell. This idea correctly leads to the innovation that to create a biotherapeutic, one could transfer DNA segments between organisms to engineer systems to produce particular enzymes, which could then be delivered to patients who lacked those enzymes.[14] The early days of the biotechnology industry were in fact ushered in by the discovery of ways in which researchers could transfer DNA sequences from one organism into another.[15] This process of recombining DNA sequences affected the transfer of mammalian protein-coding genes into (primarily) bacterial hosts, and it shortly became possible to generate mammalian proteins on industrial scales using bacterial bioreactors.[16] In the ensuing decades, the basic technology was refined in minor ways, but the essential steps of (1) removing a gene from a mammalian cell; (2) splicing it into a construct from which the protein could be produced in another organism;[17] (3) directing the production of the protein in

14. This is the case with recombinant glucocerebrosidase, sold as Cerezyme® for the treatment of Gaucher's disease. *See* Cerezyme Prescribing Information, Genzyme Corp., *available at* http://www.cerezyme.com/~/media/CerezymeUS/Files/pdf/cerezyme_pi.pdf (last visited Nov. 8, 2014).

15. *See, e.g.*, Arnold L. Demain, *History of Industrial Biotechnology*, *in* Industrial Biotechnology: Sustainable Growth and Economic Success 17, 55 (Wim Soetaert and Erick J. Vandamme, eds., 2010).

16. *See, e.g.*, Scripps Clinic and Research Found. v. Genentech, Inc. 927 F.2d 1565 (Fed. Cir. 1991) (describing litigation over the emergence of recombinant production methods for a biologic drug that had previously been produced by extracting it from mammalian tissue). This case resulted in a settlement on remand, after the Federal Circuit found that recombinant production was so profoundly different from extraction that a drug produced by one process may not, in fact, infringe the same drug produced by the other process.

17. The coding region of a gene is, according to the "central dogma" of molecular biology, first transcribed into a messenger RNA and then translated by the cellular machinery into the final protein. This occurs so long as special signaling elements, which vary by species, are present in the DNA. Thus, a mammalian gene can be expressed in a bacterium so long as it is placed into a larger DNA molecule known as a plasmid that contains the necessary signals

the new "heterologous" biological system; and then (4) harvesting the mature protein, have remained the same.[18] This process, known as recombinant protein expression, led to an explosion in the number of therapeutically relevant proteins that could be produced. Suddenly, diseases that could be treated most effectively by the administration of a protein (such as enzyme deficiencies) became amenable to treatment with this new class of "biologic" drugs.

Concurrent with these technological developments were developments in patent law that enabled the protection and monetization of these discoveries. In *Diamond v. Chakrabarty*, (source of the famous dictum that patentable subject matter encompassed "anything under the sun that is made by man"),[19] the Court decided that engineered microorganisms were legitimate subjects for patenting. After this decision, patents on biological materials, including DNA molecules and the gene sequences they embodied, were relatively freely granted.[20] By claiming isolated DNA molecules with a given sequence, researchers were able to effectively patent the genetic information underlying their biological discoveries.[21] Gene patents provided early biotech companies with two major advantages: first, they represented an intellectual property asset that could be used to attract investment; and second, they provided a protected sphere in which further research could be undertaken to develop the genetic information into a deployable product.[22]

A distinct subset of the industry emerged to treat those diseases that were amenable to protein biologics. As the subset of the industry matured, patent practitioners developed strategies to protect not just the underlying genetic data, but also the eventual products and manufacturing processes.[23] At the same time, it became plausible to use the underlying genetic data to develop high resolution diagnostic tests, even where development of a protein therapeutic was not necessarily feasible.[24] Thus, the same ability to pat-

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directing the bacterial cell to express the protein. Plasmids are an example of an extrachromosomal element that can be used for these purposes. Others include Bacterial Artificial Chromosomes, and Yeast Artificial Chromosomes. Expression systems can also be developed in essentially the same way by integrating a gene into the bacterial genome itself, or into a virus that directs gene expression as part of its infection process.

18. *See generally*, Michael R. Green & Joseph Sambrook, MOLECULAR CLONING: A LABORATORY MANUAL (4th ed. 2012).

19. Diamond v. Chakrabarty, 447 U.S. 303, 309 (1980).

20. Roger D. Klein, *Gene patents and genetic testing in the United States*, 25 NATURE BIOTECHNOLOGY 989, 989–90 (2007).

21. *See, e.g.*, U.S. Patent No. 8,623,836 (filed Nov. 23, 2010) (issued Jan. 7, 2014).

22. *See* Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J. LAW ECON. 265, 271–275 (1977).

23. *See* Klein, *supra* note 20.

24. Goldgar, David E. et al., *A Large Kindred With 17q-Linked Breast and Ovarian Cancer: Genetic, Phenotypic, and Genealogical Analysis*, 86 J. NAT'L CANCER INST. 200 (1994).

ent genetic sequences that supported the early-stage development of protein therapeutics also supported the development of diagnostic tests.

As the science progressed however, it became clear that not all diseases could be approached by targeting proteins for pharmaceutical intervention. The early days of molecular biology had focused on the use of DNA to study and manipulate coding regions—those genes that are responsible for producing proteins. Now, however, biologists understand that non-coding DNA, the elements of the genome that do not encode proteins, far from being the "junk DNA" they were derided as in the past, can have tremendous impacts on human health.[25] These sequences are often expressed as RNA molecules (following the first step of the "central dogma"[26]) which perform regulatory functions within the cell, or other as yet unknown functions.[27] These sequences are only now being explored for their potential as therapeutics and diagnostics. Paralleling the biotechnology industry of the late 1970's and early 1980's, these discoveries describe a wide-open frontier in which it is clear that some fraction of these sequences will be medically relevant, though their precise identities are not yet known. However, post-*Myriad*, these particular sequences are unlikely to be patentable. In the next section I will discuss the problems raised by this *per se* exclusion, as well as the reordering of incentives in the biotechnology industry that *Myriad* precipitates.

A. *Patent Incentives in Traditional Biotherapeutics*

Biotherapeutics traditionally comprise protein-based therapeutic compounds that have formed the canonical output of successful biotech companies. These include antibody therapeutics; peptides, such as insulin and Beta-Natriuretic Peptide; enzymes; and other bioactive proteins such as erythropoietin and Bone Morphogenetic Protein.[28] The success of these ventures is widely credited to the presence of robust IP protection in the sequences of the genes encoding the proteins of interest.[29] However, it has long been noted that the value of a gene patent for a therapeutic product lies primarily in providing the ability to exclude competitors from using the sequence to produce proteins of interest rather than in maintaining a monopoly

25. Wahlestedt, *supra* note 13.

26. *See supra* note 17.

27. Wahlestedt, *supra* note 13.

28. *See* Benjamin Leader et al., *Protein Therapeutics: a Summary and Pharmacological Classification*, 7 Nature Reviews Drug Discovery 21, 22–32 (January 2008); *see, e.g.*, Cerezyme, *supra* note 14.

29. This is such a broadly accepted principle that it is often proffered without question. *See, e.g.*, Rebecca S. Eisenberg, *Re-Examining the Role of Patents in Appropriating the Value of DNA Sequences*, 49 Emory L. J. 783 (2000); Michael A. Heller and Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 Science 698 (1998). More robust analysis of this proposition is generally lacking.

over the information contained within the sequence.[30] However, the patenting of genetic sequences for therapeutic development is also valuable in that it allows researchers to preclude efforts by competitors in the early stages of drug development, prior to the development of the final product.[31]

In the early days of the industry, it was not always clear what the result of research into newly discovered genes would be.[32] Therefore, patents on genes underlying biological discoveries served, in the case of each individual project, to keep the innovation horizon open until the contours of the final product could be determined.[33] This suggests that, for more mature segments of the industry, patent protection for underlying discoveries is less of a pressing concern, as a more developed understanding of the types of products that will ultimately result from a technology will provide a tighter focus for drafting patent claims.

Mature products, developed over decades of research, are protectable through webs of overlapping patent rights, including methods of use, methods of manufacture, and possibly formulation, or by FDA-granted regulatory exclusivities.[34] These product-level protections have been developed and honed over the development of the biotechnology industry as patent practi-

30. *See* Eisenberg, *supra* note 29, at 788 ("The commercially significant aspect of these discoveries was not the informational value of knowing what the sequence was, but the tangible value of being able to use the DNA molecules in recombinant production facilities to make therapeutic proteins for sale.").

31. *See id.* at 788–89. Professor Eisenberg argues that patent protection is especially useful in cases in which it is clear that the final product will be valuable, but it is not clear what exactly it will be.

32. Though it may seem self-evident that, for example, the ultimate product derived from cloning the insulin gene would be the insulin molecule itself, the nature of biomolecules is such that substantial modifications must often be made after the gene is expressed in order to transform the gene product into a biologically useful form. Moreover, further modifications may be necessary to render a biomolecule "drug-like" enough that it can be administered to patients. Thus, the final drug product may well be a fragment of the expressed molecule, an adduct (the molecule attached to another, better behaved molecule), a chemically modified version of the molecule, or, in fact even something totally separate, such as an activating or inhibitory antibody, or an unknown, yet-to-be-invented pharmaceutical moiety. The drug development process is full of surprises.

33. This is an embodiment of the prospect theory of patents, in which early patenting protects the ability of inventors of rudimentary technologies to develop commercial applications. *See* Kitch, *supra* note 22, at 270–71.

34. 21 U.S.C. § 355(c)(3)(E) (2012); *See also* John R. Thomas, Cong. Research Serv., R42890, The Role of Patents and Regulatory Exclusivities in Pharmaceutical Innovation (2013) for an overview of exclusivities available to new pharmaceutical products. Briefly, new drugs are generally granted a period of 5 years, with some exceptions, from the date of approval of their New Drug Applications before the data that supported the application can be exploited by other manufacturers in filing Abbreviated New Drug Applications to bring generic drugs to market. *See id.* at 4–5. Due to the expense of developing these data, the effect of this is to bar the introduction of generic forms of a drug until 5 years after the original version is approved. *Id.* at 4. *See also* Gregory Dolan, *Exclusivity Without Patents: The New Frontier of FDA Regulation for Genetic Materials*, 98 Iowa L. Rev. 1399, 1459–62 (2013) for a comparison of the patent and FDA-granted exclusivities and suggestions on improvements.

tioners grappled with the legal aspects of protecting new technology alongside the scientists and engineers working to develop the technology.

B. *Patent Incentives in Traditional Genetic Diagnostics*

The essence of a genetic diagnostic is the correlation between a gene sequence and a physiological condition. Historically, the observation of these correlations has preceded the identification of potential therapeutics for the same conditions. The genetic diagnostics family tree reaches back, if not quite so far as Mendel and his peas, at least to the practice of karyotyping, which in the early to mid-20th century allowed correlations to be drawn between large-scale rearrangements of chromosomes and gross congenital pathologies.[35] The emergence of the field of molecular biology that spawned the biotechnology revolution was inseparable from the practice of identifying genetic markers that were correlated with phenotypes, which were often disease states.[36] The invention of DNA sequencing in the late 1970's[37] represented a wholesale shift in the way this analysis could be carried out, allowing disease states to be mapped onto the coding regions of specific proteins. In many cases, DNA sequencing operated hand-in-glove with the emergence of biotherapeutics development, addressed above.

Perhaps because these technological developments occurred against the backdrop of the emergence of gene patentability, and in part because of the sophisticated expertise and equipment required, the concept of a genetic diagnostic as a salable product emerged as well. In essence, these tests function by obtaining genetic data about a patient, and comparing it to reference sequences obtained from both healthy and diseased populations. As in the case of the BRCA1/2 genetic tests, the discovery and patenting of a genetic sequence that is correlated with a human disease leads quite readily to the development of a diagnostic "product" that can be ordered by physicians, paid for by insurers, and otherwise integrated into our current practice of medicine.[38] Development of a diagnostic can be, in principle, much faster and conceptually simpler than development of a biotherapeutic.[39] However,

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35. Tom Strachan & Andrew Read, HUMAN MOLECULAR GENETICS 48, fig. 2.18 (4th ed., 2011).

36. *See generally* Lewin, *supra* note 5, at 59-69.

37. Frederick Sanger et al., *DNA Sequencing With Chain-Terminating Inhibitors*, 74 PROC. NAT'L ACAD. SCI. U.S. 5463 (1977).

38. *See* Milunsky, Aubrey, *The New Genetics: From Research to Reality*. 27 SUFFOLK U. L. REV. 1307, 1312 (1993) (asserting that as early as 1993, identification of potential diagnostics was a routine part of genetic research); *see also* H. Z. Noorani, *et al. Cost Comparison Of Molecular Versus Conventional Screening Of Relatives At Risk For Retinoblastoma*, 59 AM. J. HUMAN GENETICS 302, 302 (Aug 1996) (Describing the process for financial valuation of a genetic diagnostic test).

39. Identification of the gene/disease correlations that mark the proof of concept stage for a genetic research project represents substantial completion of a diagnostic development effort, but is only the beginning of a drug development effort. Here, I consider "proof of

because the core of a diagnostic technology is the underlying sequence information itself, these products are also at greater risk from alterations in patentable subject matter doctrines.

Exploitation of genomic data in the development of genetic diagnostic tests is the area in which the *Myriad* decision would be expected to have its most obvious impacts. However, the focus of diagnostics development (as was the case in biotherapeutics development) on protein coding regions helps to insulate it from the worst effects of *Myriad*. The *Myriad* decision only removed patent protection for genomic DNA sequences, not for cDNAs which encompass specific protein coding regions.[40] Because cDNA sequences can be protected, diagnostics that rely on comparisons of sequences of protein coding genes can continue to assert their patent rights on this basis.[41]

Additionally, patentability of genetic diagnostics is also called into questioned by a series of other § 101 decisions in addition to *Myriad*, including *Mayo Collaborative Services v. Prometheus Laboratories*, *Bilski v. Kappos*, and most recently, *Alice Corp. Pty. Ltd. V. CLS Bank, International*.[42] In *Prometheus*, the Court held that a diagnostic method based on a comparison of drug metabolite levels to known reference values was unpatentable as having been drawn to a "Law of Nature."[43] In *Bilski v. Kappos*, the Court held that a method for hedging risk in energy markets was drawn to an unpatentable set of "mental steps,"[44] a holding that has since been extended by at least one lower court to invalidate medical diagnostic methods as well.[45] The *CLS Bank* decision ostensibly dealt with software-related claims, but purported to offer additional structure for the analysis of "laws of nature" or "abstract ideas."[46] One lower court has since used the *CLS Bank* framework to affirm *Prometheus*' analysis of diagnostic methods in the genetic context,

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concept" the point at which alterations in a specific gene are found to be correlated with a specific disease state. The development path for a diagnostic, then, consists mainly of refining these correlations in order to provide reliable diagnoses, while the drug development path consists of attempts to manipulate this correlation by altering the activity (broadly construed) of the gene or its product. Notably, both paths can diverge from initial studies of the same gene.

40. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2117–19 (2013).

41. Myriad Genetics, the defendant in the *Myriad* suit, has relied on just this aspect of the decision to continue to assert its patent portfolio against accused infringers. *See* First Amended Complaint Demand for Jury Trial at ¶ 33, Univ. of Utah Research Found. v. Ambry Genetics Corp., No. 2:13-cv-00640-RJS (D. Utah, July 19, 2013).

42. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S.Ct. 1289 (2012); Bilski v. Kappos, 563 U.S. 593 (2010); Alice Corp. v. CLS Bank Int'l, 134 S. Ct. 2347 (2014).

43. *Prometheus*, 132 S. Ct. at 1305.

44. *Bilski*, 563 U.S. at 600.

45. Smartgene, Inc. v. Advanced Biological Laboratories, SA, and ABL Patent Licensing Techs., Sarl, 555 F. App'x 950 (Fed. Cir. Jan. 24, 2014).

46. *CLS Bank*, 134 S. Ct. at 2355–58.

rendering one gene-based diagnostic *per se* unpatentable.[47] The combination of these decisions could comprise a formidable barrier to the extension of patent protection to genetic diagnostics, though so far the decisions have been limited in their application to simple one-step diagnostics, and thus their effect on more complex diagnostic methods remains to be seen.

On the other hand, genomic diagnostics benefit from a wide set of alternative incentives that support their development, which may help to offset the uncertainty currently lingering over the patent monopolies at the core of each individual test. For example, the underlying data, in which large populations are "mined" for correlations between disease states and specific genetic mutations, are often generated by large-scale, university-based, publicly funded research efforts. The patents at issue in *Myriad*, for example, were based on research carried out at the University of Utah, the Toronto Hospital for Sick Children, and the National Institutes of Health, among others, primarily using public funding.[48] While this is largely in keeping with the objectives of the Bayh-Dole Act,[49] it suggests that much of the work that leads to the development of a genetic diagnostic test can be accomplished prior to the need for private investment. This in turn suggests that perhaps even weakened patent incentives would be sufficient to support development of additional tests.

A comparison to drug development is instructive here. The most onerous and expensive elements of drug development are by and large carried out using private funding.[50] These early stages of drug development require

47. Genetic Techs. Ltd. v. Lab. Corp. of America, No. 12–1736–LPS–CJB, 2014 WL 4379587 at *10–13 (D. Del. Sept. 3, 2014) (granting motion to dismiss under F.R.C.P 12(b)(6) on the grounds that application of *Prometheus* under the framework given in *CLS Bank* required a finding that a patent claim drawn to a genetic diagnostic was unpatentable as claiming a Law of Nature).

48. *See* Goldgar, *supra* note 24, at 200–209, for descriptions of the genetic efforts that correlated the BRCA1 gene with breast cancer and acknowledgement of the funding sources that paid for these efforts; see also L. H. Castilla et al., *Mutations in the BRCA1 gene in families with early-onset breast and ovarian cancer* 8 NATURE GENETICS 387, 391 (1994), for details of the cloning of the BRCA1 gene and discovery of its sequence, as well as acknowledgement of the funding sources that made this possible. At issue in Myriad were U.S. Patents No. 5,693,473 (filed Jun. 7, 1995), No. 5,747,282 (filed Jun. 7, 1995) and No. 5,837,492 (filed Apr. 29, 1996). These list among their initial assignees the University of Utah Foundation, the U.S. Department of Health and Human Services, and the Trustees of the University of Pennsylvania, among others. No privately funded organization is listed as a primary assignee of any of these patents.

49. The Bayh-Dole Act, 35 U.S.C. § 200–212 (2012), was enacted in 1980 with the goal of incentivizing the commercialization of publicly-funded research results by allowing publicly funded entities to patent their discoveries. A detailed discussion of this legislation is beyond the scope of this Note.

50. *See* DIACEUTICS, *supra* note 10 (giving a range of $20–106M for the full development path of novel diagnostic tests); *cf.* Christopher P. Adams and Van V. Brantner, *Estimating The Cost Of New Drug Development: Is It Really $802 Million?*, 25 HEALTH AFFAIRS 420, 420 (2006) (giving a range of $500M–2B for total cost of developing a therapeutic drug).

very strong incentives, especially with regard to sales exclusivity for successful drugs, to induce investors to shoulder the significant risks and massive financial outlays required to push a drug through the development and approval process. The most significant development cost is the risk of failure—that significant investments will not be recouped due to the drug being unsafe or ineffective. By contrast, the risks in the development of molecular diagnostics arise almost entirely in the proof of concept stage. Because the protocols for extracting DNA samples are now routine, and analysis of the samples is carried out outside the body, safety concerns are ameliorated and the risk of failure of the diagnostics is reduced to the risk of ineffectiveness only. The development of molecular diagnostics can also involve less in-house development, since the work that must be done to validate a diagnostic method (calculating the correlations between disease states and gene variants) can, and in fact must, be done at the proof of concept stage.[51] This leaves developers with high confidence that a diagnostic method will work, further reducing the risk of failure. This reduction in the risk of failure correspondingly reduces the need for a patent monopoly as an incentive for investment.[52]

In addition, state and federal regulatory policies provide other incentives for diagnostic development. For example, when drugs are developed for use in personalized medicine or as "targeted therapeutics," the FDA informally requires the simultaneous development of "companion diagnostics:" diagnostic tests that serve to identify the probability that a patient will benefit from the drug.[53] Producers of the underlying drug products, in addition to their patent monopolies, also benefit from exclusivities granted by the FDA. These exclusives, among other incentives, generally grant new drugs a 5-year period of exclusive sales before generic competitors are allowed to enter the market.[54] The ability to co-brand a diagnostic with a drug that enjoys sales exclusivity helps create a powerful market position due to the familiarity of the brand name and the status of the diagnostic as the "offi-

51. *See* Sanger, *supra* note 37.

52. *See* WILLIAM M. LANDES AND RICHARD A. POSNER, THE ECONOMIC STRUCTURE OF INTELLECTUAL PROPERTY LAW 300 (1st ed. 2003) ("The greater the fixed costs of research and development and the easier it is to invent around the patent, the greater will be the degree of patent protection required to create adequate incentives to invest in developing the invention in the first place."); *see also* Lori B. Andrews, *Genes and Patent Policy: Rethinking Intellectual Property Rights*, 3 NATURE REVS.: GENETICS 803, 805 (2002).

53. FOOD AND DRUG ADMIN., U.S. DEP'T OF HEALTH AND HUMAN SERVS. DRAFT GUIDANCE, IN VITRO COMPANION DIAGNOSTIC DEVICES, section IV (A and C) (2011), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf.

54. *See* Kitch, *supra* note 22. It has been argued that a version of this system of exclusivities could be developed to protect genomic diagnostics, s*ee* Gregory Dolan, *Exclusivity Without Patents: The New Frontier of FDA Regulation for Genetic Materials*, 98 IOWA L. REV. 1399, 1456 (2013), but this discussion is beyond the scope of this Note.

cial" test.[55] Certainly not all genetic diagnostic tests will be able to benefit, but this serves as an example of the alternative modes of obtaining market power that are available to diagnostics developers.

Makers of diagnostic tests can also pursue market share, though not outright exclusivity, at the state level. The first molecular diagnostics case to be decided on the basis of *Myriad* pitted two purveyors of prenatal genetic diagnostic tests against one another. The question before the court was whether circulating fetal DNA (cfDNA) constituted patentable subject matter.[56] Though the Northern District of California held cfDNA to be unpatentable, Ariosa Diagnostics has moved forward aggressively with a strategy of attempting to register their service as a preferred diagnostic test with various state health authorities.[57] Though this falls short of the monopoly provided by a patent on the underlying genetic sequences, this type of lesser regulatory advantage provides a mechanism through which a company can deploy a diagnostic test in a way that allows it to recoup is development costs.

Genomic diagnostics thus benefit from a combination of factors that support their development in the presence of greatly diminished patent incentives. They are able to utilize publicly-funded research for a greater proportion of their development costs, and they have reduced downstream risk. The ability of developers to avoid the worst consequences of the *Myriad* decision by focusing on protein coding genes suggests that this segment will survive, if not thrive, in a post-*Myriad* world. However, not all medically important genomic alterations reside within protein coding regions. Noncoding regions are, as it turns out, home to a rich array of sequences that affect human health in ways that are only beginning to be understood. These comprise a radically new area of biotechnology that is under dire threat in the *Myriad*-induced absence of patent protection, and thus will form the basis of Part II.

C. *Impacts on the Exploitation of Next-Generation Genomic Data*

As mentioned above, relatively mature areas of biotechnology development benefit from the fact that the basic parameters of the technology are known. The outputs from conventional biotechnology will generally be biotherapeutics or bio-produced compounds. For patent practitioners, this

55. *See* Landes and Posner, *supra* note 51, at 314 for a discussion of "trademark-reinforcing patents" in the pharmaceutical industry for an analogous case.

56. Ariosa Diagnostics, Inc. v. Sequenom, Inc., No. C 11-06391 SI, 2013 WL 5863022 at *11 (N.D. Cal. Oct. 30, 2013).

57. *See Illumina, Natera, Ariosa tests win contracts with CA's prenatal Dx program*, FierceDiagnostics (Nov. 1, 2013), http://www.fiercediagnostics.com/story/illumina-natera-ariosa-tests-gain-contracts-cas-prenatal-dx-program/2013-11-01; *Ariosa's prenatal test gains crucial New York lab licensing certification*, FierceDiagnostics (Feb. 14, 2014), http://www.fiercediagnostics.com/story/ariosas-prenatal-test-gains-crucial-new-york-lab-licensing-certification/2014-02-14.''

means that these molecules can be protected by targeted patent strategies emphasizing their roles as treatment methods, as compositions of matter, or as processes of production. Though it may not be ideal from the standpoint of limiting investment risk, patent protection for the gene sequence underlying the development of the technology can fall to a matter of secondary importance.

Likewise, in the realm of genetic diagnostics, the ultimate output is foreseeable: a test in which specific genetic sequences are correlated with disease states and disease risks. It is slightly more difficult to separate patent protection for a gene sequence from patent protection for a genetic diagnostic. However, the reduced development path for these products relative to therapeutics, as well as the availability of secondary incentives, means that in theory, diagnostic tests can be developed in the absence of the kind of direct patent incentives provided by a gene patent.[58] Both drugs and diagnostics benefit from decades of effort by inventors and patent practitioners to identify effective strategies to protect innovation in these sectors. Therefore the loss of patent protection for gene sequences is unlikely to destroy either enterprise.

It is less clear how rendering genomic DNA unpatentable *per se* will affect emerging sectors of the biotechnology industry. Most notably, the use of "non-coding" gene sequences, often referred to as "genomic dark matter," will be directly affected.[59] Because the number of diseases that are amenable to traditional biotherapeutics is relatively small, non-coding RNA (ncRNA) has gained importance as an emerging area of drug and diagnostic development. Those diseases whose etiology is rooted in the lack of a necessary enzyme, or a mutated or dysfunctional variant of a single protein represent the low hanging fruit of biotechnology. However, many diseases instead involve *misregulation* of a gene, where the gene product itself is perfectly functional, but the cellular machinery make too much or too little of it.[60] Conventional therapeutics offer very little in the way of treatments for this type of disorder. By contrast, the world of ncRNAs discussed below contains a large number of disease-relevant modulators of gene expression, and gives hope that treatments for several as yet intractable human diseases may be within reach.[61]

Simultaneously, developments in drug delivery, and especially in nanotechnology, have made it possible to deliver RNA molecules in clinically

58. *See generally* Note, *Diagnostic Method Patents and Harms to Follow-On Innovation*, 126 HARV. L. REV. 1370 (2013) (presenting a more thorough evaluation of the arguments for and against the idea that barring gene patents will be detrimental to the development of future diagnostic technologies).

59. Lance Martin & Howard Y. Chang, *Uncovering the Role of Genomic "Dark Matter" in Human Disease*, 122 J. CLINICAL INVESTIGATION 1589 (2012).

60. *Id.*

61. *Id.*

relevant ways.[62] This means that, for the first time, the idea of manipulating gene regulation in disease using RNA molecules can be realistically pursued. Furthermore, the same RNA-encoding "gene" that is used to diagnose a health issue may also be deployed directly to treat it. Thus, it is possible that this area of biotechnology may be extraordinarily sensitive to the loss of patent protection for specific genomic sequences.

II. Away From the Central Dogma: Noncoding RNA's in Human Health

The completion of the human genome project in 2000 was rightly heralded as a major milestone in the evolution of the biomedical sciences. In the ensuing years, the breakthroughs that were promised in the hyperbolic buildup to the project largely failed to materialize.[63] Though the availability of such an enormous mass of genomic information *did* revolutionize the way genetic science was done, it did not lead immediately to cures for diseases (and in many cases, even credible diagnostic modalities for disease).[64] Notably, the human genome (as well as most eukaryotic genomes) contains large amounts of untranslated DNA—that is, DNA whose sequence does not encode any protein. This DNA, formerly referred to as "junk DNA" is located between protein coding genes, and sometimes even interjected within the sequence that encodes a protein.[65] It has been appreciated for some time that many diseases with their origins in human genes result from misregulation of protein coding genes, rather than mutation.[66] As the search for these regulators moved forward,[67] it emerged that a number of these clinically relevant

62. RNA molecules are not chemically stable enough to be delivered to the body using conventional formulations, but when they are specially protected, they can be readily delivered to their sites of action. *See, e.g.*, Rosemary Kanasty et al., *Delivery Materials for siRNA Therapeutics*, 12 Nature Materials 967 (2013); U.S. Patent No. 8,673,875 (filed Dec. 11, 2012).

63. *See* Nicholas Wade, *A Decade Later, Genetic Map Yields Few New Cures*, N.Y. Times, June 13, 2010, at A1; *but see* Declan Butler, *Science After the Sequence*, 466 Nature 1000, 1000–01 (2010).

64. *Id.*

65. The sequences "interjected within" protein coding genes are the infamous "introns" that Justice Thomas referred to in the Myriad decision. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct 2107, 2111 (2013). The coding sequences are generally referred to as "exons." Protein coding genes that contain multiple exons separated by introns are referred to as "polycistronic" and those protein coding genes that lack introns are referred to as "monocistronic.

66. *See* Wahlestedt, *supra* note 13.

67. As in the case of the genome effort, much of the productive work in this area emerged from academic consortia such as the Encyclopedia of DNA Elements (ENCODE) consortium and the RNA-focused follow-on effort, GENCODE. *See* The Encode Project Consortium, *An Integrated Encyclopedia of DNA Elements in the Human Genome*, 489 Nature 57 (2012); Thomas Derrien, et al., *The GENCODE v7 Catalog of Human Long Noncoding RNAs: Analysis of their Gene Structure, Evolution, and Expression*, 22 Genome Research 1775 (2012).

regulatory molecules were in fact RNAs that were encoded by the "junk" DNA that had so long been ignored.[68]

Non-coding RNAs (ncRNAs) exist in a number of types, including long non-coding RNAs, short inhibitory RNAs, MicroRNAs, Natural Antisense Transcripts, among others, all of which serve as powerful modulators of gene expression.[69] These molecules can exert tremendous control over gene expression. A large number of diseases that are not amenable to treatment with conventional pharmaceuticals or the canonical biotherapeutics can be potentially attacked if the correct RNA therapeutic can be developed.[70] Further, since many of these RNAs are transcribed from the normal genome, disease states that result from ncRNA-mediated misregulation of genes can be detected through the use of ncRNA-targeted diagnostic tests.[71]

The potential clinical impact of these molecules should not be understated. NcRNAs have been implicated in human diseases including various cancers, Alzheimer's disease, Parkinson's, Huntington's, Schizophrenia, and Heart Disease, among others.[72] Conventional drug discovery approaches have shown significant success in treating most cancers, but the discovery of a new class of potential treatments remains welcome news. What is most enticing about the list of conditions implicating ncRNAs, however, is that many of them represent conditions for which conventional approaches have *not* been successful. In fact, for conditions such as Alzheimer's, Parkinson's, and Schizophrenia, conventional biotechnology has not even provided a means of reliably diagnosing the condition prior to the onset of symptoms. NcRNAs thus have significant potential as diagnostics and therapeutics for some of our most intractable diseases.[73]

As noted above, in the early days of biotechnology, it was possible to lay claim to a gene sequence, even where it was not perfectly clear what form the final product would take. Thus, some measure of protection was afforded to developers as they pursued their work and the investment needed to pursue it. In the post-*Myriad* world, however, this protection is sharply limited. The categorical subject matter exclusion created by the *Myriad* decision allows developers who have discovered novel intron-containing, protein-encoding genes to protect the sequences of cDNA versions of their discoveries, but such protection is unavailable to developers working with viral genes, bacterial genes, monocistronic mammalian genes, or genes (in a

68. *See generally* Encode Project, *supra* note 67; Derrien, *supra* note 67; *see also* Martin and Chang, *supra* note 59, at 1593; Ismael A. Vergara, et al., *Genomic "Dark Matter" in Prostate Cancer: Exploring the Clinical Utility of ncRNA as Biomarkers*, 3 FRONTIERS IN GENETICS 1 (2012).

69. Wahlestedt, *supra* note 13, at 438.

70. *Id.* at 433

71. Vergara, *supra* note 68, at 3.

72. Wahlestedt, *supra* note 13, at 436; *see also* Martin and Chang, *supra* note 59, at 1593.

73. *See, e.g.*, U.S. Patent No. 8,697,359 (filed Oct. 15, 2013).

broader sense of the term than is recognized by Justice Thomas in his opinion) that code for ncRNAs.

Nevertheless, the search for ways to exploit these discoveries in the clinic has begun. In recent years, attempts have been made to develop diagnostic[74] and therapeutic[75] approaches based on non-coding RNA sequences.[76] The combination of newly discovered disease targets with the development of formulations that allow delivery of RNA therapeutics to disease sites[77] has triggered a rush of new development. This rush to develop is so enticing that industry players such as Sanofi SA and AstraZeneca are partnering with smaller biotech companies for the development of ncRNA drugs.[78] A brief sample of biotech activity in the ncRNA space reveals R&D stage companies developing these molecules as platform technologies for drug development,[79] diagnostics,[80] and vaccine development.[81] There is little, if any, sign that this activity has abated since the June, 2013 announcement of the *Myriad* decision. Importantly, this suggests that either companies have found other ways of protecting their R&D investments, or the impacts of *Myriad* simply have not yet caught up with them.

Patent activity in the area of ncRNA has also been robust: as of January 2014, the USPTO listed 737 issued patents and 1,982 published patent applications that were drawn in some fashion to ncRNA, for diagnostic, therapeutic, or agricultural purposes.[82] Tellingly, even in the wake of the *Myriad* decision, some of these patents still claim genetic sequence information.[83]

While development of ncRNA technologies continues, the exclusion of genomic sequences from the realm of patentable subject matter may ultimately increase the uncertainty—and thus the perceived risk—surrounding the development of these technologies to the point at which this promising area of biotechnology no longer attracts the necessary investment. It seems

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74. *See* Vergara, *supra* note 68.

75. *See* Dirk Haussecker, *The Business of RNAi Therapeutics*, 19 HUMAN GENE THERAPY 451, 453–55 (May 2008).

76. *See* Martin and Chang, *supra* note 59; Wahlestedt, *supra* note 13.

77. *See supra* note 62.

78. *See, e.g.*, Robert Weisman, *Boston Area is Leading RNA Renaissance*, BOSTON GLOBE, Feb. 5, 2014, http://www.bostonglobe.com/business/2014/02/05/companies-developing-rna-therapeutics-are-suddenly-upswing-biomedical-world/CmN09T59A6qu7nteLhzIjP/story.html.

79. *E.g.*, *RaNA Therapeutics*, RANA, http://ranarx.com (last visited Nov. 7, 2014).

80. *E.g.*, *GenomeDx: Informing Decisions for Prostate Cancer Treatment*, GENOMEDX BIOSCIENCES, http://genomedx.com (last visited Nov. 8, 2014).

81. *See, e.g.*, Alphavax, Inc., http://www.alphavax.com/home.html (last visited 11/30/2014); U.S. Patent No. 8,680,258 (Issued March 25, 2014).

82. The field of agricultural biotechnology is not a focus of this Note, but many of the IP pressures and incentives affecting genetic discoveries in plants are common to biomedicine as well.

83. *See, e.g.*, U.S. Patent No. 8,623,836 col. 244 ll.15-30 (filed Nov. 23, 2010); U.S. Patent No. 8,685,735 cols. 75–77 (filed Jun. 23, 2009).

unlikely that such a wide area of clinical development will be allowed to fail (in fact, it presently appears to be thriving).[84] Nevertheless, the uncertainty introduced into the law and the market by *Myriad*, *Prometheus*, and *Bilski* remains, keeping with it the potential for significant disruption to emerging sectors of the biotechnology enterprise. It is difficult to imagine that the Supreme Court *intended* to introduce such a sharp asymmetry of incentives into the biotechnology industry

In part III, this Note will address ways in which some of the most deleterious consequences of the *Myriad* decision can be defused before they detonate.

III. Ways to Fix a Broken System: Potentially Viable Approaches to Patentable Subject Matter Analysis

The fundamental flaws in the *Myriad* decision largely originate in the failure of the Supreme Court to acknowledge that the difference between genomic DNA and cDNA, at the sequence level, encompasses many more distinctions than that between a man-made product and a natural product. The Court did not address the reality that a "gene" may encompass any number of genetically heritable biological units other than protein coding regions. Thus, it failed to accommodate the ramifications of declaring a small subset of genes to be patentable while casting the rest of the DNA in the biosphere into the public domain. Given the potentially disastrous consequences of this decision for the future of biomedical research, it is unlikely that the Supreme Court intended this. Rather, this decision partially reflects the fact that the Court was faced with a matter of greater technical complexity than it could reasonably be expected to accommodate.[85] However, even with the *Prometheus*/*Myriad*/*Bilski* triad in place, reasonably stable intellectual property estates are likely to continue to play a key role in technology development. In assessing possible ways forward, there are three major approaches: ignoring the problem, avoiding the problem, and solving the problem. Below, I address each approach, pointing out the dangers of ignoring the issues raised by *Myriad* and other recent patentable subject matter decisions; assessing the likelihood that avoidance mechanisms might succeed; and suggesting a plausible mechanism for solving these problems. In the

84. *See, e.g.*, Weisman, *supra* note 78.

85. Justice Thomas obviously went to great lengths to describe the world of molecular biology in the *Myriad* decision, but it evinced a grasp of the subject that would cause any individuals "ordinarily skilled in the art" to wince—one commentator famously compared it to "[A]n earnest seventh-grader's book report." *The Supreme Court's Sketchy Science: Their BRCA Patent Ruling Reads Like an Earnest Seventh Grader's Book Report*, Slate (June 14, 2014, 12:15 AM), http://www.slate.com/articles/health_and_science/science/2013/06/supreme_court_patent_case_science_the_justices_misunderstand_molecular_biology.html; *see also* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2120 (2013) (Scalia, J., concurring).

end, as is generally true, a simple, effective, and easily deployable solution should prevail. I will argue that this solution has already been suggested by the Court, and by a slight reordering of the present "Law of Nature" analysis, order can be restored.

A. *Ignoring the Problem by Embracing the Current Landscape*

The fact that significant numbers of patents are still being issued claiming genomic sequences suggests that the PTO is willing to construe *Myriad* narrowly.[86] It should, of course, never be assumed that PTO actions are predictive of what the courts downstream will do, and the instability that is introduced by upheavals in a definition of patentable subject matter offers numerous opportunities for mischief. At the level of the District Courts and the Federal Circuit, however, the decision in *Ariosa v. Sequenom*, that circulating fetal DNA is unpatentable as being identical to genomic DNA, suggests that the courts are willing to apply *Myriad* in a more broad and straightforward way.[87] On the other hand, in one of the two other recent decisions regarding molecular diagnostics, *Smartgene v. A.B.L*, the diagnostic in question was found to be unpatentable on the basis that the algorithm was drawn to a set of mental steps, rather a law of nature.[88] This may suggest that in the realm of genomic diagnostics, patentable subject matter determinations can be made on the basis of the diagnostic algorithm, rather than the sequence of the underlying gene. Determining the courts' view of *Myriad* with regard to genetic diagnostics is not helped by the fact that the only post-*CLS Bank* decision relating to a genetic diagnostic involved facts that were significantly similar to those in *Prometheus* (the claim was based on a correlation between a single gene and a single phenotype).[89]

Overall, these decisions point to an incoherent view of patentable subject matter doctrines as applied to biotechnology. In dealing with gene-centric technologies, this uncertainty with regard to the "law of nature" or "product of nature" determinations may continue to be problematic. Development of drugs and next-generation diagnostics is extremely expensive, and the patent monopoly is the primary mechanism we use to allow innovators (and their investors) to recoup their substantial inputs. Endangering patent protection carries with it the risk of endangering the innovation it incentivizes.

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86. *See supra* note 83. However, it must be noted that formal examiner guidelines based on *Myriad* have not been issued.

87. Ariosa Diagnostics, Inc. v. Sequenom, Inc., No. C 11-06391 SI 2013 WL 5863022, at *11 (N.D. Cal. Oct. 30, 2013).

88. SmartGene, Inc. v. Advanced Biological Labs., SA, 555 F. App'x 950, 955 (Fed. Cir. 2014), *cert. denied*, 13-1299, 2014 WL 1669340 (U.S. Oct. 6, 2014).

89. Genetic Technologies Ltd. v. Lab. Corp. of America Holdings, No. 12-1736-LPS-CJB, 2014 WL 4379587, at *2 (D. Del. Sept. 3, 2014).

Though simple diagnostics relying on the correlation between a single gene and a single phenotype may still lead to deployable diagnostic tests with reduced patent incentives, as described above, the more complicated case of diagnostic algorithms that require sequencing of more than one gene has not yet been treated under the existing Supreme Court § 101 analysis. Further, the case of *therapeutic* ncRNA molecules that do not deviate from their genomic sequences (that is, their cDNA sequences are identical to their genomic sequences) provides a conundrum: a drug that, though it may be a distinct and useful composition of matter, may yet be unpatentable under *Myriad*. A doctrinal solution is preferable to this confusion in order to assuage the fears of investors or at least to limit the number of spurious cease and desist letters flying about

B. *Avoiding the Problem*

1. Widening the Experimental Use Exemption

In her concurring opinion in *CLS Bank Inc., v. Alice Corp.* (Fed. Cir., 2013), Judge Newman suggested that a more robust experimental use exception would provide an escape hatch allowing courts to bypass the determination of the patentability of subject matter.[90] Though this is not a new idea,[91] Judge Newman offers a compelling new version. In this conception, the courts would abandon determinations of statutory subject matter beyond identifying whether the claim reads on a "process, machine, manufacture, or composition of matter,"[92] with the language of 35 U.S.C § 101 to be interpreted broadly, in keeping with the court's previous practice.[93] To address problems of the potential preemption of entire fields of innovation, Judge Newman would allow other inventors to carry out research on patented items in order to determine their properties, understand their mechanisms, or to develop improvements.[94]

The experimental use exception to patent infringement, as derived from the case law, is currently limited in most cases to satisfying "idle curiosity" or "philosophical inquiry" and nothing more.[95] This is a narrow opening in most cases. However, the fields of biotechnology and pharmaceuticals benefit from a unique history of statutory experimental use exceptions. In *Roche v. Bolar*, the Federal Circuit initially held pharmaceutical research to the same standard as every other field, holding virtually all experimental uses of

90. CLS Bank, Inc. v. Alice Corp., 717 F. 3d 1269, 1321–27 (Fed. Cir. 2013), *aff'd*, 134 S.Ct. 2347 (2014).

91. *See generally* Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017 (1989).

92. 35 U.S.C. § 101 (2013).

93. *CLS Bank, Inc.*, 717 F. 3d at 1326–27.

94. *Id.* at 1324–35.

95. Madey v. Duke Univ., 307 F.3d 1351, 1362 (Fed. Cir. 2002).

patented compounds to be infringing.[96] In order to provide greater access to generic drugs, Congress responded by enacting the Hatch-Waxman amendments. In relevant part, these amendments provide that researchers pursuing therapeutic biotechnology products regulated by the FDA are exempt from infringement liability so long as the research activities are in preparation for a required regulatory submission.[97] The goal was to allow generics manufacturers to prepare their FDA submissions prior to the expiration of the patents on the pioneer drug. This created a wider experimental use exception for therapeutic development. In a later case, *Merck v. Integra*, the Supreme Court held that the experimental use exemption was to be interpreted broadly, and could encompass preclinical studies of a patented product, including those geared toward the generation of improvements, so long as a future regulatory filing could be reasonably anticipated.[98]

The existence of this relatively broad exception does not, however, mitigate the confusion that is generated by trying to parse the patentability of information, which may or may not fall into one of the explicit § 101 categories.[99] Put another way, biotechnology and pharmaceuticals already possess a significant exemption to infringement liability for experimental uses. Nevertheless, as demonstrated by the continuing waves of § 101 cases that have come before the courts, there remains a need to occasionally litigate patent validity on the basis of patentable subject matter.

The broader issue is that granting an exception for experimental uses leaves the patents in place, and thus there is a continuing potential for damaging assertions or litigation attempts. The probability that a legally unsophisticated scientist may respond to a cease-and-desist letter by abandoning otherwise allowable research without complaint should not be discounted, nor should the sort of risk-balancing required of small, tenuously funded R&D-stage companies.[100] Thus, a doctrine that has the potential to prevent overbroad patents from issuing in the first place is preferable.[101]

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96. Roche Prods. v. Bolar Pharmaceutical, 733 F.2d 858, 863–64 (Fed. Cir. 1984).

97. 35 U.S.C. § 271(e)(1) (2012).

98. Merck KGaA v. Integra Lifesciences I, Ltd., 545 U.S. 193 (2005).

99. *See, e.g.*, Kevin Emerson Collins, *Propertizing Thought*, 60 SMU L. Rev. 317, 344–45 (2007).

100. *See* Maureen E. Boyle, *Leaving Room for Research: The Historical Treatment of the Common Law Research Exemption in Congress and the Courts, and Its Relationship to Biotech Law and Policy*, 12 Yale J. L. & Tech. 269, 302–3 (2010); *see also* Lori B. Andrews, *Genes and Patent Policy: Rethinking Intellectual Property Rights*, 3 Nature Reviews Genetics 803, 806 (2002).

101. Though the remainder of the Note will treat the ways in which judicial actors can structure patentable subject matter analysis, these rules, insofar as they affect the section 101 criteria for patentability, will also be given effect in USPTO examination guidelines; thus it is important to remember that changes in judicial treatment of patentable subject matter can also prevent such problematic patents from issuing through their influence on the PTO.

2. Avoiding Patentable Subject Matter Analysis

Patentable subject matter analysis under the Supreme Court's interpretations of 35 U.S.C. §101 is contentious and rife with unexpected effects. Creating an objective standard for the grant of a patent by abandoning §101 analysis as a test for patentability in favor of an amalgam of novelty, nonobviousness, and enablement thus becomes enticing. It seems on the surface that objectively, either the prior art exists or it doesn't; and if it does exist, it either anticipates every element of a claim or it doesn't.[102] Likewise, the patent as a whole enables one of ordinary skill in the art to practice the invention, or it doesn't; it evidences in its written description that the applicant was in possession of the invention at the time of filing or it doesn't.[103] By comparison, the appeal to judicial fiat (see below) inherent in the present patentable subject matter analysis barely makes sense.

It remains possible, however, that a discovery may be novel, nonobvious, and enabled, while there exist significant policy reasons to deny it a patent. This seems to be the fundamental logic behind the "law of nature" and "product of nature" exceptions from patentable subject matter. There is a longstanding strain in patent law to bar patenting of inventions that would remove too much of a natural law from the public domain, or lay a monopoly on all uses of a natural product, thus denying the use of the fundamental raw materials of innovation to other inventors.[104] As Katherine J. Strandburg points out, patentable subject matter analysis provides a necessary safety valve, allowing the courts to deny patent protection to those discoveries that, even though they would meet the other criteria for patentability, would also encroach unconscionably onto the public domain.[105]

If we must grant that patentable subject matter analysis is a necessary evil, it should be carried out in a more coherent way. The present conception of the patentable subject matter question formulates the judicially created patentability requirements, at least rhetorically, as a threshold that must be met before other requirements can be invoked.[106] Given the tortured path of any patent before it reaches the stage of judicial invalidity determination, it is not clear that in practice subject matter considerations are truly a "threshold."[107] However, the fact that cases continue to be decided on the basis of patentable subject matter is concerning, especially when alternative grounds

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102. 35 U.S.C. § 102 (2012).

103. 35 U.S.C. § 112.

104. *See, e.g.*, Gottschalk v. Benson, 409 U.S. 63, 71–72 (1972); *see also* Rebecca S. Eisenberg, *Wisdom of the Ages or Dead-Hand Control? Patentable Subject Matter for Diagnostic Methods After In Re Bilski*, 3 CASE W. RES. J.L. TECH. & INTERNET 1, 61 (2012).

105. Katherine J. Strandburg, *Much Ado About Preemption*, 50 HOUS. L. REV. 563, 616 (2012).

106. *See, e.g.*, Application of Bergy (In re Bergy), 596 F.2d 952, 960 (C.C.P.A. 1979), aff'd, 447 U.S. 303 (1980); Parker v. Flook. 437 U.S. 584, 593 (1978).

107. *See* Strandburg, *supra* note 105; *see, e.g.*, Bilski v. Kappos, 561 U.S. 593, 601 (2010).

for patent invalidity are readily apparent suggests that courts still view some element of primacy in the patentable subject matter determination.[108]

Acknowledging this reality, Dennis Crouch and Robert Merges suggest the approach of reviewing all of the elements of patentability simultaneously, taking patentability analysis as a cohesive whole rather than a set of arbitrarily ordered steps.[109] Viewing patentability doctrines all at once has the advantage of allowing the reviewing court to select the point of greatest weakness in invalidating a bad patent. This would allow courts to sidestep patentable subject matter analysis in a majority of cases.[110] This is not a complete solution, as it does not account for the small percentage of patents for which invalidity must be found in order to protect the public domain. For these difficult cases, a coherent approach to patentable subject matter analysis is required.

C. *Solving the Problem by Revising the Patentable Subject Matter Test*

As noted above, a patent claim that recites a "law of nature,"[111] "mental process,"[112] or "abstract idea"[113] will be held to be invalid as being drawn to unpatentable subject matter. While the Court has handed down these three standards, there has been little real guidance in how to apply them.[114] In its present form, patentable subject matter analysis proceeds nominally in two steps: first, courts determine whether the subject matter of an invention is drawn to one of the excluded categories, and then the invention as a whole is scrutinized to identify an "inventive concept."[115] As a subsidiary concern, the scope of the claim is examined to determine whether it preempts a law of nature or abstract idea, or whether it is otherwise overbroad.[116] As a part of this, courts can determine whether the claim is drawn to an unpatentable law of nature, or whether it is drawn to a patentable *application* of a law of nature.[117] This shifts the focus of the inquiry to the degree of the human contribution to the invention,[118] rather than the express claim language. No-

108. *See* Dennis Crouch & Robert P. Merges, *Operating Efficiently Post*-Bilski *by Ordering Patent Doctrine Decision-Making*, 25 Berkeley Tech. L.J. 1673 (2010).

109. *Id.* at 1680–81

110. *Id.* at 1686–87

111. *See*, *e.g.*, Diamond v. Chakrabarty, 447 U.S. at 309 (citing Parker v. Flook, 437 U.S. 584); Gottschalk v. Benson, 409 U.S. at 67.

112. Bilski v. Kappos, 561 U.S. 593, 608–11 (2010).

113. *See*, *e.g.*, Bilski, 561 U.S. at 608–11 (citing Diamond v. Diehr, 450 U.S. 175 (1981); Parker v. Flook, 437 U.S. 584 (1978); Gottschalk v. Benson, 409 U.S. 63 (1972)).

114. Crouch and Merges, *supra* note 108, at 1677–78; Eisenberg, *supra* note 104, at 66–65; Kane, *supra* note 4, at 5, 33.

115. Alice Corp. v. CLS Bank Int'l, 134 S. Ct. 2347, 2355 (2014).

116. Strandburg, *supra* note 107, at 588.

117. Gottschalk, 409 U.S. at 71–72; CLS Bank, 134 S. Ct. at 2355.

118. *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116 (2013) ("The location and order of the nucleotides existed in nature before Myriad found them.

tably, this analysis makes use of a two-step test in which *neither* step is required to objectively address the invention as it is formally claimed.

In practice in the post-*Myriad* world, the analysis continues to be exercised in exactly this way, with the preemption analysis explicitly relegated to the status of a secondary consideration.[119] *Ariosa v. Sequenom* is the first biotechnology patentable subject matter case to reach the Federal Circuit since *Myriad*. The case involves the patentability of diagnostic tests utilizing circulating cell-free fetal DNA for prenatal genetic diagnosis. The Federal Circuit did not rule on subject matter eligibility, and after carrying out claims construction, remanded the case to the Northern District of California. In a fairly conventional move similar to the reasoning in *Prometheus*, the district court held that Ariosa had not added enough to the "natural phenomenon" to merit patentability.[120] As a secondary consideration, the court also held Ariosa's patent would effectively preempt all uses of the phenomenon; this was taken as an element supporting the policy underlying subject matter exclusions rather than as a dispositive element of the inquiry.[121] As in *Myriad*, the court first determined that the underlying principle was either a law or product of nature, before deciding the case based on the value added by the inventors.

What constitutes a "law of nature" or a "product of nature" as opposed to a patentable "process, machine, manufacture, or composition of matter, or any new and useful improvement thereof,"[122] is not always clear, even to the inventors, practitioners, and PTO examiners who straddle these lines on a daily basis.[123] If laws and products of nature are *per se* unpatentable, it makes no sense to require judges to make that determination when even those ordinarily (or even extraordinarily) skilled in the art may not be able to easily decide. On the other hand, the question of whether all uses of a law or product of nature are preempted by a claim is one that is at least amenable to analysis. Traditionally, even as acknowledged by the *Myriad* court, preemption has formed the basic rationale for the exclusion of laws and products of nature from patentability.[124] Though it may seem circular at first blush, one

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Nor did Myriad create or alter the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13. The question is whether this renders the genes patentable."); *see also id.* at 2114–15 (characterizing the underlying Federal Circuit decision as relying on competing formulations of the amount of human contribution to the invention); *id.* at 2119 (characterizing cDNA as patentable because it is made by human intervention).

119. Ariosa Diagnostics, Inc. v. Sequenom, Inc., No. C 11-06391 SI, 2013 WL 5863022 at *11 (N.D. Cal. Oct. 30, 2013).

120. *Id.* at *8–9.

121. *Id.* at *11.

122. 35 U.S.C. § 101 (2012).

123. *See, e.g.* Kelly Servick, *Biotech Feels A Chill From Changing U.S. Patent Rules*. 345 Science 14, 15 (July 4, 2014).

124. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2116 (2013).

of the elements that *defines* a fundamental law of nature is that a claim drawn to it will preempt all other attempts to solve the problem by similar means, by barring other innovators from using the same "basic tools of scientific and technological work"[125] to solve other problems unforeseen by the first inventor. Thus, operationalizing the preemption analysis offers an approach to determining subject matter eligibility that, though it necessarily leaves significant room for judicial discretion, is at least bounded by an objective standard, and more importantly, can be executed by non-experts. Achieving this may be as simple as reversing the order of the current patentable subject matter analysis: instead of asking whether the claim is drawn to a law or product of nature, and only then asking whether it would preempt entire areas of innovation, judges could instead simply ask about the extent of the preemption. If the claim would preempt all inquiries into a field of study or all other uses of a material that was not a product of human ingenuity, then it can be said to read on an unpatentable law or product of nature and should not be allowed to stand.

The following provides an example of how this type of analysis may be carried out. First, the court should construe the claim carefully, and in doing so, identify the underlying physical premise of each element of the claim. Next, the court should identify how much of each underlying premise is foreclosed by the claim as construed. Finally, the operative questions can be asked: does this foreclosure eliminate either, 1) all uses of one or more of the underlying premises, or 2) all possible solutions to the problem addressed by the claim? Fundamentally this inquiry addresses whether there is any foreseeable space left for further innovation in a field—space for competition being a key element of using the patent system to advance progress in the useful arts.[126] This inquiry addresses the claim as it stands, rather than trying to parse out the importance of the inventor's contribution. Ultimately it is the claim that defines the invention, not the process by which the invention was arrived at.[127]

There are relatively few cases one can imagine in which a claim would be novel, nonobvious, meet the §112 requirements for written description and enablement, and yet still preempt unanticipated or unforeseeable areas of innovation or discovery. Unfortunately, the patenting of genetic sequence information is one of those rare examples, making it important to finally develop a patentable subject matter analysis that works. Utilizing the test proposed above, the specific claims at issue in *Myriad* would still have been held to be unpatentable, as would genetic *information* generally. However, the categorical protection for cDNA sequences likely would not be upheld

125. *Id.* (citing Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S.Ct. 1289 (2012)).

126. Parker v. Flook, 437 U.S. 584, 593 (1978).

127. *See* Merrill v. Yeomans, 94 U.S 568 (1876)

either. What the field would gain from an operationalized preemption test is the certainty that comes from a uniform predictable standard across all areas of biotechnology and pharmaceutical development. Eliminating the distortions in incentives that come from holding that some areas of drug and diagnostic development are eligible for patent protection and others are not, may well be worth the trouble of having to rearrange our thinking on patentable subject matter.

Applying the test above to "abstract ideas" would have a more immediate side benefit in biotechnology as well: it would hold open the possibility that genetic diagnostics are not *per se* unpatentable. Though the tests at issue in *Prometheus* may not have survived this analysis, it is likely that other, more complex diagnostic methods would. A more complex algorithmic comparison is unlikely to monopolize the phenomenon underlying the test, or to claim all solutions to a problem.[128] Providing an opening within which diagnostic product developers can maintain strong protection for the key elements of their technology (their correlations and algorithms, if not the underlying genes) keeps the patent system in a position of support for a key element of the future of medicine.

Conclusion

In the more mature areas of biotechnology, the development of biotherapeutics will continue apace, and the alignment of incentives is still such that diagnostic development will proceed. As for the younger fields, it is not yet known what will emerge from the world of ncRNA, but it is inconceivable that the Supreme Court meant to limit such a promising sector of health innovation. *Myriad* makes it much more difficult to obtain protection for early stage development in this area, while *Prometheus* makes life difficult for those that would develop genomic diagnostics. At present, as in the past, patent protection for biotechnology innovation relies on the creativity of patent practitioners and inventors to work around the amorphous restrictions on subject matter eligibility. *Myriad* and *Prometheus* provide another chance for patent practitioners to figure out what aspects of the biotechnology industry are eligible for patent protection. Barring a more objective approach to patentable subject matter, such as the one suggested here, it is inevitable

128. *See, e.g.*, U.S. Patent No. 7,700,286 (filed Apr. 13, 2012) (describing a complex, multigenic sequencing-based method of cancer diagnosis). Under *Mayo Protective Servs. v. Prometheus Labs. Inc.*, 132 S.Ct. 1289 (2013), this method could reasonably be seen as having been drawn to a "law of nature"—the preexisting relationship between genetic mutations and cancer progression (though the fact that the patent issued suggests that the PTO does not share this view—but the worry is in what the *courts* would do). The claims given clearly do not foreclose all possible uses of the cited genes or all possible means of detecting cancer. Thus, reliance on preemption analysis provides diagnostic methods cover that a strict reading of *Prometheus* does not.

that another change of course will arise in the near future. Innovation will continue, however, and innovators will be watching how patent law tries to keep pace with the work in the lab.