
MUCH ADO ABOUT GENES: UNTANGLING THE EVOLVING LAW OF SUBJECT MATTER ELIGIBILITY

Sardiaa Leney*

I. INTRODUCTION

Recent claims from the biomedical industry, the patent bar and the United States Patent and Trademark Office (USPTO), that the Courts have radically reshaped the law of subject matter eligibility for patents are overstated. A more measured reading of these cases indicates that, while these rulings have not resolved every future issue, they have given clarity to patent eligibility questions concerning genes, genetically engineered product and methods that address the biological and genetic states of patients. In its attempt to provide clarification to examiners while the Courts continued to work through the issues, the USPTO's published "Guidances" have unfortunately contributed to the uncertainty. It is suggested that USPTO's Guidance practice would be improved by a narrower focus on the meaning of key precedents, while still being free to highlight and discuss issues that remain incompletely defined that are relevant to currently developing technologies.

Recent litigation concerning diagnostic methods and gene patenting, particularly the BRCA (breast cancer) genes, has led to an evolution of the standards for patent subject matter eligibility.¹ This

* Sardiaa Leney, J.D.

¹ See *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2110 (2013) (establishing that patent claims comprising or otherwise foreclosing the use of naturally occurring nucleic acids are invalid as drawn to ineligible subject matter); see also *Mayo Collaborative Serv. v. Prometheus Laboratories, Inc.*,

note examines the efforts by the USPTO to clarify the implications of the rulings.² The Supreme Court decisions occasioning the reshaping of subject matter eligibility are also analyzed. This note contends that the patent system is best served by the Court's concise clarification of the underlying principles, and further illustrates that such a clarification has now emerged. A solid understanding of the uncertainties along the road to this new clarity will assist inventors and patent counsel in framing claims consistent with the new eligibility synthesis. The Supreme Court's newly enunciated criteria can be framed with remarkable simplicity after a careful reading of the cases that shape and conclude the BRCA litigation.

Biotechnology employs over 1.4 million Americans, and remains one of the most reliable growth areas in our economy, even in the face of the adverse global economic situation over the last decade.³ In 2014, seven of the top ten grossing drugs were biotechnolo-

132 S. Ct. 1289 (2012) (establishing that diagnostic method patents that seek to monopolize measurement of natural phenomena are drawn to ineligible subject matter).

² See United States Patent & Trademark Office, *Past Subject Matter Eligibility Guidance and Training Materials*, USPTO (2014), archived at <http://perma.cc/AC2D-DDCN> (showing that in the last few years, the USPTO has issued numerous "Guidance" materials aiming to assist Examiners in making subject matter eligibility determinations). At the close of 2014, the USPTO essentially rescinded the Guidance that had been in effect for most of the year, which itself replaced Guidance less than a year old. See Memorandum from Andrew H. Hirshfeld, Deputy Commissioner For Patent Examination Policy, United States Patent and Trademark Office, to Patent Examining Corps, 2014 Procedures for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, and/or Natural Products (Mar. 4, 2014) (on file with USPTO.gov) [hereinafter *March 2014 Guidance*] (superseding the June 13, 2013 memorandum to the patent examining corps titled "Supreme Court Decision in Association for Molecular Pathology v. Myriad Genetics, Inc."). This document was then replaced by new draft guidance, including hypothetical examples drawn from the life sciences, published in December 2014 by USPTO Acting Director Michelle K. Lee in the Federal Register. See 2014 Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74618 (Dec. 16, 2014) [hereinafter *December 2014 Guidance*] (superseding the *March 2014 Guidance*). The availability of additional guidance, including further life science related examples augmenting the *December 2014 Guidance*, was subsequently announced in May 2016 by USPTO Director Michelle K. Lee in the Federal Register. See May 2016 Subject Matter Eligibility update, 81 Fed. Reg. 27381 (May. 6, 2016) [hereinafter *May 2016 Guidance*].

³ See Peter M. Pellerito, *How to Grow Jobs Through Biotech Industry Development: High-Skill, High-Wage Jobs Support And Diversify the Economy*,

gy products.⁴ While the patent system has enabled the first few generations of synthetic-biotechnology-derived drugs to flourish,⁵ the therapies earning big dollars have relied on patent protection for novel recombinant molecules that are synthesized as drugs to *modify* biological activity in patients.⁶ To date, only a few (and notably in smaller markets) have provided a *replacement* for something that a healthy patient would naturally have.⁷ Increasingly, however, it seems likely that medicine will be able to solve some problems by

BIOTECHNOLOGY INNOVATION ORG. (Nov. 2011), *archived at* <http://perma.cc/SKZ4-3UU3> (making the case that the development of the life-science-based industry will produce needed product as well as providing sustainable economic development, attract investment and generate premium employment opportunities).

⁴ See Alex Philippidis, *The Top 25 Best-Selling Drugs of 2014*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Feb. 2015), *archived at* <http://perma.cc/995B-HYNR> (listing details of the top selling drugs in 2014, including AbbVie's Humira at number one, two other recombinant antibodies, Remicade and Rituxan, at three and four respectively, as well as Enbrel, Lantus, Avastin and Herceptin, all biotech products also in the top ten). Between these seven, annual sales of over \$63 billion were reported. *Id.*; see also Eric Palmer, *The 10 Best-Selling Drugs of 2013*, FIERCEPHARMA (Mar. 2014), *archived at* <http://perma.cc/MN4U-XYDX> (reporting that the three top selling drugs in 2013 were Humira, Enbrel, and Remicade, and six of the top ten were biotechnology products).

⁵ See *Media Release: Roche Delivers Strong 2013 Results*, ROCHE.COM (Jan. 30, 2014), *archived at* <http://perma.cc/UC9X-HUDU> (providing recent Roche data on strong earnings supported by biologic drugs).

⁶ See CHARLES A. JANEWAY, JR., PAUL TRAVERS, MARK WALPORT, & MARK J. SHLOMCHIK, *IMMUNOBIOLOGY, THE IMMUNE SYSTEM IN HEALTH AND DISEASE* 14 (5th ed. 2001) (discussing the development of early synthetic antibody strategies).

⁷ See ENBREL, *archived at* <https://perma.cc/7ACL-WFNX> (marketing the immune modulator etanercept, which uses antibody therapy to inhibit inflammatory tumor necrosis factor to treat inflammatory diseases such as arthritis or psoriasis); see also AVASTIN, *archived at* <http://perma.cc/4VJC-XXE4> (marketing the drug bevacizumab); RITUXAN, *archived at* <http://perma.cc/682Q-FR27> (marketing rituximab, which is also marketed under the names MabThera and Zytux). Rituxan and Avastin are used in oncology applications to target VEGF-A and CD20 respectively, both endogenous human molecules. *Id.* This is in contrast to drugs such as Fabrazyme (a synthetic enzyme that replaces a required enzyme that is deficient in those suffering from Fabry's Disease) or Synagis (which is used as a "natural antibody," dosed to pediatric patients to provide passive immune protection against respiratory syncytial virus (RSV) in cases where infection is progressing too rapidly to safely rely on the child's own antibody production). See FABRAZYME, *archived at* <http://perma.cc/YAA9-SDEV> (marketing agalsidase beta for treatment of Fabry's Disease); SYNAGIS, *archived at* <http://perma.cc/8HQQ-VF6E> (marketing the synthetic antibody drug palivizumab for treatment of RSV in infants).

replacing, repairing, adding or subtracting, activating or deactivating patient genes, cells, and tissues directly.⁸ This next generation of therapies, so-called “Advanced Therapy Medicinal Products” (ATMPs), may not be individual blockbuster drugs in the mold of the earlier generation, but will likely have major impacts on health through increasingly specialized drugs, each tailored for and applied to smaller and more specific patient populations – perhaps as small as a single patient, and perhaps developed and made by entities other than major pharmaceutical corporations.⁹ Many such products will be genes themselves, will contain genes or gene-modifying components, and as with many more conventional therapies, will increasingly be dosed to patients on the basis of analyses of their individual genetic makeup.¹⁰ Although ATMPs have been slow to come to market in the United States,¹¹ the commercialization of gene therapies began in Europe several years ago.¹² In addition, diagnostic tests for genes and gene variants are already important to identifying which patients are candidates for modified interventions or therapies with both ATMPs and conventional drugs.¹³

⁸ See Joshua Eaton, *Industry, Regulators Collaborate on ATMPs*, PARENTERAL DRUG ASS’N (Sept. 2014), archived at <http://perma.cc/4KNH-7F6L> (noting the potential challenges associated with the development, regulation and commercialization of next generation biologic therapies).

⁹ See Egbert Flory & Jens Reinhart, *European Regulatory Tools for Advanced Therapy Medicinal Products*, 40 TRANSFUSION MED. & HEMOTHERAPY 409, 409-12 (2013) (giving illustrative examples of ATMP development, the European perspective being particularly useful given the more rapid advance of the implementation of the technologies in Europe).

¹⁰ See Terence R. Flotte, *Gene Therapy Progress and Prospects: Recombinant adeno-associated virus (rAAV) vectors*, 11 GENE THERAPY 805, 805–10 (2004) (reviewing the field of gene therapy).

¹¹ See *Cellular and Gene Therapy Products*, FDA (2013), archived at <http://perma.cc/TZ4R-DEPX> (noting that no human gene therapy products had yet been approved by the U.S. Food & Drug Administration, though the volume of research and testing indicate that products will come to market soon).

¹² See, e.g., Ben Hirschler, *Dutch Gene Therapy Pioneer Raises \$82 Million in U.S. IPO*, REUTERS (Feb. 2014), archived at <http://perma.cc/GU8D-5E4B> (discussing Dutch manufacturer UniQure’s gene therapy product Glybera, and its European regulatory approval).

¹³ See, e.g., *Roche Molecular Sys., Inc. v. Cepheid*, No. C-14-3228-EDL, 2015 WL 124523, at *1 (N.D. Cal. Jan. 7, 2015) (illustrating the importance of genetic screening methods that can distinguish which types of antibiotics will be effective against drug resistant strains of pathogens, in this case a method for detecting a genetic variant in bacteria that confers resistance to the drug Rifampicin).

Americans now have a statutory commitment to universal healthcare, a system that, at least rhetorically, seeks to keep people healthy rather than treating them after they get sick.¹⁴ How health care technologies are developed, commercialized, and paid for will remain an important focus of debate in our society, while the underlying details will inevitably become more and more intricate and complex.¹⁵ An economically and scientifically vibrant biotech sector will serve this need, but to flourish it requires stability and certainty in the patent system to secure adequate investment.¹⁶

While the USPTO must apply legal precedent, it should also seek to do so in a patent-specific manner, rather than pursuing the practice of generalizing and extending guidance to hypothetical situations that somewhat overstep the boundaries of what the courts have actually said.¹⁷ Where possible, the courts also need to frame the principles of the system as clearly and unambiguously as possible to avoid confusion or unintended consequence. If both the USPTO and the courts stay in their respective lanes, then innovative, biotechnology-derived therapeutics will likely flourish in the U.S.¹⁸

¹⁴ See Howard Koh & Kathleen Sebelius, *Promoting Prevention Through the Affordable Care Act*, 363 NEW ENG. J MED. 1296, 1298 (2010) (highlighting important preventative measures in the Act). The then-Assistant Secretary of Health and the Secretary of Health and Human Services suggests that moving prevention to the mainstream of medical practice may be the most enduring impact of the legislation. *Id.* at 1299.

¹⁵ See, e.g., Robert Farley, *ACA Impact on Per Capita Cost of Health Care*, FACTCHECK.ORG (Feb. 2014), archived at <http://perma.cc/D59P-MTR4> (evaluating the competing claims of the Obama administration and their Republican critics over whether the ACA is accelerating or slowing the growth in the cost of healthcare, and concluding that despite the intensity of discussion, the detailed economics of healthcare remain remarkably hard to pin down).

¹⁶ See Lisa Ferri & Emily Nash, *Assessing the Post-'Myriad' and 'Mayo' Landscape*, MAYER BROWN (Jan. 2014), archived at <http://perma.cc/QAW8-UX5R> (discussing how companies rely on patents to secure investment needed to develop inventions into application, especially in the biomedical field).

¹⁷ See *March 2014 Guidance*, *supra* note 2 (creating the impression that patent examiners need to take into account a complex series of steps that have no clear basis in statute or precedent when evaluating subject matter eligibility); see also *December 2014 Guidance*, *supra* note 2 (retracting many of the unsupported examination procedures proposed in the *March 2014 Guidance*, and proposing and examining hypothetical inventions and claims).

¹⁸ Cf. Laura Cassidy, *Medical Research: Gene-Therapy Reboot*, 509 NATURE 651, 651 (2014) (suggesting that gene therapy development in the US has faltered). But see David Gancberg et al., *European Union Support of Gene Therapy Re-*

II. HISTORY

Patent-issuing authorities fulfill a balancing function within the scope of the patent law, and, in the inevitably changing landscape of technology, courts assist in guiding this balance.¹⁹ In the United States, the inventors or improvers of a new and useful process, machine, manufacture, or composition of matter are allowed to patent it, subject to the other provisions of Title 35 of the United States Code.²⁰ Consumers, payers, users, and the general public have direct interests in accessing the fruits of invention, and indirect interests in the fostering of a healthy and progressive, knowledge-based economy.²¹ The broader interests of the United States and her citizens in the management of transnational economic policy are also relevant, particularly the perceived benefits of an internationally-harmonized approach to intellectual property as exemplified by the TRIPS Agreement.²² Uncertainty in the intellectual property regime, and differences between the approach to subject matter eligibility in the U.S. and that operating in other major markets including Australia, Canada, China, the European Union, India, and Japan, can only serve as a brake on American innovation and the American economy.²³

search: A Success Story, 20 MOLECULAR THERAPY 2191, 2191 (2012) (describing development of a flourishing gene therapy sector in Europe).

¹⁹ See *Mayo*, 132 S. Ct. at 1305. Writing for the unanimous court in weighing the policy arguments of *amici*, Justice Breyer noted that:

[p]atent protection is, after all, a two-edged sword. On the one hand, the promise of exclusive rights provides monetary incentives that lead to creation, invention, and discovery. On the other hand, that very exclusivity can impede the flow of information that might permit...invention [] by...raising the price of using the patented ideas...requiring...costly and time-consuming searches.

Id.

²⁰ See 35 U.S.C. § 101 (2012) (defining patentable subject matter).

²¹ See Sean B. Seymore, *Making Patents Useful*, 98 MINN. L. REV. 1046, 1046-47, 1049 (2014) (dissecting the utility requirement and discussing its purpose).

²² See Agreement on Trade-Related Aspects of Intellectual Property Rights, Apr. 15, 1994, Marrakesh Agreement Establishing the World Trade Organization, Annex 1C, THE LEGAL TEXTS: THE RESULTS OF THE URUGUAY ROUND OF MULTILATERAL TRADE NEGOTIATIONS 320 (1999), 1869 U.N.T.S. 299, 33 I.L.M. 1197 (1994) [hereinafter *TRIPS Agreement*] (establishing, *inter alia*, consensus minimum standards for the operation of a patent system in signatory states).

²³ See Lawrence M. Sung, *Medical Alert: Alarming Challenges Facing Medical Technology Innovation*, 6 J. BUS. & TECH. L. 35, 58 (2011) (concluding that, “a sea change [in] recent jurisprudence on patentable subject matter creates immeasurable

In seeking to balance these interests, the courts of the United States have refined their interpretation of 35 U.S.C. §101, containing the statutory criteria for patent subject matter eligibility.²⁴ While the §101 inquiry is a formality for most inventions, the courts have generally recognized that natural phenomena, including the unmodified products of nature such as physical and biological phenomena, as well as natural laws, such as abstract ideas and physical and mathematical principles, are not, by themselves, inventions because they merely describe something preexisting, and are therefore not eligible subject matter for a patent.²⁵ As biotechnologists can now, in principle, construct living things from scratch, and routinely make and sell products genetically engineered using components recombined from naturally-occurring organisms, a fine line has to be drawn between inventive (and patentable) use of natural materials and the (illegitimate) monopolization of the products of nature.²⁶

uncertainty. Without the confidence that investment-backed expectations can be realized, innovation will be retarded”).

²⁴ See, e.g., *Diamond v. Diehr*, 450 U.S. 175, 184 (1981) (creating a precedent allowing patenting of natural phenomena that are integrated as a specific inventive application).

²⁵ See, e.g., *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 130 (1948) (providing a classic formulation of this principle). The court opined:

[P]atents cannot issue for the discovery of the phenomena of nature. The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none. He who discovers a hitherto unknown phenomenon of nature has no claim to a monopoly of it which the law recognizes.

Id. at 130. Although “abstract” and “natural” have sometimes been treated separately, they have the common predicate of being emergent properties of the world, which might be discovered by man but are not actually his creation. *Id.* at 130. For the purposes of the patent law, the abstract/mathematical and natural/phenomenal are sometimes grouped as the “judicially recognized exceptions” to subject matter eligibility under §101. See e.g., *December 2014 Guidance*, supra note 2, at 74622 (elucidating the extent of the judicial exceptions to subject matter eligibility).

²⁶ See, e.g., Daniel G. Gibson et al., *One-step Assembly in Yeast of 25 Overlapping DNA Fragments to Form a Complete Synthetic Mycoplasma genitalium Genome*, 105 PROC. NAT. ACAD. SCI. 20404, 20404 (reporting the *de novo* synthesis and assembly of an entire genome).

A. Key Precedents in Subject Matter Eligibility

*Diamond v. Diehr*²⁷ remains the leading case defining what, in addition to a natural phenomenon or law of nature, is sufficient to transform a process claim into patent-eligible subject matter.²⁸ The Arrhenius equation utilized by the *Diehr* invention provides a quantitative description of how the rates of chemical reactions change with varying temperature.²⁹ The *Diehr* invention envisages a process that uses continuous monitoring of the temperature in a molding press, and applies the Arrhenius equation to compute when the curing reaction of raw rubber placed in the mold will have progressed to the desired point, and then automatically opens the press.³⁰ The court found that, to the extent that the equation described a natural law, the patentees sought to monopolize only a specific inventive application of that law rather than substantively preempting use of the law itself.³¹

In contrast, the invention in *Parker v. Flook*³² proposed a novel algorithm to compute limits in relation to a changing variable used to monitor a chemical process, and thereby control process alarms.³³ Like *Diehr*, the *Flook* algorithm as a stand-alone was agreed to be non-patentable subject matter, but the Court found that

²⁷ See *Diehr*, 450 U.S. at 177 (drawing the distinction that, whereas a natural law cannot be patented, an inventive application of the natural law can).

²⁸ See *id.* at 177-78 (describing an invention for timing the release of a heated press to achieved a desired heat cure).

²⁹ See *id.* (discussing the invention, and the use made of the Arrhenius equation). The equation describes how typical chemical reactions proceed faster at higher temperatures, as there is more energy in the system to overcome the activation energy required to precipitate the activity required. *Id.* Thus, a desired endpoint can be reached in different times depending on the temperature prevailing during the process. *Id.* Where the quality of the product or the efficiency of the process depends on knowing when the endpoint is attained, it is useful to be able to take into account changing temperatures in order to more precisely define the time at which the endpoint will be attained. *Id.*

³⁰ See *id.* (describing how the fundamental principle that relates the rate of a chemical reaction to temperature at which the reaction is carried out is integrated into the invention).

³¹ See *id.* at 187 (indicating that other uses of the Arrhenius equation were not significantly foreclosed by the claims).

³² *Parker v. Flook*, 437 U.S. 584 (1978).

³³ See *id.* at 586 (discussing a patent that sought to monopolize a basic mathematical description of measurement error); see also *Mayo*, 132 S. Ct. at 1299-1300 (discussing the application of *Flook*).

the *Flook* invention lacked the “inventive concept” seen in *Diehr* because all other elements added nothing more than well-understood, routine, and conventional steps for the field.³⁴

A useful starting point for examining §101’s application to biotechnology is *Funk Bros. Seed Co v. Kalo Inoculant Co.*³⁵ Funk Bros. infringed Kalo’s patent for a mixture of nitrogen-fixing bacteria.³⁶ Although Kalo’s mixture solved the existing problem of mixtures of bacteria inhibiting one another’s function by reciting the discovery of a mixture that was mutually non-inhibitory, the Court invalidated the patent as ineligible subject matter on the grounds that nothing was invented.³⁷ Kalo’s discovery was but “one of the ancient secrets of nature now disclosed.”³⁸

The *Diamond v. Chakrabarty*³⁹ decision was a watershed for the new science of genetic engineering.⁴⁰ Although a patent for yeast had been granted to Louis Pasteur as far back as 1873,⁴¹ the USPTO argued that, as a living thing, Chakrabarty’s *engineered* microbe was non-patentable subject matter.⁴² The Court found in Congress’s spe-

³⁴ See *id.* at 594-95 (holding that the subject matter of the claim at issue fell outside the scope of §101 because the application of the *Flook* algorithm would have been generic to many kinds of process alarms, and failed to include limitations such as those the court in *Diehr* found sufficiently inventive).

³⁵ See *Funk Bros. Seed Co.*, 333 U.S. at 131 (holding that combinations of naturally-occurring articles may not be patented where the function of the combined items simply reflects their individual functions in nature).

³⁶ See *id.* at 128 (describing the invention as a mixture of bacterial strains that are mutually non-inhibitory).

³⁷ See *id.* at 132 (indicating that nothing was invented, but rather naturally-existing materials were simply combined).

³⁸ See *id.* (noting that discovery of natural biological phenomena is not invention).

³⁹ See *Diamond v. Chakrabarty*, 447 U.S. 303, 305 (1980) (concerning the patentability of an organism that was genetically modified to create something distinct from any natural phenomenon).

⁴⁰ See *id.* at 314 (deciding the patentability of one of the first genetically-engineered organisms).

⁴¹ See *Manufacture of Beer and Yeast*, U.S. Patent No. 141,072 A (filed July 22, 1873) (claiming, *inter alia*, “[y]east, free from organic germs of disease, as an article of manufacture”).

⁴² See *Chakrabarty*, 447 U.S. at 305-06 (deciding the eligibility of organisms that have been modified to create something distinct from anything that can be found in nature). Chakrabarty’s microbe had extra (functional) genes inserted on plasmids. *Id.* at 305. While naturally-occurring bacteria were known to have single plasmids, Chakrabarty had created a bacterial lineage with more than one, adding a series of new genes to the organism, resulting in something that was structurally and functionally distinct from any naturally-occurring organism. *Id.* at 310.

cific intent that *microorganisms* be excluded from the Plant Variety Protection Act (PVPA), an intention that organisms generally, other than the types of plant varieties explicitly protected, should not be monopolized with patents.⁴³ Nevertheless, the *Chakrabarty* Court, looking back to Thomas Jefferson's intent in authoring the original Patent Act of 1793, felt that the scope of §101 was intended to be extremely broad: “*any* new and useful art, machine, manufacture, or composition of matter, or *any* new or useful improvement [thereof]” (emphasis added), and that this should extend to genetically-modified organisms.⁴⁴ The key distinction is that the invention in *Funk Bros.* merely assembled naturally-occurring organisms and sought to monopolize their natural functions, whereas the inventor's creative intervention was clear in *Chakrabarty* – an organism with a structure and resultant function not known in nature was recited – this distinction making it §101 eligible.⁴⁵

⁴³ See *id.* at 319-21 (Brennan, J., dissenting) (arguing that living organisms, with the exception of plant varieties, should not be patentable, modified or otherwise). The dissent infers that Congress had implicitly acknowledged that living organisms *per se* were excluded from the scope of §101 when they carved out special protections for plants in the 1930 Plant Patent Act, and again in the 1970 Plant Variety Protection Act. *Id.* at 319-20.

⁴⁴ See *Chakrabarty*, 447 U.S. at 310 (finding no explicit statutory bar to a genetically engineered organism, and recognizing a presumption that something manufactured must be eligible subject matter). In four rewrites of the patent law, this language remained essentially intact, with the 1952 amendment simply replacing the (by then archaic usage) “art” with “process”, but crucially retaining the “any.” *Id.* Indeed, the *Chakrabarty* court indicated that congressional intent in 1952 was to include “anything under the sun that is made by man.” *Id.* at 309. In contrast, the *Chakrabarty* dissent argued for narrower judgment, to preserve *Chakrabarty*'s monopoly on processes and methods of manufacture, but not the genetically modified organism itself, and to exclude living material from patentable subject matter, but leave *Chakrabarty* with reward for the product of his ingenuity. *Id.* at 318-22. Nevertheless, *Chakrabarty* has stood the test of time, and genetically modified organisms have remained patentable. See, e.g., Use of Genetically Modified Organisms to Generate Biomass Degrading Enzymes, U.S. Patent No. 8,318,436 (filed Oct. 7, 2011) (claiming novel, genetically-modified organisms in the *Chakrabarty* tradition).

⁴⁵ See *Funk Bros. Seed Co.*, 333 U.S. at 130 (finding that the structure and function of the organism claims were as found in nature); see also *Chakrabarty*, 447 U.S. at 310 (holding that the structure and function of the *Chakrabarty* microbes were not to be found in nature).

III. FACTS

The line of precedent from *Diehr* to *Chakrabarty* leads us to the recent rulings in *Mayo* and *Myriad*.⁴⁶ In *Mayo*, the patent claims involved administering a drug, measuring a metabolite of that drug, and then adjusting the dose based on the level of the metabolite.⁴⁷ At the heart of the invention in *Mayo* was the principle that too little metabolite indicates that the patient is receiving less drug than they need, while too much metabolite indicates that the drug dose is too high for the particular patient.⁴⁸ The *Mayo* Court noted that this principle – that the metabolism of the drug in patients is related to its efficacy – is a “natural law”, and thus is not patentable subject matter by itself.⁴⁹ The Court then moved to address the question of whether or not the claims added enough to the law of nature referenced to make the described process an eligible application of the natural phenomenon.⁵⁰ Justice Breyer restated the rule, “[i]f a law of nature is not patentable, then neither is a process reciting a law of nature, unless that process has additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself.”⁵¹

The court went on to analyze the “administering,” “measuring,” and “determining” steps recited in the claim, finding that “administering” merely referenced a pre-existing audience of doctors al-

⁴⁶ See *Mayo*, 132 S. Ct. at 1305 (holding that patents were invalid for attempting to monopolize a natural phenomenon); see also *Myriad*, 133 S. Ct. at 2107 (holding that isolated genes were naturally occurring and not patent eligible, but complementary DNA (cDNA) synthesized from the “edited” mRNA transcripts of those genes did not occur in nature, and therefore was patent eligible subject matter).

⁴⁷ See *Mayo*, 132 S. Ct. at 1296-97 (discussing how the action of the patient’s own body chemistry processes the drug to produce another molecule, the drug metabolite, the concentration of which is subject to measurement in the method described by the *Mayo* invention).

⁴⁸ See U.S. Patent No. 6,355,623 (filed Apr. 8, 1999) (claiming, *inter alia*, a method of measuring the serum level of thiopurine drug metabolite in a patient sera, and then adjusting the dose of the drug to improve therapy).

⁴⁹ See *Mayo*, 132 S. Ct. at 1298 (reasoning that the metabolism of the drug is something that already occurs naturally in patients, and will occur in any patient receiving this class of drug without any intervention by the claimed invention to precipitate the process).

⁵⁰ See *id.* at 1297 (analyzing claim elements that framed the use of the natural phenomenon recited in the claimed invention).

⁵¹ See *id.* (containing Justice Breyer’s rejection of artful drafting in attempting to monopolize natural phenomena).

ready using the drugs, noting that precedent warns that the “prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.”⁵² In addition, the measurement of a metabolite was “well-understood, routine, conventional activity,”⁵³ whereas the court in *Flook* had already established that “conventional or obvious pre-solution activity is not normally sufficient to transform an unpatentable law of nature into a patentable application.”⁵⁴ The dose-determining step simply, “tell[s] a doctor about the relevant natural laws, at most adding a suggestion that he should take those laws into account.”⁵⁵

Finally, the Court noted that in *Diehr* they had allowed “a new combination of steps . . . may be patentable even though all the constituents . . . were well known and in common use.”⁵⁶ The invention in *Mayo*, however, contained none of the inventive application of the natural law seen in *Diehr* but rather, even taken in combination, still failed to limit the claim such that “putting the formula to the side, there was no inventive concept.”⁵⁷ The implication of this ruling was that patents probably cannot be framed to exclude others from accessing or using a natural process and specifically, a patent on a diagnostic method could not be made sufficiently broad to exclude others from using alternate means to access, measure, or otherwise use the same underlying biological phenomena.⁵⁸

⁵² See *id.* (quoting *Bilski v. Kappos*, 561 U.S. 593, 610 (2010)) (illustrating scope limitations that fail to make natural phenomena patent eligible).

⁵³ See *id.* at 1298 (further highlighting that post-solution instructions as to how to apply a natural law do not render it patent eligible).

⁵⁴ See *id.* (quoting *Flook*, 437 U.S. at 590) (indicating that the level of transformation achieved by framing the natural phenomenon with extra-solution activity remains insufficient to make a naturally-occurring phenomenon patentable).

⁵⁵ See *Mayo*, 132 S. Ct. at 1297 (dismissing the relevance to §101 eligibility of the “determining” step in deciding the level of drugs to administer for optimal results).

⁵⁶ See *id.* at 1298 (citing *Diehr*, 450 U.S. at 188) (suggesting that the court may uphold a patent on a process even where the individual steps are already known).

⁵⁷ See *id.* at 1299 (citing *Flook*, 437 U.S. at 594) (pointing to lack of inventive concept in the claimed process in *Mayo*); see also, *Diehr*, 450 U.S. at 192 (representing the touchstone precedent of a case where inventiveness made a law of nature patentable in a narrow application).

⁵⁸ See *Mayo*, 132 S. Ct. at 1301 (noting that “[t]his Court has repeatedly emphasized a concern that patent law not inhibit future discovery by improperly tying up the use of laws of nature and the like”). Unlike *Diehr*, which did not seek ownership of the natural principle (the Arrhenius equation), but simply sought protection of a narrow, new, inventive and useful application of it, the natural principle in

Public policy, public interest, and the patenting of components of a living system reached a significant new intersection in *Myriad*, concerning as it did a medical advance that impacts the population as whole.⁵⁹ *Myriad*'s invention was based on the discovery of two genes, now designated "breast cancer, early onset" (BRCA1 and BRCA2).⁶⁰ By controlling the right to make and use DNA molecules that characterize the normal and mutated states of these genes in patients, *Myriad* staked out a monopoly over genetic testing services screening these critical breast cancer genes.⁶¹

In reviewing the challenged patent claims, the Supreme Court found that claims written to (naturally-occurring) genomic DNA that

Mayo (the relationship between metabolite level and effective dose) would have been entirely foreclosed to others if the patent in *Mayo* was allowed to stand. *See id.* at 1301; *Diehr*, 450 U.S. at 185. The additional elements of the claim lacked any limitation outlining a particularly inventive use of the natural principle that would still leave the natural principle itself free to be utilized by others in other potentially novel, inventive, and perhaps unanticipated ways. *See Mayo*, 132 S. Ct. at 1301-02.

⁵⁹ *See Myriad*, 133 S. Ct. at 2112 (deciding the patent eligibility of genetic markers for predisposition to breast and ovarian cancer, also linked to prostate cancer and possibly to pancreatic cancers); *see also BRCA1 and BRCA2: Cancer Risk and Genetic Testing*, NAT'L CANCER INST. (Apr. 2015), archived at <http://perma.cc/KQ24-AMLH> (providing a lay primer on BRCA testing and which types of common cancers are or may be associated with variants of the BRCA genes).

⁶⁰ *See BRCA1*, NAT'L CTR. FOR BIOTECH. INFO. (2016), archived at <https://perma.cc/JE8Z-QL9P> (providing an exemplary sequence of the human BRCA1 gene); *see also BRCA2*, NAT'L CTR. FOR BIOTECH. INFO. (2016), archived at <https://perma.cc/X23C-HS9L> (providing an exemplary sequence of the human BRCA2 gene). The functional BRCA genes produce a protein that functions as a tumor suppressor. *See also* Mary Ellen Moynahan, *The Cancer Connection: BRCA1 and BRCA2 Tumor Suppression in Mice and Humans*, 21 ONCOGENE 8994, 8994 (2002) (illustrating how mutations in either gene are known to be associated with significantly elevated risk of developing breast and ovarian cancer); *Myriad*, 133 S. Ct. at 2112 (describing that screening for these mutations identifies patients at such risk, and thus permits risk-focused interventions such as elective mastectomy or, less radically, more frequent and extensive early detection methods); *see, e.g.*, Robert Klitzman & Wendy Chung, *The Process of Deciding About Prophylactic Surgery for Breast and Ovarian Cancer: Patient Questions, Uncertainties, and Communication*, 152A(1) AM. J MED GENETICS ACAD. 52-66 (2010) (discussing the decision to elect prophylactic surgery).

⁶¹ *See e.g.*, *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d 755, 765 (Fed. Cir. 2014) (concluding litigation by patent holders and licensees including *Myriad Genetics* who sued *Ambry Genetics Corporation*, one of several competitors who brought medical kits testing for BRCA mutations to the market).

has simply been “isolated” were ineligible subject matter, but that claims written to cDNA⁶² remain eligible subject matter.⁶³ In so doing, the Court emphasized that in the case of cDNA, they felt that the removal of introns created something “not found in nature,” “except insofar as very short series of [genomic] DNA may have no intervening introns to remove [so that]... a short strand of cDNA may be indistinguishable from natural DNA.”⁶⁴ In addition, the Court further circumscribed their ruling by explicitly noting that they “express no opinion whether cDNA satisfies... §§ 102, 103 and 112,”⁶⁵ and by stressing that method and application-based claims directed at natural DNA were not foreclosed.⁶⁶ Finally, the Court noted that the issue of whether *modified* DNA sequences as patentable subject matter under §101 “presents a different inquiry [about which]... we express no opinion... we merely hold that genes *and the information they encode* are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material” (emphasis added).⁶⁷

⁶² See TOM STRACHAN & ANDREW P. READ, HUMAN MOLECULAR GENETICS 72 (2d ed. 1999) (discussing fundamentals of DNA technology and the importance of DNA cloning). Although DNA and RNA molecules do have other functional modalities, in most organisms, genomic DNA in a cell’s chromosomes is transcribed to make messenger RNA (mRNA). *Id.* The transcript is then ‘edited’ to remove sections of sequence known as “introns,” and the remaining sequence (“exons” only), is translated into a sequence of amino acids to form the basis of a specific protein. *Id.* Some enzymes, principally found in certain viruses (retroviruses), have the ability to translate an mRNA back into DNA – this is called complementary DNA or cDNA. Molecular biologists often use such enzymes to make DNA copies of the DNA exons, *i.e.* the sequence that actually codes for protein amino acid sequence. *Id.*

⁶³ See *Myriad*, 133 S. Ct., at 2117-19 (distinguishing as ineligible molecules indistinguishable from those found in nature from those containing the same genetic information but in a format that does not normally occur naturally).

⁶⁴ See *id.* at 2119 (acknowledging that the cDNA distinction may be hard to support in all cases).

⁶⁵ See *id.* at 2119 n.9 (specifically limiting the scope of the holding to a §101 eligibility determination).

⁶⁶ See *id.* at 2119-20 (noting that the methods in the *Myriad* patent were purely conventional, and could not in this case, be patented). The Court also cited the lower court dicta of Judge Bryson, noting that “[m]any of [Myriad’s] unchallenged claims are limited to such applications.” *Id.* at 2107 (citing *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1349 (Fed. Cir. 2012)).

⁶⁷ See *id.* at 2120 (including the addition of the intriguing phrase ‘and the information they encode’, cementing the idea that it is the information in the DNA that is the central question). The phrasing is makes clear that the naturally-occurring

In upholding Myriad's patents, at least one Justice in the Federal Circuit had allowed that her decision on gene patenting was influenced by deference to the established practice at the USPTO of granting gene-based patents and the reliance interests of patent holders.⁶⁸ The Supreme Court explicitly dismissed this "reliance" argument, including in its rationale a lack of any specific legislation or other indication of Congressional intent that gene patenting was explicitly sanctioned, and the Government's *amici* briefs arguing *against* the patenting of "isolated DNA."⁶⁹ As such, although in the eyes of the Court the *Myriad* judgment was merely the logical extension of the long-established principles enshrined in *Flook* and *Chakrabarty*, it represented some disruption of the contemporary policy of the USPTO on the matter of gene patenting, leading the Deputy Commissioner for Patent Examination Policy, Andrew Hirshfeld, to issue a new guidance to the patent-examining corps which aimed to synthesize the impact of *Mayo* and *Myriad* on §101 determinations.⁷⁰

protein, the mRNA transcript used to build it, and the genomic sequence from which the mRNA is transcribed, are all patent ineligible. *Id.* It remains hard to reconcile this statement of principle with the actual judgment that cDNA remains eligible under §101, as cDNA contains nothing more than information encoded in the gene. See STRACHAN & READ, *supra* note 62, at 72 (illustrating the fundamentals of nucleic acid biology, as well as DNA cloning technology).

⁶⁸ See *Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1332 (Fed. Cir. 2012), *aff'd in part, rev'd in part sub nom.* *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2110 (2013) (finding that "isolated DNA molecules are patent eligible"). The court noted in conclusion that "our decision that isolated DNA molecules are patent eligible comports with the longstanding practice of the PTO and the courts. The Supreme Court has repeatedly stated that changes to longstanding practice should come from Congress, not the courts." *Id.*

⁶⁹ See *Myriad*, 133 S. Ct. at 2118-20 (holding that, although some granted patents may have effectively allowed "inventors" to patent genes that they had simply found and described, the government's actions were not sufficiently coherent to justify a deference argument, particularly in the light of the *amici* briefs that appeared to argue the alternate position).

⁷⁰ See *March 2014 Guidance*, *supra* note 2 (instructing patent examiners to follow new procedures in the light of perceived changes to the law of subject matter eligibility following *Myriad* and *Mayo*).

A. The USPTO March 2014 Guidance

Hirshfeld's March 2014 Guidance purported to explain to patent examiners how they should utilize the rulings provided in *Mayo* and *Myriad* to build on the established precedent of *Chakrabarty* to make §101 determinations for claims "reciting" materials found in nature.⁷¹ The March 2014 Guidance contained two substantive sections: Section II outlining a complex, multi-factor test for "significantly different," and Section III outlining and discussing several examples that were offered as models of how the included flow chart and the "significantly different" test outlined, were to be applied.⁷² The USPTO then actively solicited comments on the Guidance and received a large number of submissions from commercial entities, academic institutions, non-profits, law firms, professional bodies, and private individuals.⁷³ The comments were generally negative, drawing attention to inconsistency and lack of clarity, as well as the USPTO's apparent departure from the actual content of the *Myriad* and *Mayo* rulings.⁷⁴

The resulting lack of clarity in domestic and international patent practice in the area of biotechnology intellectual property made it inevitable that this March 2014 Guidance would have to be withdrawn or significantly amended.⁷⁵ Although already superseded, the

⁷¹ See *March 2014 Guidance*, *supra* note 2 (expanding the scope of the instructions to encompass the overly broad scope of all claims reciting or involving natural phenomena, regardless of whether they fell within the scope of questions raised in *Mayo* or *Myriad*).

⁷² See *March 2014 Guidance*, *supra* note 2, at 3 (testing for "significantly different" and setting forth examples). In addition, the Guidance included a preliminary section containing a flow chart that directs examiners to conduct an analysis for significant difference from materials found in nature for every claim that does *or may* recite or involve material found in nature, and a final section providing a form paragraph for claim rejection. *Id.* at 2, 18.

⁷³ See *Public Comments on Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products*, USPTO, archived at <http://perma.cc/UY54-RZSW> [hereinafter *Public Comments on March 2014 Guidance*] (providing a listing of, and links to, all input received by the USPTO in response to its request for comments on the *March 2014 Guidance*).

⁷⁴ See *id.* (reporting feedback received on the March 2014 Guidance).

⁷⁵ See *December 2014 Guidance*, *supra* note 2, at 74619 (noting the change in the guidance recommendations with the issue of revised guidance issued in December 2014). In fact, the *March 2014 Guidance* was superseded entirely by the *December 2014 Guidance*, thus any rejections under §101 encountered between March and

issues raised by the published comments on the March 2014 Guidance both suggest that it is risky to attempt to use an analytical tool synthesizing the logic of the Supreme Court unless the Court itself has explicitly created such a tool, and also illustrate the underlying concerns of the various parties.⁷⁶ How these concerns have been addressed in the subsequently-issued December 2014 Guidance says much about §101 analyses for 2015 and beyond, and also draws attention to the ongoing uncertainty and inefficiency in the operation of patent jurisprudence in emerging technology applications in the U.S.-uncertainty that has not been diminished by the USPTO's efforts in this area.⁷⁷

Understanding the flaws in the March 2014 Guidance best proceeds from first understanding what it attempted to do.⁷⁸ The document, as issued by the USPTO, required Examiners to reject any claim that involves or recites a judicial exception to §101 (including a law of nature, natural phenomena or natural product) that, as a whole, fails to recite something “**significantly different**” from the exception.⁷⁹ The March 2014 Guidance required a 12-factor test for “significantly different” and for the “natural” exceptions.⁸⁰ The factors, six weighing towards eligibility and six weighing against, were principally constructed in pairs.⁸¹ However, not all factor pairs were log-

December 2014 should be reviewed against the shifting ground in the guidance to examiners. See *December 2014 Guidance*, *supra* note 2.

⁷⁶ See *Public Comments on March 2014 Guidance*, *supra* note 73 (indexing the predominantly critical commentary received by USPTO concerning the *March 2014 Guidance*).

⁷⁷ See International Bioindustry Associations, Comment Letter on the USPTO Interim Guidance on Patent Subject Matter Eligibility (Mar. 16, 2015), *archived at* <https://perma.cc/Z3LP-Y9AV> [hereinafter International Bioindustry Associations, March 2015] (expressing concerns, *inter alia*, over the stability of the biotechnology patent system in the US).

⁷⁸ See *March 2014 Guidance*, *supra* note 2 (explaining, in Deputy Commissioner Hirshfeld's cover letter, the purpose of the guidance as effecting a procedure to address recent court decisions related to subject matter eligibility).

⁷⁹ See *March 2014 Guidance*, *supra* note 2, at 2-3 (advancing the “significant difference” criterion, a test of the PTO's own devising).

⁸⁰ See *March 2014 Guidance*, *supra* note 2, at 3-5 (outlining the 12-factor test, while mandating the process prescribed in the MPEP at §2106(II) for “abstract idea” exceptions the “significantly different” test was directed at §101 judicial exceptions arising from nature).

⁸¹ See *March 2014 Guidance*, *supra* note 2, at 4 (instructing that **Factors a** and **g** are two sides of the same coin; after analysis, the apparent claim to the exception is

ically exclusive, and overall there was no guidance as how the 12-factors should be used, scored, weighted or decided in the event that they were numerically split.⁸² While the USPTO surely intended their hypothetical examples provide the further guidance that would be required to fathom the operation of the “12-factor test,” in actuality commentators found little that could usefully or realistically illuminate how the “12-factors” might be applied.⁸³

either actually “markedly different in *structure*” (fulfilling **Factor a**) or “**not** markedly different in *structure*” (fulfilling **Factor g** (emphasis added)).

⁸² See *March 2014 Guidance*, *supra* note 2, at 4 (showing that Factors, **b** vs. **h** and, redundantly factor **i**, concerning the degree to which a natural phenomenon is foreclosed, do not comprise such simple binary exclusive provisions). Under the *March 2014 Guidance*, to fulfill Factor **b** the claim is narrowed so that “others are not substantially foreclosed from using the judicial exception” while to meet Factor **h** a claim is so general that substantially all practical applications are covered and, somewhat redundantly, Factor **i** weighs against eligibility where the elements/steps recited in addition to the exception “must be used/taken by others to apply the judicial exception.” *Id.* Thus, where a claim is found to preclude *many but not all* applications (however this was to be quantified the USPTO never explained) then none of the conditions for Factors **b**, **h**, or **i** would be satisfied. *Id.* Factors **c** vs. **k** and **d** vs. **l** respectively, returned to the pattern of more or less exclusive inverses – weighing in favor of eligibility are claims that add elements or steps to the judicial exception. *Id.* Factors **c** and **k** function essentially as logical inverses, in that claims are that are more than “nominally, insignificantly or tangentially related” satisfied Factor **c**, weighing in favor of §101 eligibility, while claims where the additional steps or elements are “insignificant extra-solution activity...merely appended to the judicial exception” satisfied Factor **k**, weighing against eligibility. *Id.* The factors proceed in this vein. This author believes that all these issues could have been captured more succinctly. For example, the same 12-factor material could have been expressed as:

A claim is not drawn to eligible subject matter if it recites something that is not structurally different from the exception, where all use of the exception is foreclosed to others, and where the applicant fails to add elements and steps that are both relevant to the exception and not nominal, tangential, well-understood, conventional or appended extra-solution activities.

Id. While such a more compact summary still leaves a lot of open questions, the 12-factor formulation did nothing to aid the patent drafter or examiner to answer such questions; it simply disguised them under a veneer of formalism. *Id.*

⁸³ Cf. Suzannah K. Sundby, Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 8 (Jul. 31, 2014), *archived at* <https://perma.cc/7VXP-TDR9> [hereinafter July 31 Sundby Letter] (writing “Instead, in the Supreme Court decisions where the Court has found the claims being directed to patent eligible subject matter, all that was required was one factor that indicated the claim was directed to more than the judicial exception itself”). *But*

B. March 2014 Guidance Hypotheticals

The first example, Example A, did nothing more but reprise the *Chakrabarty* issues.⁸⁴ Example B again showed that a naturally-occurring, organic molecule is not eligible, but a simple modification is sufficient to meet §101 requirements.⁸⁵ Where the natural molecule itself is used in a novel clinical indication in a specific dose and duration, then USPTO used its 12-factor test to argue that such a claim is drawn to eligible subject matter.⁸⁶

see American Association of Retired Persons (AARP), Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 3 (July 31, 2014), *archived at* <https://perma.cc/TSH2-Y9PT> [hereinafter AARP Comment on March 2014 Guidance] (suggesting that “if any one of the listed factors weighing against eligibility in the *March 2014 Guidance* applies, the claim should be held invalid”). The Comments on the March 2014 Guidance thus illustrate how unhelpful this “weighting test” was, as some argued that a single positive factor was dispositive as to eligibility, while others argued that a single negative factor required a finding of ineligibility.

⁸⁴ *See March 2014 Guidance, supra* note 2, at 5-7 (illustrating, in Claim 1 of Example A, that a naturally-occurring plasmid is ineligible because it is not significantly different from something found in nature, thus fulfilling factor **g** and failing factor **a**, while all other factors can be ignored because no elements are recited in addition to the naturally occurring plasmid) (emphasis added). On the other hand, in Example A, Claim 2, a bacterium with two added plasmids where bacteria in nature are known to have one plasmid, is said to comprise eligible subject matter; Factor **a** is fulfilled, Factor **g** fails – again, all other factors need not be considered because the claim recites only the two plasmid bacterium (emphasis added). *Id.* This is merely an elaborate formalism for repeating that the *Chakrabarty* Court found his genetically-modified bacteria eligible because it was structurally distinct from anything found in nature. *See Chakrabarty*, 447 U.S. at 310.

⁸⁵ *See March 2014 Guidance, supra* note 2, at 7-8 (indicating that methylation at carbon-5 of the natural molecule makes it eligible subject matter because Factor **a** is satisfied and Factor **g** is not, all other factors again irrelevant following the argument above for Example A) (emphasis added).

⁸⁶ *See March 2014 Guidance, supra* note 2, at 8-11 (explaining that Factors **a** and **g** are “not relevant” to a process claim, and Factors **b**, **c**, **d** and **f** weighing in favor of eligibility are satisfied because the dose and timing steps (1) narrow the claim sufficiently, (2) add steps meaningfully related to the natural molecule that are not well-known, conventional or routine, and (3) are more than general instructions to use the molecule) (emphasis added). Although *pro* eligibility Factor **e** is not met per the USPTO’s example analysis, none of the factors *against* eligibility are fulfilled, so “when relevant factors are analyzed, they weight towards significant difference.” *Id.* It could, however, be argued that Factor **e** is actually fulfilled here, although there is no machine or transformation, the use of the natural molecule to treat a specific disease with a specific dose regimen appears to “integrate the [natu-

Example E⁸⁷ of the March 2014 Guidance covered a DNA primer pair (Claim 1), and described a routine *Taq*-based PCR⁸⁸ ap-

ral molecule] into a particular practical application.” *Id.* at 4. Nevertheless, it easy to see how the weighting was done here. *Id.* Even under the USPTO’s analysis, for the 6 positive factors, 4 are fulfilled, one is not, and one is irrelevant, while for the 6 negative factors, one is irrelevant and 5 are not fulfilled. *Id.* While one might count this as 9-to-1 in favor, with 2 neutral, the USPTO does not actually provide a mechanism for scoring that might have been used for more equivocal cases, except where they suggest that the Factor **a** vs. **g** analysis (Example A and B) preempts the other factors. *Id.* Again, the 12-factor test contrives formalism here, but this example is nothing more than a hypothetical depicting the reverse-case of the *Mayo* ruling, or *Diehr* applied to a pharmaceutical molecule. *See Mayo*, 132 S. Ct. at 1305; *Diehr*, 450 U.S. at 191-93. Those precedents don’t call for anything like this 12-factor analysis, and in turn the 12-factor analysis, despite its elaborate structure, added nothing but confusion. *See Mayo*, 132 S. Ct. at 1297-1302; *Diehr*, 450 U.S. at 181-89.

⁸⁷ *See March 2014 Guidance, supra* note 2, at 9-10 (highlighting a non-biotechnology Example). Example C is not analyzed in full here as it concerns a firework, which is outside the biomedical thrust of this note. *Id.* Nevertheless, the USPTO analysis managed to find the fueling chemicals plus cardboard and plastic container eligible subject matter, although remarkably it seemed closer than one might expect, with only 7 of the 12 factors weighing in favor and 5 against. *Id.* at 10. However, to reach this tortured position, the USPTO was required to conclude that gunpowder was “not markedly different from what exists in nature” because its components, sulfur, carbon and potassium nitrate, occur in nature. *Id.* Thankfully, the USPTO was able to dig out of their 12-factor hole by finding the plastic, card, and fusing sufficiently particular and applied to warrant patentability nevertheless, although the analysis required seems unnecessarily onerous for such an obvious outcome. *Id.* Example D was a *Funk Bros*-type problem in which naturally-occurring bacteria are mixed together in a useful way but remain nevertheless ineligible. *Id.* at 10-11. Paralleling the analysis of the plasmid in Claim 1 of Example A, none of the bacteria are different from nature, so Factor **a** fails while **g** is fulfilled, and the ten other factors are “irrelevant.” *Id.* While this example was obviously and explicitly intended to recapitulate the *Funk Bros*. precedent as revisited and confirmed in *Myriad*, it is instructive to examine why Example A Claim 2 (natural occurring plasmid added to a naturally-occurring bacteria) is eligible, while Example D (a plurality of naturally occurring bacteria combined) is not. *See id.*; *Myriad*, 133 S. Ct. at 2117. Facially, the difference is slight—in the latter, natural occurring articles are placed side-by-side, while in the former, one naturally-occurring article is placed inside another naturally-occurring article. *See March 2014 Guidance, supra* note 2, at 5, 10. Somehow the action of putting a plasmid into a bacterium is different from putting it alongside the bacteria—even though, in nature, such plasmids are already known to occur inside bacteria, and in fact have no substantive natural existence in anything other than an intracellular context. *See* Anders Norman, Lars H. Hansen, & Søren J. Sørensen, *Conjugative Plasmids: Vessels of the Communal Gene Pool*, 364 PHIL. TRANSACTIONS ROYAL SOC’Y OF LONDON B BIOLOGICAL SCI. 2275, 2275 (2009) (discussing the nature of plasmids

plication using the primer pair (Claim 2).⁸⁹ Following the analyses above, the primer pair was found ineligible subject matter because primers are short stretches of DNA that, although isolated, occur in nature.⁹⁰ On the other hand, Claim 2 is found eligible, even though the *Taq* PCR is routine and well understood, and there is no machine or transformation, the process is meaningfully related to the solution and does not substantively foreclose other uses of the primers.⁹¹

as mobile genetic elements). The difference is that intervention is necessary to insert the plasmid, while nature herself might easily combine the bacteria, but the USPTO fails to distill this point. See *March 2014 Guidance*, *supra* note 2.

⁸⁸ See RK Saiki et al., *Primer-directed Enzymatic Amplification of DNA with a Thermostable DNA Polymerase*, 239 (4839) *SCIENCE* 487-91 (1988) (describing the DNA amplification method now known as the polymerase chain reaction or “PCR”). *Taq* is one of many naturally occurring polymerases and is routinely used in DNA amplifications by PCR because it is thermostable and continues functioning through many thermal cycles. *Id.* Primers themselves are pairs of DNA molecules which are specific for a DNA sequence targeted for amplification, themselves about 15–25 nucleotides long, such primers are required to target selective amplification by PCR. *Id.* After the primers are added to denatured template DNA, they bind specifically to complementary DNA sequences at each end of the target site. *Id.* DNA polymerase such as *Taq* then extends the primers to synthesize new copies of the DNA strands, which are complementary to the individual DNA strands of the target DNA segment. See *STRACHAN & READ*, *supra* note 62, at 19 (discussing basic features of PCR).

⁸⁹ See *March 2014 Guidance*, *supra* note 2, at 11-12 (correctly anticipating the decision of the Court of Appeals for the Federal Circuit in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 760, which indicates that the “primers before us are not distinguishable from the isolated DNA found patent ineligible in *Myriad*... [and]... short strands identical to those found in nature are not patent eligible”).

⁹⁰ See *March 2014 Guidance*, *supra* note 2, at 12 (indicating that, lacking any claim limitations, primers are ineligible subject matter).

⁹¹ See *March 2014 Guidance*, *supra* note 2, at 12-13 (noting, *inter alia*, that a process that used the primers without *Taq* would not be foreclosed by this type of claim, which seems to gut the protection that this type of claim could afford, as the sequence data in the useful primers identified by the inventors remains unprotected from the trivial design around once the “others not substantially foreclosed” condition is met). *Taq* polymerase—a DNA copying enzyme that is stable at high temperatures derived from *Thermus aquaticus*, a thermophilic bacteria—is just one of many thermostable DNA polymerase enzymes. See, e.g., Kelly S. Lundberg et al., *High-fidelity Amplification Using a Thermostable DNA Polymerase Isolated from Pyrococcus furiosus*, 108 *GENE* 1, 1 (1991) (introducing a novel DNA polymerase). Numerous other enzymes could be used to complete a PCR amplification, and several are routinely and commercially available. *Id.* Nevertheless, in tightly regulated markets, such as pharmaceuticals or medical diagnostics, a narrowly-framed patent based on a specific use or application of naturally-occurring DNA sequence

Example F in the March 2014 Guidance, “Process Claim Involving A Natural Principle and Reciting Natural Products,” was a *Mayo*-like scenario where a diagnostic test is used to detect a misfolded protein in patient blood indicating a disease diagnosis.⁹² However, the method was particularly recited to include a specific reagent and method.⁹³ Although the misfolded protein itself is naturally occurring, because others are not prevented from using the protein to diagnose the disease, the USPTO found that the claim would be drawn to patentable subject matter.⁹⁴

might suffice to exclude competitors from marketing the type of exact copy of a drug, device, or test that could capitalize on the development and regulatory approval pathway blazed by the original product. See Jeff Safran, *Genentech, Inc. v. Chiron Corp.*, 220 F.3d 1345 (Fed. Cir. 2000) *Should A Patent for A Genetic Sequence Cover Its Resultant Protein?*, 21 TEMP. ENVTL. L. & TECH. J. 69, 91 (2002) (explaining the benefits of narrowly-described patents as reaching beyond market competition). An optimally framed claim disclosing use of a DNA sequence would thus be carefully written to retain sufficient specificity to survive §101 eligibility analyses, but yet have enough breadth to prevent a competitor from marketing a non-infringing invention sufficiently similar to take advantage of any short-cut along the regulatory path that might be created by simply following the innovator product as a “generic” copy for purposes of regulatory, clinical, or technical acceptance. See Joanna M. Grigas, Note, *Defining Patent Eligibility by Extrapolating the Judicial Outlook of Software Onto Biotechnology Patents*, 18 SUFFOLK J. TRIAL & APP. ADVOC. 221, 241-42 (2013) (discussing the consequences of too many parties possessing ownership rights).

⁹² See *March 2014 Guidance*, *supra* note 2, at 13-14 (stating the hypothetical claim which involves “a method for determining whether a human patient has degenerative disease X”).

⁹³ See *March 2014 Guidance*, *supra* note 2, at 13-14 (analyzing the hypothetical wherein the method described utilizes an antibody as the detecting reagent and flow-cytometry as the specific method). USPTO declared that the reagent antibody was not “naturally occurring”, although they failed explore how that might be proven conclusively, or exactly how that might be relevant in the analysis. *Id.* at 14. The question of when and why antibodies are natural remains an important question and is revisited below.

⁹⁴ See *March 2014 Guidance*, *supra* note 2, at 14 (suggesting that, by using an *alternate* antibody, other than the one specified in the in the flow cytometry claim, or even by using the same antibody in an *alternate* platform (e.g. ELISA), the judicial exception itself remains available, while the specific invention is monopolized to the patentee). Again, it is unclear why a 12-Factor test is required or helpful here, and it is hard to understand what the USPTO felt it was illustrating in the example beyond the presentation of another example of applying *Mayo*'s logic — that a biological phenomenon, even one usefully related to diagnosis and treatment of disease, may not itself be patented except insofar as a narrowly framed utilization of the phenomenon is circumscribed by the claimed invention. See *Mayo*, 132 S. Ct. at 1297-99.

Example G, “a process claim involving a natural principle” was more intriguing, in that the USPTO found ineligible a method to treat mood disorders by exposure to sunlight, and similarly rejects an analogous claim that substitutes synthetic white light for sunlight.⁹⁵ Following the USPTO reasoning, the additional steps limited the claim and integrated the natural phenomena in a more than insignificant and tangential way, but the claim remains a general instruction to apply the phenomena, there is no machine or transformation, and the method is well understood, purely conventional, and routine.⁹⁶ Accepting the USPTO’s analysis here means that relevant factors favoring eligibility were outnumbered 4 to 6 (two of the twelve factors were held “not relevant”).⁹⁷ But, this hinges on the analysis of factors **f** and **j**, which in turn, under the hypothetical proposed, itself hinges on the predicate that “the step of exposing patients to white light is well-understood, purely conventional.....”⁹⁸ Thus, when all is analyzed, it seemed that the difference here between eligible an ineligible subject matter is simply what is and is not “well-understood, purely conventional and routine in the art,” which seems curiously akin to a §103 obviousness analysis.⁹⁹ The USPTO illustrated the alternate by examining a third hypothetical claim where the light is filtered, and exposure is at specific distances and for specific times.¹⁰⁰ The twelve-factor analysis unfolds similarly except that, because the time and distance limitations are not “well-understood, purely conventional and routine in the art,” and now provide a “specific practical application,” the claim thus meets the USPTO’s §101 requirements under their March 2014 guidance.¹⁰¹

⁹⁵ See *March 2014 Guidance*, *supra* note 2, at 15 (setting out an additional hypothetical invention and claims).

⁹⁶ See *March 2014 Guidance*, *supra* note 2, at 15-17 (providing USPTO analysis of the first two claims under the 12-Factor test).

⁹⁷ See *March 2014 Guidance*, *supra* note 2, at 15-16 (providing USPTO analysis of the first two claims by applying the 12-Factor test).

⁹⁸ See *March 2014 Guidance*, *supra* note 2, at 15-16 (providing USPTO analysis of the first two claims under the 12-Factor test).

⁹⁹ See *March 2014 Guidance*, *supra* note 2, at 16-17 (giving USPTO’s conclusions as to ineligibility of the first two hypothetical claims).

¹⁰⁰ See *March 2014 Guidance*, *supra* note 2, at 15 (setting out an additional, more specific claim).

¹⁰¹ See *March 2014 Guidance*, *supra* note 2, at 17 (giving USPTO’s conclusions as to eligibility of the third hypothetical claim). The USPTO’s illustrative examples also included a final example, Example H, “Process Claim Reciting an Abstract Idea and a Natural Product,” mirroring Claim 1 of Myriad’s ‘857 patent, reciting a

C. The Aftermath of the March 2014 Guidance

It was unfortunate for the USPTO that just as they refined and published their Guidance concerning the *Mayo* and *Myriad* rulings, the Supreme Court itself was deciding *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*,¹⁰² which provided a different, but obviously more authoritative interpretation of *Mayo*.¹⁰³ As 2014 drew to a close, two significant developments seem to have drawn a line under the uncertainty: the *Myriad* litigation itself appeared to have reached its final conclusion,¹⁰⁴ while the USPTO again attempted a synthesis of subject matter eligibility by issuing the December 2014 Guidance.¹⁰⁵

The January 2015 developments in the BRCA litigation represented the end-game in the court battle that led up to the Supreme Court's decision in *Myriad* and the fallout from that decision, at least insofar as it applies to the BRCA case itself.¹⁰⁶ While the January

process where a suspected allele is compared to the wild-type (i.e. typical) BRCA2 nucleotide sequence in order to identify a mutant. *Id.* at 18. Because this claim recited the application of an abstract idea (to a natural product), the procedure proposed by the USPTO in the *March 2014 Guidance* mandated the MPEP §2016(II) rules and found the claim drawn to ineligible subject matter (an abstract idea, i.e. "comparison") without reaching the question of the patentability of the BRCA2 sequence. *Id.*

¹⁰² See *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2347 (2014) (clarifying the application of *Mayo*).

¹⁰³ See *March 2014 Guidance*, *supra* note 2; see also *Alice*, 134 S. Ct. at 2347.

While the USPTO was preparing their March 2014 Guidance in the early part of 2014 for publication on Mar. 4, 2014, *Alice* was argued in the Supreme Court on Mar. 31, 2014, and the decision published on Jun. 19, 2014. *Id.*

¹⁰⁴ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 765 (deciding the fate of the remaining claims of the Myriad BRCA patents that were not directly invalidated by *Myriad*).

¹⁰⁵ See *December 2014 Guidance*, *supra* note 2 (replacing the nine-month-old March 2014 Guidance with a significantly reworked approach).

¹⁰⁶ See *Myriad Settles BRCA Testing Patent Fray with Pathway Genomics, Invitae, GENOMEWEB* (Jan. 2015), archived at <https://perma.cc/J6UZ-5495> (demonstrating that, following the *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation* decision, Myriad started to settle litigation with other parties who had marketed BRCA-based testing). The limited nature of the decision (only specimen claims from the '282 and '473 patent were litigated which, as it turned out, did not address all the issues), plus narrowing language in the judgment (specifically relevant here "it is important to note what is not implicated...there are no method claims before this Court") left the door open to a continued assertion of patent rights over subject matter enabling BRCA testing. See *Myriad*, 133 S. Ct. at 2113, 2119 (invalidating Myriad's gene-sequence-based claims, but not reaching the re-

2015 concession by *Myriad* to its competitors in the BRCA market represented the formal cessation of hostilities, the conflict was essentially decided in December 2014 by the ruling in *Ambry*.¹⁰⁷ And, while at least one commentator has noted that the issue remains alive because the court in *Ambry* left open the question of the eligibility of gene comparison claims limited to genetic differences individually identified and enumerated in the specification,¹⁰⁸ with the remaining suits settled, further litigation seems unlikely, and it is thus now settled that patents may not monopolize naturally-occurring genetic variants.¹⁰⁹

This brings us to the other event in the last days of 2014 that claimed to consolidate the refreshed approach to §101: the publication of the USPTO's December 2014 Interim Guidance on Patent Subject Matter Eligibility.¹¹⁰ Unlike the USPTO's March 2014 Guidance, which was addressed as a memo to the "Patent Examining Corps," the December document was issued as a more formal (albeit "interim") document that took some pains to emphasize that it did not constitute substantive rule making, and was simply the USPTO's attempt to interpret and illustrate the impact of the *Mayo*, *Myriad* and

lated method claims). *Myriad* pushed at that open door, filing suit against a raft of competitors who were bringing their own BRCA-based tests for genetic propensity to breast cancer to the market in the wake of the Supreme Court ruling in *Myriad*. See, e.g., *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 760 (holding that comparison of naturally-occurring genetic variants to a wild type sequence may not be generally monopolized as a patented method).

¹⁰⁷ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 765 (refuting the last of *Myriad*'s arguments supporting its remaining BRCA claims, and providing a *de facto* end to the BRCA patent litigation).

¹⁰⁸ See John A. Bauer & Shovon Ashraf, *Federal Circuit Court of Appeals Delivers Another Decision on Patentability of Myriad Patents*, THE NAT'L L. REV. (Jan. 2015), archived at perma.cc/9C85-GWDG (dissecting possible gene-patenting loopholes in the *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation* holding).

¹⁰⁹ See *Myriad Settles BRCA Testing Patent Fray with Pathway Genomics, Invitae*, *supra* note 106 (announcing settlement of BRCA-related disputes in the wake of the *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation* ruling).

¹¹⁰ See *December 2014 Guidance*, *supra* note 2, at 74619 (acknowledging that the USPTO's understanding of subject matter eligibility under 35 U.S. §101 had evolved as a result of Supreme Court decisions made throughout 2014, as well as the comments solicited and considered with respect to the previous guidance documents).

Alice rulings.¹¹¹ However, the December 2014 Guidance serves to amend the MPEP,¹¹² and although the USPTO also emphasizes that the MPEP has no independent legal standing beyond the statutes and regulations on which it is based, it will nevertheless be the starting point from which examination and prosecution in the United States will proceed for practical purposes.¹¹³

The upheaval in subject matter eligibility is now over (for the moment), and the new “rules” are remarkably simple when digested to their basic principles.¹¹⁴ It is further suggested that, at least as far as this analysis of the implications of the “new” eligibility analysis impact the life sciences, less is definitely more.¹¹⁵ Both the Supreme Court and the USPTO are ill-served by elaborate analogies and explanations. Subject matter eligibility, like so much of the broader patentability issue, is a profoundly fact-based inquiry, and so ineluctably tied up with novel facts in particular, that it resists all but the most abstract of generalizations.¹¹⁶ In condensing and compressing an eligibility analysis that works as broadly as possible, the Supreme Court has done the best that can be expected from a panel lacking a

¹¹¹ See *December 2014 Guidance*, *supra* note 2, at 74619 (indicating that “[t]his Interim Eligibility Guidance has been developed as a matter of Internal Office management and is not intended to create any right or benefit, substantive or procedural, enforceable . . . against the Office”).

¹¹² See *December 2014 Guidance*, *supra* note 2, at 74620 (indicating that “MPEP 2015 is also superseded by this . . . Guidance . . .”).

¹¹³ See *Foreword: Manual of Patent Examination Procedure*, USPTO, archived at <https://perma.cc/2F4E-L2CN> (acknowledging that the manual lacks the authority of statute, or of 37 C.F.R., but yet also states that it “outlines the current procedures which the examiners are *required* or *authorized* to follow . . .” (emphasis added)).

¹¹⁴ See *December 2014 Guidance*, *supra* note 2, at 74621-25 (summarizing the relevant §101 precedent).

¹¹⁵ See *December 2014 Guidance*, *supra* note 2, at 74625-28 (pointing to the USPTO’s numerous hypothetical examples - like those discussed above in the *March 2014 Guidance*, these either recapitulate the precedent cases explicitly (adding little) or are based on contrived and simplistic examples that do little to illustrate how the USPTO might treat realistic problems). The hypotheticals add little to debate over what would actually comprise a patent-eligible utilization of a natural phenomenon beyond what one can glean from *Diehr*. See *December 2014 Guidance*, *supra* note 2, at 74625-28; see also *Diehr*, 450 U.S. at 185.

¹¹⁶ See, e.g., *Myriad*, 133 S. Ct. at 2119 (having struggled with the biology for several pages, the court fails to draw any bright line between patentable and non-patentable subject matter, except that generally a product of nature is not patent eligible, whereas something newly created is patent eligible).

single degree in science, engineering, mathematics or any field of technology between them.¹¹⁷

On the other hand, the USPTO may have muddied the water while attempting to clarify it.¹¹⁸ Even the December 2014 Guidance, while much improved, is accompanied by a set of examples intended to assist in eligibility analyses but that may actually confuse examiners and the patent bar to the extent that they are drawn from hypothetical scenarios.¹¹⁹ This note argues that USPTO would do better with examples of real, or at least realistic, patent prosecutions, or even restatements of principles alone.¹²⁰

¹¹⁷ See *Biographies of Current Justices of the Supreme Court*, SUPREMECOURT.GOV, archived at <http://perma.cc/7KK5-JH44> (showing that no justice has a degree in a field related to science or engineering, the closest being Anthony Kennedy who majored in a social science). Thus, while of the 1.2 million persons that the U.S. Census Bureau records as working in the legal profession, some 17% have at least a bachelor's degree in a STEM discipline (Science, Engineering, Technology and Math), but none of them sit on the Supreme Court, and thus not one of the Justices would meet the educational prerequisite to even sit the examination for admission to practice before the USPTO under 37 C.F.R. §§ 11.5 - 11.9. See *Where do college graduates work? A Special Focus on Science, Technology, Engineering and Math*, U.S. CENSUS BUREAU (July, 2014), archived at <https://perma.cc/YW49-LAV3> (displaying occupation data for STEM college graduates). Contrast this with the seventeen active and senior status justices sitting on Court of Appeals for the Federal Circuit, where at least five justices are actual patent attorneys or possess qualifying education. See *United States Court of Appeals for the Federal Circuit, Judges*, CAFC.USCOURTS.GOV, archived at <http://perma.cc/N4E8-6EFM> (providing a listing of brief biographical details of the justices). The significantly greater breadth and diversity of education on the CAFC as compared to the Supreme Court may explain some of the unpredictability when the Supreme Court takes up technology cases. *Id.*

¹¹⁸ See *Nature-Based Products*, USPTO (Dec. 2014), archived at <http://perma.cc/M6TE-6YEH> [hereinafter *Nature-Based Products Examples*] (providing several generally unhelpful and unrealistic example hypotheticals that are neither precedent nor representative of actual patents prosecuted).

¹¹⁹ See *id.* (offering the USPTO's interpretation of §101 eligibility of a series of USPTO-generated hypothetical inventions and claim sets).

¹²⁰ Cf. International Bioindustry Associations, March 2015, *supra* note 77, at 3 (expressing the alternate view that even more examples are required to delineate eligibility because the nuances between "markedly different" and "significantly more" might be lost in translation, but neglecting the fact that, while the USPTO might further define its own interpretation, this does nothing to make that interpretation authoritative).

IV. ANALYSIS

A. Criticism of the March 2014 Guidance

So, how far off the mark was USPTO's March 2014 Guidance? While practitioners continued to report unexpected §101 rejections under the March 2014 Guidance,¹²¹ the USPTO itself soon indicated that it intended to revise the document, and invited and published comments.¹²² Very few comments were generally accepting of the USPTO's approach in the March 2014 Guidance; even the American Association of Retired Persons (AARP),¹²³ itself an *amicus* opposing patentability in both *Mayo* and *Myriad*, noted that the March 2014 Guidance failed to cover differences in function as well as structure.¹²⁴ AARP also noted that the "12-factor" test was not consistent with Supreme Court rulings, and was potentially confusing.¹²⁵ In considering the dozens of often-lengthy comments submitted, the faults found with the USPTO's efforts to address the issue

¹²¹ See International Bioindustry Associations, March 2015, *supra* note 77, at 3 (noting more frequent and inconsistently applied §101 rejections in the summer of 2014); see also Joanna T. Brougher & David A. Fazzolare, *USPTO Guidance On Patentable Subject Matter: Impediment to Biotech Innovation?* 20(3) J. COMM. BIOTECHNOLOGY (2014) (claiming unanticipated rejections in the wake of *Myriad*).

¹²² See *Guidance For Determining Subject Matter Eligibility Of Claims Reciting Or Involving Laws of Nature, Natural Phenomena, & Natural Products*, USPTO (2014), archived at <http://perma.cc/BDF3-BL3B> (narrating recent history of §101 guidance, and indicating that it took only two months for the USPTO to concede (on May 9, 2014) that the *March 2014 Guidance* needed revision). The comments received and published by USPTO are now indexed. See *Public Comments on March 2014 Guidance*, *supra* note 73.

¹²³ See AARP, archived at <https://perma.cc/5Z2S-9WY4> (describing the organization as a nonprofit entity with membership limited to persons age 50 or older). The AARP's constituency is, of course, uniquely placed to benefit from cheap drugs now, and less likely to benefit from new discoveries that might give rise to new drugs in the future, given the timeline to progress from bench to pharmacy.

¹²⁴ See AARP Comment on March 2014 Guidance, *supra* note 83, at 3 (arguing that both structure *and* function needed to be markedly different from the natural state to meet the threshold of eligibility under §101, rather than simply a structural difference as indicated in the Guidance—an argument consistent with AARP's objectives in limiting the scope of drug and diagnostic patents).

¹²⁵ See AARP Comment on March 2014 Guidance, *supra* note 83, at 3 (arguing that AARP finds no Supreme Court language promoting a weighing test, and argues that if any single factor weighing against eligibility is fulfilled, the invention claimed should not be patentable subject matter).

had several principal themes, and thus the bulk of the criticism can be grouped under a few general headings.¹²⁶

The core criticism leveled at the USPTO was that the March 2014 Guidance sought to broaden the impact of *Myriad* and *Mayo* well beyond the explicit and implicit limitations proclaimed in those rulings.¹²⁷ A broad coalition of biotechnology industry bodies condemned the USPTO for departing from their traditional approach of careful interpretation of new case law, together with the “complete absence of policy justification for [adopting] such a far-reaching interpretation of judicial decisions.”¹²⁸

¹²⁶ See *Public Comments on March 2014 Guidance*, *supra* note 73 (providing the roster of comments, almost exclusively critical in tone, including submissions from 39 individuals –mostly patent attorneys, 8 technology companies, 6 law firms, 7 academic and research institutions and 21 submissions representing 32 regional, national, and international professional organizations, and non-profits).

¹²⁷ See, e.g., DuPont, Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 2 (July 31, 2014), *archived at* <http://perma.cc/D3UN-MHYT> [hereinafter July 31 Dupont Letter] (presenting DuPont’s opinion that “in formulating the [March] Guidance, the USPTO appears to have interpreted the Supreme Court decision in *Myriad* in a way that results in the unjustified expansion of the intentionally narrow holding in that case,” made by DuPont’s chief intellectual property counsel). It is indicative of Boston’s position as a biotechnology hub that the Boston Patent Law Association (BPLA) wrote one of the more comprehensive rebuttals of the March 2014 Guidance. See BPLA, Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 2-3 (July 28, 2014), *archived at* <http://perma.cc/E5Y2-F9VS> [hereinafter July 28 BPLA letter] (arguing, *inter alia*, that USPTO over-reached in seeking to apply a multi-factor test to inventions that simply *involve* a judicial exception when the court indicated that simply transcribing the coding sequence from spliced messenger RNA (occurs in nature) into cDNA (does not occur in nature) was sufficient to cross the threshold of §101, and also pointing out that that the court “found the man-made origin of cDNA dispositive on its own”).

¹²⁸ See International Bioindustry Associations, Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 5-6 (July 31, 2014), *archived at* <http://perma.cc/H9SK-8WXE> [hereinafter International Bioindustry Associations, July 2014] (containing the joint comments of ASEBIO (the Spanish Bioindustry Association), AusBiotech (Australia’s Biotechnology Organisation), Belgian Biotechnology Industry Organisation, BIA (The UK BioIndustry Association), BIO Deutschland, BIOTECanada, Biotechnology Industry Organization (BIO), CropLife International, EuropaBio, HollandBIO, Japan Bioindustry Association, and P-BIO (Portugal’s Biotechnology Industry Organization) all registering their concern regarding the absence of justification for heightening the standard for

The International Federation of Intellectual Property Attorneys (FICPI) noted that the USPTO had no authority to “reinterpret” such precedent, particularly as the March 2014 Guidance appeared to do so while ignoring other controlling precedent, and flying in the face of specific language in both *Myriad* and *Mayo*, limiting their scope.¹²⁹ Some even argued that cases such as *Funk Bros.* are not particularly useful in defining the basis of §101 eligibility in an examination of judicial exceptions.¹³⁰ Several comments noted that the

patentability). Several other comments reiterate similar criticisms. *See, e.g.*, John Storella, Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product (July 21, 2014), *archived at* <http://perma.cc/4EB3-H3XH> [hereinafter Storella Comments] (remarking that the Guidance exceeded the scope of the Supreme Court precedent on which the USPTO claimed to have based it).

The Supreme Court cases on which the Guidance is predicated are narrow decisions based on specific fact patterns. Prudence dictates proceeding with caution. Yet the Guidance goes far beyond what the Supreme Court has decided. It calls into question the patent eligibility of subject matter there is no evidence it was ever the intention of the Supreme Court to withdraw.

Id.; *see also*, Ass’n of U. Technology Managers et al., Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 2 (July 29, 2014), *archived at* <http://perma.cc/KZJ9-674X> [hereinafter AAU and APLGU Comments] (suggesting that such a broad reinterpretation should not have been published as a guidance for examiners without an opportunity for public comment, and thus USPTO had exceeded its authority).

¹²⁹ *See* International Federation of Intellectual Property Attorneys (FICPI), Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 4-6 (July 30, 2014), *archived at* <http://perma.cc/TE6U-NS8L> [hereinafter 30 July FICPI Letter] (discussing how the March 2014 Guidance oversteps the language in *Mayo*, and how the *March 2014 Guidance* oversteps the scope of the *Myriad* ruling). FICPI also notes that the specific language in *Myriad* indicated that the ruling did not apply to process claims. *Id.* at 6-7. FICPI’s criticisms of USPTO’s failure to conform to precedent, and the problems of incongruity between the U.S. approach to eligibility and the international norms and treaty obligations, took a distinctly more international approach. *Id.* at 1-2. FICPI, which represents over five thousand intellectual property attorneys in private practice in 86 countries, also registered its general disagreement with the *Myriad* and *Mayo* rulings themselves, but acknowledged that the USPTO was, of course, bound to follow the new U.S. precedent. *Id.* at 2.

¹³⁰ *See* The Chartered Institute of Patent Attorneys (CIPA), Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 6-7 (July 30, 2014), *archived at* <http://perma.cc/ZF4E-YCUA> [hereinafter Chartered Institute of

USPTO's attempt in the March 2014 Guidance to narrow the scope of eligibility also exceeded the authority found in precedent, specifically that *Mayo* does not require a particular *level* of limitation or application of a natural law; it simply stands for the proposition that if there is *no* limitation on the application of the natural law, a claim is drawn to ineligible subject matter.¹³¹ Other commentary submitted to

Patent Attorneys, July 2014] (failing to find any basis for an absolute judicial exception to the patenting of natural objects). CIPA also found *Funk Brothers* particularly unconvincing in this regard, arguing that the judgment implies eligibility of the invention, but finds that it was not patentable because it failed to "disclose an invention or discovery" in not adding to known (natural) properties of the bacteria - CIPA saw this as more a §103 issue than §101. *Id.* In contrast, the *March 2014 Guidance* included, in example D, a hypothetical closely based on the *Funk Bros.* finding of non-eligibility, and citing *Myriad's* reference to that case presented the scenario as an example of §101 ineligible subject matter. *See March 2014 Guidance, supra* note 2 (citing *Myriad*, 133 S. Ct. at 2117).

¹³¹ *See* 31 July Sundby Letter, *supra* note 83, at 2 (providing an interpretation of the court's analysis).

The Court's analysis should not be interpreted to mean that a claim must recite at least one step that is not 'well-understood, routine, conventional activity' in order to make the process claim patent eligible.... [i]t should be noted that some of the process claims which have been found to be patent eligible by the Court recite seemingly simple steps. Nevertheless, the seemingly simple steps are ones which practically apply the given law of nature.

Id.; *see also* American Bar Ass'n Section of Intellectual Property Law (ABA-IPL), Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 13 (July 30, 2014), *archived at* <https://perma.cc/ZS3B-FNR4> [hereinafter 30 July ABA-IPL Letter] Arguing the composition-of-matter corollary, the ABA-IPL note:

The *Myriad* Court does not analyze the distinctions between cDNA and naturally occurring DNA to determine whether the differences are 'significant' or marked... Whether a composition, combination, application, or manufacture is 'different' from what exists in nature is the only standard for patent eligibility that the USPTO should be instructing its examiners to apply.

Id. Thus the difference required between a claimed product and its natural antecedent under *Myriad* is truly minimal—any difference will do—thus, under this reading, the attempt in the *March 2014 Guidance* to create additional obstacles to the §101 requirement was illegitimate. *Id.* It is instructive here to actually review how far the *Myriad* court went to illustrate how slight the difference was—simply the removal of non-coding intron sequence from ineligible genomic DNA creates a molecule indistinguishable from cDNA, and that but for the removal of introns, a short strand of cDNA "may be indistinguishable from natural DNA." *Myriad*, 133 S. Ct. at 2119. However, it should be noted that simply because introns represent

the USPTO noted that the March 2014 Guidance failed to adequately elucidate how matter and process claims were to be handled under *Mayo* and *Myriad*.¹³²

No comment by any author located to date had anything good to say of the USPTO's 12-factor test for "significant difference," while even those that generally support restrictions on biotech patents indicated that they "fear[ed] the results will be muddled analyses."¹³³ Several critical treatments of the March 2014 Guidance focused on the USPTO's contention that a "significant difference" is required to

sections of genomic DNA that don't code for protein, this does not necessarily mean that they are "junk DNA" or without function themselves. cDNA is actually made by copying mRNA sequence back into a DNA format, while the introns are actually removed in nature, during the process of editing the crude RNA transcript from the genomic DNA information to produce mature mRNA genetic template that is used transiently as the basis for translating the genetic code into actual protein. See STRACHAN & READ, *supra* note 62, at 336, Box 14.3 (noting that intronic DNA can and does have a range of functional attributes of its own, and thus the removal of introns to create a pure transcription unit may be more functionally significant than it is sometimes represented to be in the commentary on this issue).¹³² See, e.g., July 28 BPLA letter, *supra* note 127 (arguing that the *March 2014 Guidance* ignored specific language in *Myriad* explicitly narrowing the scope of that judgment to exclude method and process claims); see also 30 July FICPI Letter, *supra* note 129, at 9 (arguing that method/process claims should be eliminated from the scope of any revised Guidance). But see 31 July Sundby Letter, *supra* note 83, at 3-5 (representing those who argued that *Myriad* and *Mayo* should not be combined, but rather that separate tests should be devised for eligibility for processes and products).

¹³³ See College of American Pathologists (CAP), Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 3 (July 22, 2014), archived at <http://perma.cc/28Q6-WU3L> [hereinafter 22 July CAP Letter] (suggesting that, even after balancing USPTO's twelve factors, the results may still be unclear); see also American Civil Liberties Union (ACLU), Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product 1-4 (July 8, 2014), archived at <http://perma.cc/6BLS-HY8D> [hereinafter 8 July ACLU Letter] (arguing that the Guidance both missed the subtleties of the Court's treatment of §101 in *Bilski* and *Mayo*, and, in the twelve-factor test for "significant difference," imposed *de novo* a raft of tests unsupported by precedent). The ACLU comment reflected the opinions of many interested parties in suggesting "the Guidance does not comport with the Supreme Court's Section 101 decisions, specifically "we are concerned that the factor-weighting analysis...will only confuse the analysis" *Id.*

cross the §101 threshold.¹³⁴ A number of critics noted that *Alice Corp.* had since clarified that the March 2014 Guidance had exceeded the Supreme Court's intent in *Myriad* and *Mayo* in articulating the standard "significantly more."¹³⁵

Many critics also focused on the failure of the March 2014 Guidance to include functional differences amongst the properties that distinguish inventions from structurally similar natural products.¹³⁶ Specific criticism of the March 2014 Guidance Example E

¹³⁴ See 30 July FICPI Letter, *supra* note 129, at 7 (criticizing the USPTO definition of the critical term "significantly different" as essentially circular and ill-defined); see also T. Aidan Toombs, Comment E-mail on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product (July 30, 2014), *archived at* <https://perma.cc/TD2C-DPKD> [hereinafter *30 July Toombs email*] (pointing to the fact that the *March 2014 Guidance*'s "significantly different" appears to be a portmanteau synthesis of *Myriad*'s "markedly different" [from an natural product] and *Mayo*'s "significantly more" [than a law of nature], and that nothing in the rulings supported their conflation).

¹³⁵ See 30 July ABA-IPL Letter, *supra* note 131, at 13 (noting that in *Chakrabarty*, the fact that the court found the invention "markedly different" from nature was an observation and not a definition of the minimum threshold).

¹³⁶ See 22 July CAP Letter, *supra* note 133, at 3 (stating "[a] close reading of the Supreme Court's decisions, though, lays out the requirement that the composition have markedly different characteristics from any found in nature in both structure and function"). Even consistent opponents of gene patenting such the College of American Pathologists noted that the Guidance was deficient in failing to address functional differences together with structural ones in the evaluation of §101 eligibility. *Id.*; see also July 28 BPLA Letter, *supra* note 127 (noting that the *March 2014 Guidance* read too much into *Myriad*'s silence on added functionality in inventions based on nature, arguing that the *Myriad* invention did not hinge on added functions, and thus the court did not explicitly address the issue, and going on to point out that the *Myriad* opinion still reiterated that, in *Chakrabarty*, the structural novelty of the extra plasmid and the novel "capacity for degrading oil" contributed to §101 eligibility); 30 July FICPI Letter, *supra* note 129, at 2-4 (reiterating this critique; noting that *Funk Bros.* and *Chakrabarty* both emphasize that it is the presence or absence of novel function that defined the threshold of patentability in those cases; pointing to the absence of a novel functionality evaluation in the twelve-factor test proposed in the *March 2014 Guidance*, and noting that functional analysis is absent from the six factors); 8 July ACLU Letter, *supra* note 133, at 3 (similarly finding fault with this aspect of the *March 2014 Guidance*, pointing to the same error in failing to accommodate the precedent distinctions offered by *Funk Bros.* and *Chakrabarty*). Given ACLU's status as *amicus opposing* patentability in *Mayo*, *Myriad* and *Alice*, this critique was especially damning. See also 31 July Sundby Letter, *supra* note 83, at 5-8 (illustrating how a purely structural approach to difference from natural products fails to protect genuinely useful and important inventions that find new functions for biomolecules).

(concerning the eligibility of primer pairs) disagreed with the USPTO's failure to account for the *function* of primers, and argued that primers should be eligible subject matter.¹³⁷ This neatly encapsulates how uncertain the March 2014 Guidance and subsequent commenting process was because, even though the USPTO was proved right on the issue of primer eligibility, both the USPTO's position and that of their critics remained supposition until the CAFC ruling in *Ambry*, which appears to settle the issue – primers for naturally-occurring sequences are not eligible subject matter.¹³⁸ The March 2014 Guidance was also criticized for taking an unnecessarily reductionist approach to evaluating the patentability of claim elements – specifically the March 2014 Guidance fails to instruct examiners to consider all elements in combination prior to rejection.¹³⁹

A number of critical comments returned to the theme of the constitutional and statutory prerogatives that shape the patent landscape, and noted that the March 2014 Guidance unnecessarily perturbed the balance constructed by Congress, particularly with respect to clear Congressional intent to nurture and promote the biotechnology industry generally, and specifically some sub-fields, such as the discovery and development of novel antibiotics that could be particu-

¹³⁷ See, e.g., 30 July ABA-IPL Letter, *supra* note 131, at 18-19 (noting that *Myriad* taught that genetic material does not become eligible simply due to isolation, but that like *Chakrabarty's* bacteria, a DNA primer pair has an additional functional difference from genomic DNA); see also Insitut Pasteur, Comment Letter on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product (June 27, 2014), archived at <https://perma.cc/7CV8-GEHR> [hereinafter 27 June Insitut Pasteur Letter] (arguing that a primer pair is eligible subject matter as it doesn't simply *encode* the genomic information of the homologous naturally-occurring sequences (like *Myriad's* simple sequence claims), rather it *functions* as a tool to amplify target sequences between the primer binding positions).

¹³⁸ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 759-61 (finding that the remaining primer-based claims in *Myriad's* BRCA patents were drawn to ineligible subject matter, and illustrating that it is the courts and not the USPTO that provide the only definitive interpretation of the law).

¹³⁹ See, e.g., Jonathan J. Wainer, Comment E-mail on the USPTO Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Product (June 27, 2014), archived at <https://perma.cc/Q7HD-T6V> (noting that the Supreme Court clarified in *Alice Corp.*, subsequent to the issuance of the *March 2014 Guidance*, that claims need to be evaluated as a whole prior to rejection under §101).

larly hampered by the Guidance.¹⁴⁰ Finally, transnational commentators argued that the March 2014 Guidance articulated policy that conflicts with the United States' international obligations, and also frustrated U.S. attempts to promote harmonization and convergence of intellectual property regimes between regions and nations.¹⁴¹

B. Implications of Recent Decisions for Subject Matter Eligibility

Having summarized why the USPTO, at least in the opinion of the commentators, failed to helpfully or satisfactorily interpret *Mayo* and *Myriad*, it is useful to turn back to the judicial arena to analyze what occurred in the interim, the specific impacts, and the general implications for subject matter eligibility. The narrowest consequence of the litigation culminating in *Ambry* is that *Myriad* was unable to prevent competitors from continuing to provide BRCA testing.¹⁴² Looking more generally, it now appears settled that diagnostic tests, whether for genotype or phenotype, will not be protected by patents that can meaningfully exclude a competitor from providing functionally similar tests that detect and report the same underlying

¹⁴⁰ See July 28 BPLA Letter, *supra* note 127 at 8-10 (laying out grounds for Congressional intent, particularly for the promotion of biotechnology, and specifically citing the established policy interests in promoting antibiotic development); see also International Bioindustry Associations, July 2014, *supra* note 128 (emphasizing the need for antibiotic development and the history and future likelihood that useful compounds will be found in nature if suitable incentives remain in place).

¹⁴¹ See, e.g., 30 July FICPI Letter, *supra* note 129 (indicating that the *March 2014 Guidance* violated Article 27 (1) of TRIPS guaranteeing minimum protections for useful inventions regardless of the field of technology). Organizations representing the international constituency of patent prosecution professionals were particularly strident in their condemnation of the Guidance's apparent *per se* exclusion of whole categories or useful, unknown and inventive items, contrary to the TRIPS Agreement. *Id.* at 1-2; see also International Bioindustry Associations, July 2014, *supra* note 128 (condemning the departure from international norms and inconsistency with the efforts at transnational harmonization of intellectual property regimes that the U.S. has done so much to build); Chartered Institute of Patent Attorneys, July 2014, *supra* note 130, at 3 (noting that such an abrupt change in U.S. policy will frustrate future efforts to promote harmonization). While the US seeks to drive the international community to conform to US intellectual property norms, CIPA asks why other states would "change to the USA's way of doing things when the USA has just changed its own practice so radically – and may do so again?" See Chartered Institute of Patent Attorneys, July 2014, *supra* note 130, at 3.

¹⁴² See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 759-65 (invalidating specimen claims representing the composition of matter and method claims left intact by previous litigation).

ing, naturally-occurring, genetic or physiological variation because *Mayo*, *Myriad* and *Ambry* have all but foreclosed patents on naturally-occurring genes and physiological states, healthy or diseased, that are found in nature.¹⁴³

A further general deduction is that, even outside the field of diagnostics, most genes or fragments of genes will no longer be accepted as patent eligible in the United States. A gene, a gene-variant (mutant, allele, polymorphism), or a piece of a gene (for example a hybridization probe or primer) that is “naturally occurring,” is not pa-

¹⁴³ See *Mayo*, 132 S. Ct. at 1294 (finding that “the steps in the claimed process (apart from the natural laws themselves) involve well understood routine conventional activity . . .”); see also *Myriad*, 133 S. Ct. at 2117 (“Myriad did not create anything . . . it found an important and useful gene . . . but [this] is not an act of invention”); *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 760-64 (noting that “. . . even short strands identical to those found in nature are not patent eligible. . . in so much as the non-patent-ineligible elements . . . do . . . not add enough”). The remaining and limited scope for gene patenting can be read in the dicta in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*:

Even if claim 21 of the ‘441 patent were patent eligible – a question about which we express no view – [it] is qualitatively different [claiming] a method of detecting alterations . . . expressly identified in the specification. . . thus the invention in claim 21 is limited to the particular mutations the inventors discovered.

Id. at 765. The court in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation* noted Myriad’s argument that their method claims (essentially comparing patient genes to a reference sequence to determine differences) should remain eligible because a minority opinion in a previous ruling on the same patent had suggested that such a method claim (for example Claim 21 of the ‘441 patent) *might* be patent eligible - concurring in part and dissenting in part, Judge Bryson argued that “[o]f course, Myriad is free to patent applications of its discovery.” See *Ass’n for Molecular Pathology*, 689 F.3d at 1330 (establishing patent eligibility with chemicals found in nature). Judge Bryson also noted that “Myriad could easily have claimed more narrowly to achieve the utility. . .” *Id.* at 1350; cf. *Myriad*, 133 S. Ct. at 2120 (citing language in Justice Bryson’s CAFC minority opinion with approval, but failing to endorse a specific claim); see also *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 764-65 (declining to recognize the parallel between the “significantly broader and more abstract” method claims before it (Claims 7 and 8 of the ‘441 patent) and Claim 21, which had a narrower scope covering comparisons identifying only ten genetic differences enumerated in a table in the specification; a pretty thin straw for anyone attempting to patent a diagnostic method to grasp at, and apparently an avenue that Myriad has declined to pursue). *But see Myriad Settles BRCA Testing Patent Fray with Pathway Genomics, Invitae, supra* note 106 (describing how Myriad had moved to end litigation with various parties that it had sued for infringement of its BRCA patents after they had brought generic BRCA testing services to market).

tent eligible in its natural state, or if simply “isolated.”¹⁴⁴ Method claims that seek to monopolize the information in the naturally-occurring generic sequences by framing a general instruction to examine or compare the genetic material to something else (a reference sequence) are also barred because they add nothing more than an abstract idea dressed up with concrete steps that are simply generic manipulations well understood by practitioners in the art field.¹⁴⁵

Some issues remain unresolved by the recent ruling. How is it that we are to reconcile the emergence of the so-called “*Mayo* Test” with the precedent cases that remain good law, in order to achieve a practical synthesis that makes it clear to the patent office, the patent bar, inventors, and investors how the §101 inquiry will be operated going forward?

Many expert molecular biologists and commentators puzzled over the Supreme Court’s decision to uphold patents based on cDNA which, to most scientists, seems facially at odds with the rest of the decision and some of the language in *Myriad*.¹⁴⁶ Whether or not the Supreme Court made a useful *legal* distinction here remains to be seen. This note argues that they probably did, although the weakness of their *scientific* argument and the plethora of casual errors in the *scientific* matter in the ruling have not helped either the legal or the scientific communities actually engage with what the court was really trying to say about cDNA, because it has proved so much more fun for the scientific and liberal elites to make fun of the Supreme Court Justices.¹⁴⁷

¹⁴⁴ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 759-60 (quoting *Myriad*, 133 S. Ct. at 2117) (discussing primers, quoting *Myriad*’s proposition that “[s]eparating [DNA] from its surrounding genetic material is not an act of invention,” and analogizing *In re Roslin Institute*, where Dolly the cloned sheep was deemed not patent eligible, as she was not possessed of markedly different characteristics from any farm animals found in nature).

¹⁴⁵ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 765 (stating “. . . [the claim limitations] recite only routine and conventional steps”).

¹⁴⁶ See *Myriad*, 133 S. Ct. at 2119-20 (finding genomic DNA ineligible, but complementary DNA eligible); see also Heidi Ledford, *Myriad Ruling Causes Confusion: Change to Gene Patents Leaves US Biotech in a Lather*, 498 NATURE 281, 281-82 (2013) (illustrating the perplexity this precipitated in the scientific community).

¹⁴⁷ See, e.g., Steven Salzberg, *Supreme Court Gets Decision Right, Science Wrong, on Gene Patents*, FORBES (June 2013), archived at <http://perma.cc/X62J-GZMV> (representing a fairly mild example bemoaning that “[i]t’s troubling that the highest

The short concurrence written by Justice Scalia attracted the most ridicule.¹⁴⁸ Given Scalia's position as the *bête noire* of the left, it is unsurprising that his opinion attracted some opprobrium by those who read into his words: "I am unable to affirm those details [of biology] on my own knowledge or even my own belief" a disavowal of basic scientific facts.¹⁴⁹ Perhaps when Scalia wrote that he didn't believe the details of the underlying biology, he was truly revealing himself as the sort of latter-day flat-Earther who denied the scientific consensus - a fitting counterpart to his provocative statements on race, homosexuality, and torture.¹⁵⁰ But, in the rush to jump on Scalia's belief (or lack of it), have we missed the reality that his brief concurrence said all that the court needed to say, but with brevity lacking in the other justices?

Justice Thomas, with the rest of the court, takes us through a (perhaps slightly confused) explanation of how genes and DNA are

court in the land can't get even the basic facts of molecular biology right when writing a decision that has such fundamental importance to genetic testing . . ."); see also Katherine Trendacosta, *Hilariously Useless Comments About Science from the US Supreme Court*, 109 (July 2014), archived at <http://perma.cc/87BV-3VAD> (offering a more sophomoric comment, illustrating the tone of the commentary). Trendacosta says of Scalia's concurrence in *Myriad*:

[Scalia] can't even believe in the finer points of DNA. HE CAN'T BELIEVE IT. He admits to not being an expert in the details of the science, which is nice. But then he can't just believe what's he's told about it. Antonin Scalia is a Catholic who can believe the tenets of that religion, but his beliefs cannot extend to the explanation of molecular biology provided by experts.

Id. This blog post says little about science or patents and much about "culture wars" in the United States, yet unfortunately this probably represents how younger and scientifically literate voters view the Supreme Court justices.

¹⁴⁸ See, e.g., Max Read, *Antonin Scalia Does Not Believe in Molecular Biology*, GAWKER (June 2013), archived at <http://perma.cc/4L9W-DFXZ> (poking fun at Scalia).

¹⁴⁹ See *id.* (inferring from Scalia's concurrence that he does not believe in the basic principles of biological inheritance outlined in the majority opinion).

¹⁵⁰ See Sean Lengell, *Scalia "Racial" Comment on Voting Rights Law Draws Fire*, WASHINGTON TIMES (Feb. 2013), archived at <http://perma.cc/RG6H-ANPH> (discussing Scalia's negative comment on voting rights law as racial entitlement); see also Erin Fuchs, *The 6 Most Outrageous Things Scalia Ever Said About Gays*, BUSINESS INSIDER (June 2013), archived at <http://perma.cc/6G3T-FWUM> (discussing Scalia's public and vehement distaste for homosexuality); Matt Ford, *Antonin Scalia's Case for Torture*, THE ATLANTIC (Dec. 2014), archived at <http://perma.cc/8398-69RJ> (challenging the moral ambiguity displayed by the Supreme Court Justice in response to the Senate torture report).

put together.¹⁵¹ The biology lesson however is merely a preamble to case, which in reality turns almost entirely on a straightforward application of *Chakrabarty* and its antecedents.¹⁵² The majority opinion then continues for four pages articulating their decision.¹⁵³ It is instructive to compare this to what Justice Scalia accomplished in about a hundred words – including the two sentences he expended to explain that he didn't have enough knowledge or belief in biology to concur fully with Thomas's opinion.¹⁵⁴ Justice Scalia's opinion was this: “[i]t suffices for me to affirm having studied the opinions...and briefs presented, that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and that complementary DNA is a synthetic creation not normally present in nature.”¹⁵⁵ This distinction, aligning cDNA with *Chakrabarty's* bacterium with supernumerary plasmids not found in nature, while recognizing that isolated genomic DNA was as unchanged as the naturally-occurring bacteria in *Funk Bros.*, is the

¹⁵¹ See *Myriad*, 133 S. Ct. at 2111-12 (writing for the Court, Justice Thomas starts out by telling us that “[g]enes form the basis for hereditary traits in living organisms” and proceeds in that vein). While this statement is generally true, it is not exclusively true because, unknown to the Justices, genes may not be the sole mechanism of inheritance. See Michael K. Skinner, Mohan Manikkam, & Carlos Guerrero-Bosagna, *Epigenetic Transgenerational Actions of Environmental Factors in Disease Etiology*, 21 TRENDS ENDOCRINOLOGY & METABOLISM 214, 214-222 (Apr. 2010) (providing an example of transgenerational epigenetic inheritance published prior to the *Myriad* opinion); see also Moshe Szyf, *Nongenetic Inheritance and Transgenerational Epigenetics*, 21 TRENDS MOLECULAR MED. 134-144 (Feb. 2015) (showing a more recent treatment of biologic inheritance mediated by nongenetic factors).

¹⁵² See *Myriad*, 133 S. Ct. at 2116-17 (noting “our decision in *Chakrabarty* is central to this inquiry”).

¹⁵³ See *id.* at 2117-20 (revisiting *Chakrabarty*, 447 U.S. at 310, and *Funk Bros.*, 333 U.S. at 132, discussing cDNA, pseudogenes, and the deference not owed to the USPTO).

¹⁵⁴ See *id.* at 2120 (concurring in part and concurring in the judgment, Scalia makes the same point as Thomas, but uses just one substantive sentence, indulging in only two sentences of preamble).

¹⁵⁵ *Id.* at 2120. Following the same error as the others, Scalia neglected to note that cDNA may be, but is not necessarily, synthetic. *Id.* However, by stripping his predicate and conclusion down to the bare bones, only ornamented with the one phrase about his “own belief,” it is at least much easier to see where Scalia erred because he declined to dress up his concurrence with a generally unnecessary, partly erroneous, and incomplete digression into the technical details of molecular biology. *Id.* at 2119.

simple heart of the *Myriad* decision.¹⁵⁶ Whether or not one thinks that isolated DNA could have a function that it lacks in nature, or that cDNA is really no different from genomic DNA,¹⁵⁷ and Scalia's

¹⁵⁶ See *Myriad*, 133 S. Ct. at 2120 (standing, at its broadest interpretation, for the proposition that compositions not occurring in nature, such as *Chakrabarty's* modified bacterium, are eligible subject matter, whereas compositions of matter that may occur naturally such as *Funk Bros.'s* mixture of natural bacteria are ineligible).

¹⁵⁷ In addition to the issue that cDNA is commonly found in nature (retroviruses and pseudogenes are ubiquitous), and following the *structure*-oriented logic in *Myriad* cDNA might often be ineligible, there is the separate concern that as it is the *informational* content that is at the heart of the natural phenomena represented as genes, the format that the information is stored in cDNA, genomic DNA, mRNA, or for that matter paper or computer disk, seems irrelevant. In *Myriad* the court wrote, "Myriad did not create or alter *any of the genetic information encoded* in the BRCA1 and BRCA2 genes. The location and *order of the nucleotides* existed in nature before Myriad found them." See *Myriad*, 133 S.Ct. at 2116 (emphasis added). This language is referenced explicitly in *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation*. See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 759. If the "information" existed in nature, it is hard to see how simply reorganizing the information naturally occurring in mRNA by changing the format to DNA crosses the threshold of §101. Just as the assembly of a mixture of naturally-occurring bacteria, each structurally and functionally identical to their naturally-occurring state was ruled ineligible in *Funk Bros.*, then the assembly of exonic DNA having the same sequences (structure) as found in genomic DNA and coding for a specific polypeptide (fulfilling the same function) as the exons do in nature seem to be substantively identical to what is found in nature. See *Funk Bros*, 333 U.S. at 130-32 (deciding that mixtures of bacteria having the structures and functions that they possess in nature are not patentable). The *Chakrabarty* bacterium, while using building blocks provided by nature to create a novel organism, showed evidence of genuine invention, while the order of assembly of exons linked in cDNA merely mimics the order of exons and elimination of intronic sequence that occurs in nature as specifically manifested in the naturally-occurring messenger RNA from which the cDNA found eligible by the Supreme Court in *Myriad* is merely copied. It seems obvious that copying information into a different storage format does nothing inventive; the analogy might be a stretch for biotechnology, but copying a music CD into MP3 format using a conventional mechanism is not widely recognized as a creative or inventive act, and similarly (to paraphrase the *Myriad* opinion) in the case of cDNA, *none of the genetic information encoded* in cDNA has been created or altered by "inventors" that seek to monopolize it. See *Myriad*, 133 S. Ct. at 2117-20. The USPTO itself raises the issue of whether separating material of interest from surrounding material can surmount the §101 bar, concluding on the basis of *In re Marden* that properties of uranium that emerge upon purification are not themselves patentable because they are inherent in natural uranium. See *Analyzing Nature-Based Products*, USPTO, available at <http://www.uspto.gov/video/cbt/natureproducts/> [hereinafter *Computer Based Training*] (explaining and analyzing subject matter eligibility of nature based prod-

summary frames the Supreme Court's *Myriad* opinion, whether one agrees with it or not, with elegance and economy.¹⁵⁸

We can examine the proposition that Justice Scalia's concurrence is all that is needed to understand *Myriad* by comparing it to the Federal Circuit's rulings in *Ambry* and the consequent synthesis of *Mayo*, *Alice* and *Myriad* in that opinion.¹⁵⁹ The composition claims in *Ambry* concerned DNA primers – short lengths of DNA that match naturally-occurring genomic DNA – and serve to bind to single strands of DNA to initiate synthesis of the complementary strand.¹⁶⁰ Although isolated, primers are, as Justice Scalia would have it, “identical to that portion of the DNA in its natural state,” and are thus patent ineligible under §101.¹⁶¹

ucts). It could, by analogy, be argued that the properties of cDNA are equally inherent in naturally-occurring genomic DNA. *Id*; see also *In re Marden*, 47 F.2d 957 (C.C.P.A. 1931) (holding improved ductility of purified uranium was not patentable, as the ductility was characteristic of the pure element). The *Computer Based Training* audio narrative wrongly attributes the dispute in *Marden* to the properties of vanadium, but this error aside, perhaps the USPTO misunderstands what the Supreme Court intended in the *Myriad* ruling on the eligibility of cDNA. While it is hard to reconcile the ‘markedly different’ analysis presented by the USPTO with the slight difference between messenger RNA and cDNA, perhaps we should take the *Myriad* judgment at face value as the Court's indication that it will accept minimal structural differences, absent any substantive functional difference or inventive step, as sufficient to surmount §101, while leaving the subsequent sections of 35 U.S.C. to distinguish the minimally eligible from the actually patentable. See *Myriad* 133 S. Ct. at 2119 n.9 (leaving open the question of whether or not cDNA would meet other requirements, e.g. section 103).

¹⁵⁸ See *Myriad*, 133 S. Ct. at 2120 (holding cDNA is eligible subject matter, while genomic DNA is not).

¹⁵⁹ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 763-64 (applying the logic of *Mayo* and *Alice* to the remaining method claims protecting *Myriad*'s breast cancer gene testing product, and the logic of *Myriad* to the residual un-litigated composition claims).

¹⁶⁰ See *id.* at 758-59 (addressing the residual composition of matter claims in *Myriad*'s patents, specifically the claims for primer sequences).

¹⁶¹ See *Myriad*, 133 S. Ct. at 2120 (indicating, in Scalia's concurrence, that identity of DNA with the natural state is the critical determinant of non-eligibility); see also *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 760 (noting “separating [DNA] from its surrounding genetic material is not an act of invention.”)

[T]he primer binds to its complementary nucleotide sequence. Thus, just as in nature, primers utilize the innate ability of DNA to bind to itself... A DNA structure with a function similar to that found in nature can only be patent eligible as a composition of matter if it has a unique structure, different from anything found

The remaining claims in *Ambry*, those that are framed as method claims rather than composition claims, are actually addressed rather differently.¹⁶² *Myriad*, as illustrated by Justice Scalia, stands for the simple proposition that the broadest composition claims are eligible subject matter only if the composition is something not found in nature.¹⁶³ However, most claims are not as straightforward in claiming a judicial exception, containing limitations that frame (or claim) particular structural or functional features, or as in *Ambry*, a method or process for using the judicial exception.¹⁶⁴ The two method claims in *Ambry* instruct the user to compare the BRCA sequence of the subject to a reference sequence.¹⁶⁵ In both cases, the molecular embodiment of the patient and reference sequence is specified with generality to include genomic DNA, mRNA or cDNA.¹⁶⁶ Perhaps to avoid having to deal with the cDNA issue left open in *Myriad*,¹⁶⁷ the Federal Circuit opted to address this by tackling the abstract process recited at the heart of each claim – the simple instruction to compare A with B.¹⁶⁸ Declining to follow the urgings of the defendant to apply *Mayo* directly, the Court opted to focus on the analysis outlined

in nature. Primers do not have such a different structure and are patent ineligible.

Id. at 761.

¹⁶² See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 761 (addressing the residual method claims in *Myriad*'s patents, specifically those comparing subject sequence to reference sequence and determining the differences).

¹⁶³ See *Myriad*, 133 S. Ct. at 2120 (holding that naturally-occurring molecules or fragments thereof may not be patented).

¹⁶⁴ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 761-62 (discussing claims that instruct the users to compare one naturally-occurring sequence, presumably belonging to the subject or patient, to another naturally-occurring sequence representing the normal sequence seen in the genome of most healthy people).

¹⁶⁵ See *id.* (discussing method claims).

¹⁶⁶ See *id.* (describing indefinite breadth of claims).

¹⁶⁷ See *supra* note 157 (discussing the cDNA portion of the ruling in *Myriad*, the underlying error and related issues).

¹⁶⁸ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 763 (stating “the comparisons described...are directed to the patent ineligible abstract idea of comparing...sequences and determining the existence of alterations”).

in *Alice Corp.*, although as they make abundantly clear, *Alice Corp.* itself is grounded in the *Mayo* ruling.¹⁶⁹

In *Mayo*, the Supreme Court dismissed limitations framed around the abstract comparison step because they “add[ed] nothing of significance to the natural law.”¹⁷⁰ In *Alice Corp.*, an information technology case, the Court rearticulated the reasoning they had applied to the diagnostic method in *Mayo* to recognize a generalized two-step inquiry – asking first if the claim is directed at a patent ineligible concept (natural phenomenon, or law, or abstract idea).¹⁷¹ If it is, the inquiry then proceeds to a second step asking if, separately or as a whole, the elements of the claim amount to something significantly more by way of “inventive concept” to transform the claim into a patent-eligible concept.¹⁷² In applying this *Alice* articulation of the *Mayo* test to the facts of *Ambry*, the Federal Circuit found that the generally specified comparison was itself an abstract idea where the “comparisons [are] unlimited...not restricted by purpose” (*Mayo* Step 1).¹⁷³ Further – using *Mayo* Step 2 – the *Ambry* Court found that “the non-patent-ineligible elements of [the claims] do not add enough to make the claims as a whole eligible [as they] set forth well-understood, routine and conventional” instructions to apply the abstract idea.¹⁷⁴

¹⁶⁹ See *id.* (reasoning that “[r]ecently in *Alice*, the Supreme Court reiterated its two-step test [first] determine whether the claims at issue are directed to a patent-ineligible concept. If so... what else is there in the claims before us?”) (internal citations and quotations omitted).

¹⁷⁰ See *Mayo*, 132 S. Ct. at 1303 (describing limitations that do not meaningfully prevent unwarranted monopolization beyond the scope of the actual invention).

¹⁷¹ See *Alice Corp.*, 134 S. Ct. at 2355 (citing the *Mayo* Court’s use of a biomedical precedent to address the software issue in *Alice*, illustrating that, insofar as the invention is based on a judicial exception to §101 eligibility, then neither the generic extra-solution activity in *Mayo* (administering, sampling, measuring, adjusting dose, etc.) nor the generic extra-solution activity in *Alice* (data processing system, communications controller, etc....) can serve to transform the abstract idea into patent eligible subject).

¹⁷² See *id.* at 2355 (elucidating the requirement for an inventive concept to salvage eligibility for claims reciting natural phenomena, drawing on language in *Mayo*, 132 S. Ct., at 1294).

¹⁷³ See *id.* at 2355 (creating a unified framework in which abstract ideas in medicine and computer science can be subjected to equivalent analyses).

¹⁷⁴ See *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 763-64 (summarizing the second step of the *Alice/Mayo* test as “there must be a further inventive concept to take the claim into the realm of patent eligibility”).

Thus, *Alice* has set out, and *Ambry* has illustrated, a tool based in *Mayo* that manages the §101 inquiry, independent of any art field or specific technology, in a simple two-step process that leaves the lower courts with an adaptable tool to manage the fact-specific inquiry.¹⁷⁵ How the District Courts will manage this remains to be seen, and there clearly exists a large body of granted patents that may prove to be invalid if subject to the “*Mayo* Test.”¹⁷⁶

The new subject matter eligibility law overall can be best applied by first using Scalia’s *Myriad* criterion.¹⁷⁷ If it claims a “creation not normally found in nature,” a patent is drawn to eligible subject matter.¹⁷⁸ If a patent *is* directed to, or claims something, found in nature (*Mayo* Step 1), it can only be transformed into eligible subject matter if the elements of the claim transform the invention into something more than the natural phenomenon itself (*Mayo* Step 2).¹⁷⁹ The economic value of patents comes with the measure of certainty that they provide,¹⁸⁰ and this certainty will hinge on the ability of the pa-

¹⁷⁵ See *id.* at 763-65 (illustrating the application of *Alice* to diagnostic method claims); see also *Alice*, 134 S. Ct. at 2355 (synthesizing the application of the *Mayo* test into a general clarified rule concerning the ineligibility of unconstrained claims seeking to monopolize judicial exceptions to §101); *Mayo*, 132 S. Ct. at 1296-97 (outlining, with respect to a physiological marker, that a claim may not monopolize a naturally-occurring biologic state without some limitation that restricts the patent rights to an inventive utilization of that natural state).

¹⁷⁶ See, e.g., *In re Bentwich*, 566 F. App’x 941, 943 (2014) (concerning a case in which an admission made during oral argument that certain claim sequences were naturally occurring was fatal to the claim under §101 and *Myriad*).

¹⁷⁷ See *Myriad*, 133 S. Ct. at 2120 (concurring in the judgment, Scalia opines that a synthetic creation not normally present in nature is eligible while a composition identical to the natural state is not).

¹⁷⁸ See *id.* (implying that the mere possibility of a claimed composition occurring in nature would not necessarily be a bar to subject matter eligibility, provided that it met the criterion of not normally occurring in nature).

¹⁷⁹ See *Mayo*, 132 S. Ct. at 1296-1300 (distinguishing cases in which the claim transforms the natural phenomenon into an inventive application from those that do not).

¹⁸⁰ See, e.g., GlobeNewswire, *FDA Grants Orphan Drug Designations to OncoMed’s Tarextumab for the Treatment of Pancreatic and Small Cell Lung Cancer*, NASDAQ (Jan. 29, 2015), archived at <http://perma.cc/R9QT-5PC7> (exemplifying language concerning forward looking statements and the value of intellectual property in a recent press release, and illustrative of the explicit interplay of value and risk in biotech patents). In this example, clinical-stage biotech OncoMed included disclaimer language concerning “risk of third party claims alleging infringement of patents and proprietary rights or seeking to invalidate OncoMed’s patents or propri-

tent bar and the USPTO to conform patents granted to the precedent opinion, as the Supreme Court has made clear that it owes no deference to the USPTO's interpretation of the law, unless it is specifically confirmed by statute.¹⁸¹

C. Was the December 2014 Guidance Any Better?

Given that Following *Alice* and *Ambry*, it appears that *Myriad* and *Mayo* can be digested quite succinctly, so how did the subsequent Guidance from the USPTO measure up? The useful portion of the USPTO's December 2014 Guidance is that, in rejecting the approach so extensively criticized following issuance of the March 2014 Guidance, the USPTO now hews much closer to what the precedent actually dictated all along.¹⁸² The USPTO has significantly narrowed the scope of the guidance.¹⁸³ Whereas in the March 2014 Guidance the USPTO had proposed to impose an enhanced §101 threshold on any claim that *recited* or *involved* (or even *may* have recited or involved)

etary rights; and the ability of OncoMed's proprietary rights to protect its technologies and product candidates." *Id.*

¹⁸¹ See *Myriad*, 133 S. Ct. at 2119 n.7 (dismissing plaintiffs argument that the court should uphold gene patents because the USPTO had customarily granted them the court noted, "[c]oncerns about reliance interests arising from PTO determinations... are better directed to Congress").

¹⁸² Compare *March 2014 Guidance*, *supra* note 2 (outlining the 12-factor test), with *December 2014 Guidance*, *supra* note 2 (replacing the 12-factor test with the *Alice/Mayo* test and thereby narrowing the scope of the subject matter eligibility inquiry to claims directed to judicial exception rather than all claims that recite natural phenomena).

¹⁸³ See International Bioindustry Associations, July 2014, *supra* note 128, at 5-6 (criticizing the USPTO, associations were "concerned that the expansive scope of the Guidance reflects an investment-hostile extrapolation and expansion of nonstatutory U.S. patent law that was not required by the U.S. Supreme Court's decisions"). Several other comments reiterate similar criticisms. See, e.g., Storella Comments, *supra* note 128:

The Supreme Court cases on which the Guidance is predicated are narrow decisions based on specific fact patterns. Prudence dictates proceeding with caution. Yet the Guidance goes far beyond what the Supreme Court has decided. It calls into question the patent eligibility of subject matter there is no evidence it was ever the intention of the Supreme Court to withdraw.

Id.; see also AAU and APLGU Comments, *supra* note 128, at 2-3 (arguing on behalf of a broad consortium of research universities that such a broad reinterpretation should not have been published as a guidance for examiners without an opportunity for public comment and thus USPTO exceeded its authority).

any judicial exception, the December 2014 Guidance comports with *Mayo* Step 1, and asks only if the claim is *directed* to a judicial exception.¹⁸⁴ Thus, while a firework containing, *inter alia*, elemental sulfur, recited a product of nature under the March 2014 Guidance, and was therefore subject to further analysis because it contained naturally-occurring sulfur, under the December 2014 Guidance, such a device is not *directed* at sulfur (or any other exception), and thus requires no further analysis under §101.¹⁸⁵

In addition, for those claims that are directed to a judicial exception, the twelve-factor test for “significantly different” that the USPTO proposed in March 2014 is gone, replaced with a more straightforward test that comports with *Mayo* Step 2 – asking if the claim directed to a natural or abstract exception “recites additional elements that suffice to make it significantly more than the judicial exception.”¹⁸⁶

Where critics of the March 2014 Guidance noted a failure to consider difference in functions and character in distinguishing claims involving natural products as distinct from the exception itself, the December 2014 Guidance answers this directly.¹⁸⁷ The December 2014 Guidance provides that, in addition to structure and form, chemical and physical differences, biological/pharmacological functions, and phenotypic and functional characteristics are all included in

¹⁸⁴ Compare *March 2014 Guidance*, *supra* note 2, at 2-3 (suggesting that any claim that recited an element that was nature-based should be subject to an extended §101 inquiry), with *December 2014 Guidance*, *supra* note 2, at 74621-22 (narrowing the scope of the §101 inquiry).

¹⁸⁵ Compare *March 2014 Guidance*, *supra* note 2, at 9-10 (providing a hypothetical analysis of a firework as a nature-based product), with *Nature-Based Products Examples*, *supra* note 118, at 1 (illustrating that the USPTO still found the firework hypothetical to be sufficiently informative to be reprised in the *Nature-Based Products Examples* published by the USPTO with the *December 2014 Guidance*). Even under the abbreviated treatment of the two-step *Mayo* test following the December 2014 Guidance, it is hard to see what inventors and the patent examining corps can take away from this example, other than the general principle that combining naturally-occurring chemicals to produce a mixture that has functional properties not possessed by any of the natural components suffices to achieve eligibility – a principle that was not seriously debated before or after the *Mayo* and *Myriad* rulings.

¹⁸⁶ See *December 2014 Guidance*, *supra* note 2, at 74621-22 (illustrating in a revised flow chart and instructions for the *Mayo* Step 2 test).

¹⁸⁷ See, e.g., 22 July CAP Letter, *supra* note 133; cf. *December 2014 Guidance*, *supra* note 2, at 74623 (outlining numerous “non-limiting examples” of marked difference specifically referencing the key precedent cases).

a non-limiting list of factors that can contribute to making a nature-based product markedly different and thus §101 eligible at *Mayo* Step 1.¹⁸⁸

For those claims that *are* directed at judicial exceptions, the December 2014 Guidance corrects an identified deficiency of the March 2014 Guidance by emphasizing that, in the *Mayo* Step 2 analysis, the Examiner should consider whether “*any* element, or combination of elements...is sufficient to ensure that the claim amounts to significantly more than the judicial exception... considered both individually and as an ordered combination.”¹⁸⁹ The scope of what is required to satisfy the *Mayo* Step 2 inquiry is further emphasized by the USPTO’s acknowledgement of the guidance provided by *Alice*, an opinion that published the month after the USPTO had released its March 2014 Guidance.¹⁹⁰ In *Alice*, the Court looked for “an inventive concept sufficient to transform” the judicial exception to patent eligibility, and the USPTO cites this as a guiding principle in their application of Step 2 of the *Mayo* test.¹⁹¹ The recognition that inventions are to be protected regardless of their art field will go a long way to remediating the international confusion over §101 jurisprudence, as exacerbated by the March 2014 Guidance, in that the use of “inventive concept” conforms USPTO practice to U.S. commitments under TRIPS.¹⁹²

¹⁸⁸ See *December 2014 Guidance*, *supra* note 2, at 74624 (enumerating various routes to finding differences).

¹⁸⁹ See *December 2014 Guidance*, *supra* note 2, at 74624 (instructing examiners to take a broad approach to finding sufficient limitations in the claim as a whole to read as an inventive application, rather than narrowly focusing on claim elements that, by themselves, might be impermissible). Compare this to the criticism raised in the published comments on the March 2014 Guidance. See *e.g.*, *Wainer*, *supra* note 139 (calling on USPTO to correct *the March Guidance*, noting that claim elements must be considered individually and as a whole when weighing eligibility).

¹⁹⁰ See *December 2014 Guidance*, *supra* note 2, at 74624 (noting the clarification of the Court’s intent in *Myriad* by their opinion in *Alice*, and illustrating how frustrating it must be for USPTO to attempt the fill in the blanks left by the Supreme Court only to have the Supreme Court issue a different and authoritative interpretation almost immediately).

¹⁹¹ See *Alice*, 134 S. Ct. at 2357 (indicating that inventive concept is required to transform otherwise ineligible subject matter); see also *December 2014 Guidance*, *supra* note 2, at 74624 (articulating the standard used in determining whether a claim to a judicial exception is still patentable).

¹⁹² See *TRIPS Agreement* art. 27, *supra* note 22 (providing that “patents shall be available for any inventions, whether products or processes, in all fields of technology, provided that they are new, involve an inventive step, and are capable of in-

Earlier criticism that the March 2014 Guidance either failed to properly address process claims, or conflated process and composition issues, has been made moot,¹⁹³ primarily by the synthesis worked by the Supreme Court in *Alice*¹⁹⁴ which, as acknowledged by the USPTO, now offers a simple two-part analysis (the *Mayo* test) for claims directed at laws of nature, natural phenomena, and abstract ideas.¹⁹⁵

While the comments received and published by the USPTO in response to their previous attempt at a §101 Guidance in March were extensive and almost entirely negative,¹⁹⁶ most appear to have been addressed by the more recent December 2014 Guidance.¹⁹⁷ Some of the more philosophical issues raised, including the constitutional mandate underlying the patent system and the more directly expressed intent of the legislature remain, and may yet derail the apparent stabilization of the subject matter eligibility (or, more broadly, patentability) question.¹⁹⁸ A specific criticism in this vein leveled at the

dustrial application”). TRIPS Article 27 also allows for open-ended general exceptions to a right-to-patent for *ordre public*, morality, protection of life and the environment, and “essentially biological processes for the production of plants and animals,” as well as allowing specific exceptions for diagnostic, therapeutic, and surgical methods, animals and plants – although it specifies that plant varieties are to be protected, and implies that microorganisms are also not to be excluded from the scope of patent eligible subject matter. See *TRIPS Agreement* art. 27, *supra* note 22; see also 30 July FICPI Letter, *supra* note 129, at 5-6 (criticizing the March 2014 Guidance due to its incompatibility with treaty norms).

¹⁹³ See, e.g., 31 July Sundby Letter, *supra* note 83, at 3-5 (arguing for separate and distinct test process and composition claims); see also 30 July FICPI letter, *supra* note 129, at 9 (arguing that processes should be clearly patent eligible and not subject to outside factors provided for in the guidance).

¹⁹⁴ See *Alice*, 134 S. Ct. at 2354-59 (outlining how the *Mayo* holding can be generalized into a two-step test that can be used to effectively police eligibility of claims reciting or involving natural phenomena, law, or principles).

¹⁹⁵ See *December 2014 Guidance*, *supra* note 2, at 74621-22 (directing examination to follow the method illustrated in *Alice*, and repudiating the approach suggested in the March 2014 Guidance).

¹⁹⁶ See *Nature-Based Products Examples*, *supra* note 118, at 5 (providing Example 4, covering “Purified Proteins”).

¹⁹⁷ See *December 2014 Guidance*, *supra* note 2, at 74619 (explicitly rescinding the March 2014 Guidance and generally recasting the approach to the same issues covered by the previous document).

¹⁹⁸ See, e.g., 8 July ACLU Letter, *supra* note 133, at 4 (outlining concerns the constitutional mandate to “promote the progress of Science and useful Arts” is not implemented to be as progressive and useful in the lives of the people as it might). In raising the concern that overly broad patents will impact the “scientific, medical,

March 2014 Guidance was that it would inhibit the development of novel antibiotics.¹⁹⁹ The development of novel antibiotics to tackle emerging multi-drug-resistant infections remains a public health priority,²⁰⁰ and arguably Congress can, and already has, created specific tools that incentivize antibiotic development.²⁰¹ Nevertheless, an examination of the “Nature-Based Products” examples that the USPTO published “to be used in conjunction with the 2014 Interim Eligibility Guidance” reveals that the patent system itself may not be so supportive.²⁰² The “Purified Proteins” example (Example 4) describes a naturally-occurring antibiotic, but the example suggests that the antibiotic would only be eligible subject matter if there were some difference between the naturally-occurring molecule and the patented one.²⁰³ This raises the question of whether, for example, a drug based on the newly-discovered, naturally-occurring molecule Teixo-

and patient communities,” the ACLU would seek a more public-policy-oriented patent policy, contrary to the approach of the current Supreme Court, which explicitly seeks only to balance patent rights rewarding invention against overly broad patents that might inhibit invention, and declining any role in deciding what “progress” and “useful” should mean. See 8 July ACLU Letter, *supra* note 133, at 4. “[W]e must recognize the role of Congress in crafting more finely tailored rules...we need not determine here whether, from a policy perspective, increased protection [for a specific type of innovation] is desirable.” *Mayo*, 132 S. Ct. at 1305.

¹⁹⁹ See 28 July BPLA Letter, *supra* note 127, at 8-10 (discussing the consequences of placing restrictions on patentable subject matter); see also International Bioindustry Associations, July 2014, *supra* note 128, at 3 (highlighting the importance of the naturally-occurring substances which could provide a source of new antibiotic drugs); Chartered Institute of Patent Attorneys, July 2014, *supra* note 130, at 3 (agreeing with BPLA and IBA in expressing an apparently widely-held concern that USPTO’s guidance appears to prohibit the patenting of antibiotics).

²⁰⁰ See *Tracking the Pipeline of Antibiotics in Development*, THE PEW CHARITABLE TRUSTS (Dec. 2014), archived at <http://perma.cc/Q6AP-AF32> (highlighting the parlous state of the development pipeline for novel antibiotics in the face of the emerging need to tackle infections that are resistant to the current antibiotic armamentarium).

²⁰¹ See Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, 126 Stat. 993 (2012) (providing enhanced market exclusivity for new antibiotics in the form of an affirmative monopoly period, rather than a patent right subject to invalidation by a validity challenge).

²⁰² See *Nature-Based Products Examples*, *supra* note 118, at 5-7 (discussing eligibility of a newly discovered naturally-occurring antibiotic and its derivatives).

²⁰³ See *Nature-Based Products Examples*, *supra* note 118, at 5-6 (casting doubt on the eligibility of naturally-occurring antibiotics).

bactin would be able to avoid competition from a drug using the unpatentable, naturally-occurring molecule.²⁰⁴

D. Problems with USPTO December 2014 Hypotheticals

Of course, the hypotheticals explained by the USPTO in the published examples are simply that – hypotheticals.²⁰⁵ They neither record actual decisions made by the courts nor actual fact patterns occurring with respect to real inventions and real patent prosecutions, and thus it is unclear how applicable the examples will be.²⁰⁶ Specifically, it is far from clear under actual precedent that the isolation of DNA sequence excluded by *Myriad* will be analogized by future courts to the isolation of a novel, but naturally-occurring, antibiotic molecule when both are analyzed under the *Mayo* test. The courts have repeatedly indicated that they seek to balance appropriate rewards for innovation against improper monopolization of natural phenomena.²⁰⁷ If it came to litigation, one could see how the impact to innovation of creating a blanket ban on patenting of any and all of the many as-yet-unknown naturally-occurring antibiotics may cause a court to find, in the isolation of something so useful and unexpected, sufficient activity that was not routine, conventional, or well understood in the art to warrant eligibility under *Mayo* Step 2. So, it is

²⁰⁴ See Losee L. Ling et al., *A New Antibiotic Kills Pathogens Without Detectable Resistance*, 517 NATURE 455, 455-59 (2015) (announcing the discovery of the novel antibiotic). But even assuming that a modified version of the molecule was patented and developed as a therapy, presumably nothing would bar a competitor from using the naturally-occurring antibiotic or another derivative in the event that the inventors are unable to obtain broad patent on the naturally-occurring molecule and modifications of it. See also International Bioindustry Associations, March 2015, *supra* note 77, at 4-5 (expressing concerns that newly discovered naturally-occurring antibiotics that would be protected elsewhere would not be afforded patent protection in the U.S.).

²⁰⁵ See *Nature-Based Products Examples*, *supra* note 118, at 1-17 (proposing USPTO's analyses of a series of hypothetical examples of largely biology-based specification and claims).

²⁰⁶ See *Nature-Based Products Examples*, *supra* note 118, at 1 (admitting, in the USPTO's own document, the subject matter eligibility inquiry is fact based, and thus real scenarios may have different eligibility outcomes from the examples that the USPTO has authored).

²⁰⁷ See *Myriad*, 133 S. Ct. at 2116 (explaining that the court must apply this standard to determine the eligibility of both new, useful matter, as well as naturally-occurring phenomena).

quite possible that the USPTO got it wrong in their antibiotic example.

While facially accurate, some of the other examples the USPTO has published are not that helpful for examiners and the patent bar, in that they illustrate things already well understood. For instance, Example 5 “Genetically Modified Bacterium” appears to be nothing more than a recapitulation of *Chakrabarty*.²⁰⁸ Example 7, “Nucleic Acids,” is unhelpful for other reasons, as it posits a hypothetical in which a naturally occurring gene has no naturally occurring modifications.²⁰⁹ A claim directed at the gene itself is therefore not eligible – as it is directed to a product of nature (*Mayo* step 1) but adds nothing to it (*Mayo* step 2).²¹⁰ Alternately, a sequence that is the gene with one modification (that may or may not be functional) is eligible because it is markedly different from anything found in nature, because *in this hypothetical* there is no variation in the gene in nature.²¹¹ In promulgating such an example, the USPTO missed an opportunity to raise a much more interesting issue: would a claim where at least one minor but novel modification (not known to exist in nature) was made to a naturally-occurring gene sequence against a background where other similar (but not identical) modifications

²⁰⁸ See *Nature-Based Products Examples*, *supra* note 118, at 7-8 (using § 101 and *Myriad* to explain the holding in *Chakrabarty*); see also *Chakrabarty*, 447 U.S. at 305-06 (holding that genetically augmented bacteria are different from any found in nature and are thus eligible subject matter).

²⁰⁹ See *Nature-Based Products Examples*, *supra* note 118, at 9-11 (proposing the absurd hypothetical of a gene with no naturally occurring variants). While there are many genes that are highly conserved, in that they show very low levels of naturally-occurring variation, all known genes show some variation because the processes by which they reproduce themselves are imperfect. See, e.g., STRACHAN & READ, *supra* note 62, at 210 (reporting that on average any two copies of a gene vary at least at 1 in a 1000 nucleotides). At the population level, this indicates that even short genes will have some variability. *Id.* Even highly conserved genes will show at least the so-called “silent variants” that change the sequence of nucleotides but, due to the partial redundancy in the genetic code, not the sequence of amino acids. *Id.*

²¹⁰ See *Nature-Based Products Examples*, *supra* note 118, at 6 (relying on the simplistic hypothetical to reach the obvious conclusion that, where nothing like the invention exists in nature, the invention is eligible, and avoiding the more meaningful and difficult problem of deciding if an invention that represents an example variant of a natural system that itself exhibits extensive naturally-occurring variability would be eligible subject matter).

²¹¹ See *Nature-Based Products Examples*, *supra* note 118, at 6 (proposing an unrealistically simple hypothetical).

were known to occur (as in essentially all known genes) constitute eligible subject matter?²¹²

The hypothetical on antibodies is equally unhelpful because it is constructed with claims for antibodies directed to a bacterial antigen where no antibodies against the bacterial antigen are known to occur in humans.²¹³ Unfortunately, there is likely to be little real use for human antibodies to a bacteria such as the hypothetical *Staphylococcus texana* that apparently has never yet infected a human.²¹⁴ It remains likely that antibodies to organisms like Influenza, Zika or Ebola will be a lot more useful and valuable but, a reasonable extension of the argument outlined in this example suggests that an antibody cloned from a human patient would not enjoy patent protection as it already exists in nature.²¹⁵ Thus, the example may point to a problematic implication of the eligibility rules in that, if the *best* antibodies are already found in nature, there will be a perverse incentive to conceal the naturally-occurring molecule as a trade secret, while creating slightly altered synthetic molecules because, even if they

²¹² See *Nature-Based Products Examples*, *supra* note 118, at 6-7 (restating the principle that a naturally-occurring product that is unchanged from its natural state is not patent eligible). This is not the only interesting issue that the USPTO avoids addressing in this example. *Id.* After indicating that the naturally-occurring antibiotic protein is itself ineligible, the USPTO indicated that it would allow eligibility for a purified form of the protein – however, the hypothetical specification indicates that the purification introduces both structural and functional differences to the molecule. *Id.* at 5. In writing the example this way, the USPTO avoids discussion of a more interesting example – where purification resulted in a functional difference but in which the molecule remained identical to that found in nature, or in which there was a minor structural difference but where there was no apparent difference in function. *Id.* While it is easy to appreciate that, as in Example 4, Claim 2, a molecule with both structural and functional differences is markedly different, it would have been more informative to explore an example where only one of structural or functional was different, while the other remained indistinguishable from the natural form. *Id.* at 6.

²¹³ See *Nature-Based Products Examples*, *supra* note 118, at 11-13 (explaining, in Example 8 “Antibodies,” how eligibility analysis would apply to an unrealistic scenario that removes, by simplification, the key questions that would need to be answered for inventions with actual utility).

²¹⁴ See *Nature-Based Products Examples*, *supra* note 118, at 11 (tailoring the specification to create an unrealistic hypothetical that permits the analysis of the claims to proceed to an obvious answer).

²¹⁵ See *Nature-Based Products Examples*, *supra* note 118, at 12 (proposing an analysis of Claim 1 of Example 8 “Antibodies”).

function sub-optimally, they will enjoy patent protection.²¹⁶ In addition, while the hypothetical *specification* discloses human antibodies generated by challenging transgenic animals, none of the *claims* provides a specific limitation in this respect, and thus the issue of whether a human antibody found in a human would be subject to a different eligibility analysis than a human antibody found in a transgenic mouse (a mouse engineered to have a human immune system) is not only left unanswered, but undiscussed.²¹⁷

²¹⁶ See *Nature-Based Products Examples*, *supra* note 118, at 11-12 (proposing an analysis of Claim 4 of Example 8 “Antibodies”).

²¹⁷ See *Nature-Based Products Examples*, *supra* note 118, at 11-13 (failing to discuss in Example 8, concerning antibodies directed against a bacteria, the most obvious useful applications of antibodies to infectious agents). Consider, for example, the work of Chinese researchers who isolated antibodies capable of neutralizing pandemic flu from cells harvested from human subjects. See Hao Wang et al., *Generation of Human Neutralizing Monoclonal Antibodies against the 2009 Pandemic H1N1 Virus from Peripheral Blood Memory B Lymphocytes*, 10 CELLULAR & MOLECULAR IMMUNOLOGY 403, 403 (2013). These would appear to be broadly/generally not eligible subject matter following the analysis of the *Nature-Based Products Examples*. See *Nature-Based Products Examples*, *supra* note 118, at 11-13. Antibodies of this type generally exist commonly in nature as demonstrated by their discovery methods. See *Nature-Based Products Examples*, *supra* note 118, at 11-13. Wang and colleagues screened only 13,000 memory B-cells derived from just 14 subjects (each B-cell is the result of shuffling, and mutation of the antibody genes to produce one antibody) to isolate over 600 antibodies binding to influenza, of which seven were shown to have measurable virus neutralizing properties. See Wang et al., *supra* note 217, at 408. As there are about 5 million white blood cells in each milliliter of blood, of which perhaps 1% are memory B-cells, then this sort of antibody diversity probably exists in even small amounts of blood – 13,000 memory B-cells would be present in about 6 drops of blood. See B.L. Ferry et al., *Measurement of Peripheral B Cell Subpopulations in Common Variable Immunodeficiency (CVID) Using a Whole Blood Method*, 140 CLINICAL AND EXPERIMENTAL IMMUNOLOGY 532 (2005) (indicating the proportion of B-cells in a white cell preparation); *What Is a Normal Full Blood Count?*, CANCER RESEARCH UK (Oct. 2015), archived at <http://perma.cc/BQM4-ZP4G> (indicating the number of white blood cells in a given volume of healthy human blood). However, following the USPTO’s approach, antibodies in the species in question are known to exist in nature, but the claim is specific to a particular antibody molecule, so Wang et al. antibodies would be subject matter eligible if their claim was limited to specific molecules, even though those molecules were found readily in nature. See *Nature-Based Products Examples*, *supra* note 118, at 12; see also *Computer Based Training*, *supra* note 157 (in which the USPTO continued to avoid discussion of the more interesting, commercially relevant, and potentially controversial aspects of antibody patenting, opting to discuss only the simplistic scenarios outlined in hypothetical claims 1 through 3).

Finally, although Claim 5 of the antibody example sets up an example of otherwise ineligible antibodies that are made eligible by modifications to the “Fc region,” it does so in the context of a scenario in which it is specified that these regions are invariant within particular classes of antibody.²¹⁸ A much more interesting question, given the ubiquity of naturally-occurring variations even in the relatively stable areas of real, naturally-occurring proteins, is whether similar but deliberately introduced variations render the molecule patent eligible.²¹⁹ Unfortunately, the USPTO has elected to illustrate with a simplified scenario, and thus does not reach the more pressing question.²²⁰

The established commercial potential for antibodies is probably such that antibody products will continue to attract funding and commercialization efforts even if the subject matter eligibility of broad antibody claims or unmodified naturally occurring antibodies is now questionable.²²¹ On the other hand, the next generation of bio-

²¹⁸ See *Nature-Based Products Examples*, *supra* note 118, at 13 (arguing in Example 8, Claim 5, that making synthetic variants to a part of the molecule that is invariant in nature confers §101 eligibility). The USPTO’s hypothetical, as with the invariant gene of Example 4, is oversimplified to the point of being misleading here because the “Fc” or “constant” region of antibodies are only relatively constant compared to the “variable regions.” See *Nature-Based Products Examples*, *supra* note 118, at 11. “Within an antibody class” as expressed in the hypothetical specification, there is actually significant sequence diversity in the genes and the protein for which they code. See, e.g., A. M. Namboodiri & J. P. Pandey, *Differential Inhibition of Trastuzumab- and Cetuximab-Induced Cytotoxicity of Cancer Cells by Immunoglobulin G1 Expressing Different GM Allotypes*, 166 CLIN. EXPERIMENTAL IMMUNOLOGY 361, 361-65 (2011) (discussing naturally occurring functional variants *within* a class of antibodies).

²¹⁹ See Namboodiri & Pandey, *supra* note 218, at 364 (discussing such functional differences being engineered into therapeutic antibodies).

²²⁰ See *Nature-Based Products Examples*, *supra* note 118, at 11-14 (arguing in Example 8 – “Antibodies” that deliberately introduced changes make an otherwise ineligible antibody claim eligible, but within the unrealistic and simplistic hypothetical premise that similar, naturally-occurring variants do not exist). USPTO was actually prompted to construct examples that were close to line of eligibility rather than rehearsing simplistic hypotheticals. See also Donald Zuhn, *USPTO Expected to Issue Revised Myriad-Mayo Guidance in October*, PATENTDOCS.ORG (Sept. 2014), archived at <http://perma.cc/4TNL-M3M6> (reporting a presentation at the USPTO by Genentech’s VP of IP, Paul Naik, noting that hypothetical examples, such as those seen in the *Nature-Based Products Examples*, which are clearly eligible or clearly ineligible were unhelpful).

²²¹ See Philippidis, *supra* note 4 (illustrating the commercial success of antibody based drugs); see also Palmer, *supra* note 4 (expanding on the successful distribu-

tech products, ATMPs,²²² have less certain commercial and development pathways.²²³ In this regard, the Nature-Based Product Example 7 “Nucleic Acids” Claim 5 is interesting, as it clearly indicates that “vectors” comprising a naturally-occurring payload gene and naturally-occurring sequence from another organism (for example a virus) would constitute patentable subject matter.²²⁴ Whether a *broad* claim describing a payload gene and *any* heterologous sequence would ultimately be patentable as suggested here by the USPTO seems doubtful, as a claim of such generality would appear to be nothing more

tion of antibody drugs in the market). There are two ways of looking at this issue – on the one hand, nature has provided so many antibodies that patenting a few does not substantially preempt anything except a competitor’s ability to benefit from the patent holders’ development efforts. But, on the other hand, antibodies are products of nature, and “discovery does not by itself satisfy the §101 inquiry.” See *Myriad*, 133 S. Ct. at 2117. The natural biology of antibodies is based on a diversity-generating engine in which gene shuffling and somatic hypermutation generate a mind-boggling potential diversity of antibodies that are winnowed and matured by other elements of the immune system to create an adaptive immune response. See JANEWAY ET AL, *supra* note 6, at Chapter 4 (describing the generation of antibody diversity). This problem, that nature herself is inventive, and that inventiveness can be harnessed by molecular biologist thus creating a real question as to whether a claimed invention is a product of human ingenuity, is central to questions of antibody patentability but is not substantively resolved here. See *Nature-Based Products Examples*, *supra* note 118, at 13 (failing to investigate more nuanced and realistic questions arising in the antibody field with respect to the evolution of §101 law).

²²² See Committee for Advanced Therapies (CAT), *Reflection Paper on Classification of Advanced Therapy Medicinal Products* (European Medicines Agency, Paper EMA/CAT/600280/2010, 2012) hereinafter European Medicines Agency, Paper] (discussing the utility and development prospects of next generation biotechnology products).

²²³ See F. D. Ledley et al., *Why Commercialization of Gene Therapy Stalled: Examining the Life Cycles of Gene Therapy Technologies*, 21 GENE THERAPY 188, 191-93 (2013) (discussing and illustrating the pitfalls to the development and commercialization of next generation biotechnology products).

²²⁴ See *Nature-Based Products Examples*, *supra* note 118, at 10-11 (proposing eligibility analysis for a genetic vector). Vectors in the ATMP space are likely to be used for gene and cell-based therapies. See also European Medicines Agency, Paper, *supra* note 222, at 4 (discussing “advanced therapy medicinal products,” or ATMPs as a collective group comprising variously cell, gene and tissue based therapeutics). A vector is simply a means to get something inside a cell – typically a gene. *Id.* at 7. The typical approaches to this are to use vehicles that are already equipped to get into cells (e.g., viruses), that are modified either to amend their ability to cause disease and/or their ability to replicate once they get inside the target cell. *Id.* at 4. The modified virus is also engineered to carry one or more payload genes that are intended to change the function of the target cell. *Id.*

than a patent on the payload gene with an instruction to deliver it using a method that is well known and conventional in the art, nevertheless the gene in *any vector* is not something ordinarily found in nature and so (ignoring §112 issues for the moment) the claim is at least §101 eligible.²²⁵

Most of the other examples given are not of principal interest from the perspective of biotechnology.²²⁶ However, Example 9 “Cells” discussed stem cells artificially differentiated to create regenerative cells.²²⁷ Where such cells are identical to those found in nature, they fail the eligibility test at *Mayo* Step 1, as despite the non-natural means of production, the cells that a claim would seek to protect are no different from the naturally occurring cells that they mimic.²²⁸ On the other hand, if in the process of producing the differentiated cells, novel structure or functions are created, then the modified

²²⁵ See *Nature-Based Products Examples*, *supra* note 118, at 9-11 (providing USPTO’s guidance in Example 7 “Nucleic Acids,” with a hypothetical specification disclosing specific viral vectors and vector components “...such as tobacco mosaic virus . . . [and] . . . cauliflower mosaic virus 35S promoter,” but where one claim (Claim 4) is baldly generic “a vector comprising [the payload gene] and a heterologous nucleic acid sequence”). In analyzing the claim, the USPTO indicates that, because the whole vector (naturally-occurring gene plus sequence from at least one other organism) is not found in nature, it has structural difference from what is found in nature, and that “some” of the covered constructs “may” have functional differences, so the claim is drawn to §101 eligible subject matter. See *Nature-Based Products Examples*, *supra* note 118, at 11. Given that the payload gene is itself ineligible as set out in the hypothetical by USPTO, it seems as if Claim 4 as constructed might fall to the same issues identified in *Alice* when the court noted that “nothing significantly more than an instruction to apply [the exception] . . . simply appending conventional steps at high level of generality was not enough.” See *Alice*, 134 S. Ct. at 2357 (internal quotations omitted). However, while the *Alice* Court was discussing a process, and the *Nature-Based Products* Example 7 Claim 4 is a composition, the issue is different – adding “heterologous sequence” without limitation may “add[s] nothing of substance to the underlying [ineligible matter],” but it remains structurally different from the natural gene. See *Alice*, 134 S. Ct. at 2360.

²²⁶ See *Nature-Based Products Examples*, *supra* note 118, at 1, 2, 8 (covering fireworks, fruit juice, plant extracts, mixtures of bacteria and food as examples).

²²⁷ See *Nature-Based Products Examples*, *supra* note 118, at 13-16 (examining in Example 9 eligibility of inventions based cells).

²²⁸ See *Nature-Based Products Examples*, *supra* note 118, at 14 (providing USPTO’s analysis of hypothetical Example 9, Claim 1 an isolated, naturally-occurring cell).

cells are patentable; because they are different from anything found in nature, they pass the eligibility threshold at *Mayo* Step 1.²²⁹

Perhaps the most interesting claim in the whole set of hypotheticals posited by the USPTO is one found in Example 9 that combines the fully human cells (synthetically derived but otherwise identical to naturally occurring cells – found ineligible by themselves) and then adds them to a biologic scaffold also found in nature.²³⁰ When combined in therapy, these two ineligible items work to improve the tissue repair affected by the differentiated cells.²³¹ Because the two *individually* ineligible elements taken *together* amount to significantly more than either of the natural phenomena alone, their combination is transformed into eligible subject matter.²³² Although there are only three possible solutions to the *Mayo* Test,²³³ and some 37 example claims analyzed, Example 9, Claim 5 – the cells on the biologic scaffold – is the sole illustration of a claim that fails at *Mayo* Step 1 but is found eligible at *Mayo* Step 2.²³⁴ As neither *Myriad*, *Mayo*, *Alice* nor *Ambry* provide any *actual* examples of *Mayo* Step 2

²²⁹ See *Nature-Based Products Examples*, *supra* note 118, at 14-15 (providing USPTO's analysis of hypothetical Example 9, Claims 2 and 3, inventions including cells with non-natural biological structure and function).

²³⁰ See *Nature-Based Products Examples*, *supra* note 118, at 15-16 (providing USPTO's analysis of hypothetical Example 9, Claim 5, a §101 eligible invention comprising a novel combination of two naturally-occurring biologics, a biological scaffold, defined as structures composed of naturally-occurring materials unchanged from their natural states, thus ineligible by itself, together with the cells of Claim 1, also individually ineligible).

²³¹ See *Nature-Based Products Examples*, *supra* note 118, at 15-16 (describing the combination of naturally-occurring elements to yield a novel biologic structure).

²³² See *Nature-Based Products Examples*, *supra* note 118, at 15-16 (concluding that the claim qualifies as eligible subject matter because it surpasses the requirements of the judicial exception).

²³³ See *December 2014 Guidance*, *supra* note 2, at 74621-22 (indicating that a claim is either (outcome 1) eligible at Step 1 of the *Mayo* test as having a marked difference from what occurs in nature, ending the analysis, or it proceeds to Step 2). At Step 2, there is/are no additional element(s) that amount to significantly more than the exception, in which case the claim is drawn to ineligible subject matter (outcome 2), or alternately there is/are one or more elements that, taken separately or in combination, amount to something significantly more than the judicial exception, in which case the claim is §101 eligible (outcome 3). See *Alice*, 134 S. Ct. at 2355.

²³⁴ *Nature-Based Products Examples*, *supra* note 118, at 15-16 (providing the only example of a composition containing only naturally-occurring biological materials that remains subject matter eligible due to emergent functional characteristics when the claim is considered as a whole).

applied positively to claims so as to *support* §101 eligibility, this is a particularly interesting area and, given the volume of documents produced on subject matter eligibility, it is disappointing that the USPTO devoted only limited effort to this.²³⁵ Lacking any recent precedent, and none at all relating to biomedical invention, this is the least certain part of the *Mayo* test, perhaps explaining why the USPTO did little to clarify how it would draw the line.²³⁶ But, it would have served the community better if USPTO had done more to illustrate the uncertainty in this area by more clearly showing where the courts have yet to rule.²³⁷ While the USPTO provided additional worked examples in July 2015, these all addressed inventions in computing, computation, or engineering claiming or involving abstract ideas, while no additional examples of nature-based products were published.²³⁸

²³⁵ See *Alice*, 134 S. Ct. at 2357-60; see also *Myriad*, 133 S. Ct. at 2112-20; *Mayo* 132 S. Ct. at 1296-97; *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig.*, 774 F.3d at 760-65 (failing to yield, in all these cases, an example of a claim comprising material(s) drawn unmodified from nature and applied in a manner sufficiently inventive to warrant eligibility under §101).

²³⁶ See *December 2014 Guidance*, *supra* note 2, at 74622-25 (omitting to illustrate how a claim can fail at *Mayo* Step 1, and yet meet eligibility requirements at Step 2). In failing to give guidance, USPTO may feel damned either way. Lacking any recent guidance from the courts, USPTO may not wish to commit to a particular scheme. However, without provoking a discussion, they will still have to address the issue (in practice) of deciding what is enough to make a claim eligible at *Mayo* Step 2. See *December 2014 Guidance*, *supra* note 2, at 74621-22 (encouraging more in depth analysis of judicial exceptions). As USPTO must have encountered real patent claims where it has found eligibility under *Diehr* for claims that facially recite a judicial exception, it would be more helpful to compile those granted claims for review and discussion rather than leaving the issue hanging.

²³⁷ See *July 2015 Update Appendix 1: Examples*, USPTO, archived at <http://perma.cc/MFX4-QAX6> (providing only obvious examples of how eligibility analysis will proceed under the *Alice/Mayo* test as implemented by USPTO).

²³⁸ See *id.* (presenting the seven new examples); see also *July 2015 Update on Subject Matter Eligibility*, 80 Fed. Reg. 45429, 45429 (July 15, 2015) (acknowledging that, after publication of the December 2014 Guidance, there were many “requests for additional examples,” although none illustrating biotechnology or biomedical inventions were published); Kevin E. Noonan, *Biotech-specific Subject Matter Eligibility Materials Delayed*, PATENTDOCS.ORG (July 2015), archived at <http://perma.cc/CML4-NG62> (noting that “PTO sources indicate that the expected biotech and diagnostic methods materials are still in process and are expected to be put up on the PTO website in future,” and suggesting that the delay may have been occasioned by internal dissent within the office).

Looking back to how and why the *Mayo* court framed Step 2 of their inquiry, one sees that what is added by the invention that amounts to “significantly more” must be more than “conventional or obvious”, and the additional steps need to integrate the judicial exception into the solution so that the resulting claim does not foreclose other uses of the exception.²³⁹ In setting out these criteria, the *Mayo* court looked to the inventive application of the fundamental (and otherwise patent ineligible) Arrhenius equation to the problem of heat curing rubber, which was found eligible subject matter in *Diehr*.²⁴⁰ Beyond *Diehr*, the Supreme Court was forced to look back to an English case, *Neilson v. Harford*, to further illustrate how the concept of a particularly inventive application could support a limited patent on an underlying natural principle.²⁴¹ This is a slim basis on which to build a theory of what compromises “significantly more” – there must be something other than the bare exception, but how much that has to be to amount to an “inventive application” remains relatively opaque.²⁴² The clearest answer to this might come from what is *not claimed* with respect to the judicial exception. Just as the *Diehr* and *Neilson* inventions didn’t preempt other uses of the natural phenomena, but the *Mayo* and *Myriad* inventions did, the surest route to §101 eligibility may be to ensure that it is clear how other potential uses of

²³⁹ See *Mayo*, 132 S. Ct. at 1298-99 (discussing claim limitations required to make a judicial exception eligible under §101).

²⁴⁰ See *id.* at 1298-00 (indicating that inventive concept is required).

²⁴¹ See *id.* at 1300 (drawing upon *Neilson v. Harford* – which concerned whether or not the invention, a blast furnace, sought to impermissibly patent the principle that heated air promotes combustion better than cold air – the *Mayo* Court concluded that “the claimed process included not only a law of nature but also several unconventional steps...that confined the claims to a particular useful application of the principle”). Thus the *Mayo* Court noted that the invention included something else beyond the exception that was “unconventional” and “useful.” *Id.* In reaching this analysis, the *Mayo* Court quoted, with approval, the *Neilson* judgment, where Lord Parke indicated “...we think that the Plaintiff does not merely claim a principle, but a machine *embodying a principle*, and a very *valuable* one” (emphasis added), indicating that the claim is rescued from being a naked principle by the integration of the principle into the invention in a “valuable” (useful) manner. See *id.* (citing *Neilson v. Harford*, 151 ER 1266 (1841)).

²⁴² See *Mayo*, 132 S. Ct. at 1298-00 (discussing the use of the Arrhenius equation in *Diehr*, and holding that because “[t]hese other steps apparently added to the formula something that in terms of the patent law’s objectives had significance – they transformed the process into an inventive application of the formula”).

the judicial exception integrated into the claimed invention are not foreclosed to others.²⁴³

E. Further USPTO Hypotheticals – The May 2016 Guidance

It was inevitable, given the gaps in the previously published guidance and hypotheticals, that the USPTO would receive additional critical comments, and would then seek to address these with new published guidance.²⁴⁴ The May 2016 Guidance has three substantive components: two documents and an invitation.²⁴⁵ The first document addresses recent shortcomings in examiner communications concerning §101 rejections pointed out by, amongst others, the AIPLA.²⁴⁶ This document requires examiners to explicitly identify the judicial exception to which claimed matter corresponds, explain why it is not distinguishable from the exception, enumerate any additional features or limitations, and explain why each such feature/limitation, taken individually or in combination, fails to amount to significantly more than the exception itself.²⁴⁷ While some critics,

²⁴³ See *id.* at 1299 (discussing the court's view of how non-preemption occurs "the patentees did not seek to pre-empt the use of the [judicial exception] but sought only to foreclose others from the use of that [judicial exception] in conjunction with all of the other steps in their claimed process" (internal citations omitted)). *But see* *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1379-80 (Fed. Cir. 2015) (invalidating all claims in a patent that sought to claim a method of detecting novel, but admittedly natural, phenomenon (cell-free fetal DNA (cffDNA) in maternal serum) which, at least in some claims, did not appear to preempt other uses of the phenomenon of cffDNA).

²⁴⁴ See *May 2016 Guidance*, *supra* note 2, at 27381-82 (announcing the availability of a memorandum to examiners aiming to improve examiner correspondence concerning §101 rejections, and announcing the production by the USPTO of further life science examples derived from hypothetical fact patterns as well as existing case law).

²⁴⁵ See *id.* at 27381-82 (announcing the availability of the memo and new examples, and an invitation to comment).

²⁴⁶ See American Intellectual Property Law Association (AIPLA), Comment Letter on the USPTO 2014 Interim Guidance on Patent Subject Matter Eligibility 12-14 (Mar. 16, 2016), *archived at* <https://perma.cc/W6EM-ZJMT> (noting that examiners have been rejecting claims under the new §101 jurisprudence with merely conclusory assertions, and recommending that examiners need to be instructed to make a prima facie case to support §101 rejections).

²⁴⁷ See Memorandum from Robert W. Bahr, Deputy Commissioner For Patent Examination Policy, United States Patent and Trademark Office, to Patent Examining Corps (May 4, 2016) (on file with USPTO.gov) [hereinafter *Bahr Memo - May 2016*] (providing further instructions to examiners designed to improve corre-

such at the BPLA, have continued to call for a refocusing of the USPTO Subject Matter Eligibility Guidance on the issue of preemption, the USPTO declines to take this path, arguing that preemption is “inherent in” and “resolved by” the two-part Mayo test.²⁴⁸

The second document published in May 2016, containing six additional examples, continues in much the same vein as the December 2014 Guidance.²⁴⁹ Interestingly, three of the examples are now drawn directly from real case law.²⁵⁰ Two of these are vintage inventions included to illustrate scenarios where the ‘streamlined’ analysis would show that, because the claims as a whole provide an obviously limited application of an underlying judicial exception, no Mayo analysis would be required.²⁵¹ Neither provide insight into claims that the USPTO might consider marginal under current §101 law.²⁵² A vaccine example covers a scenario in which an inventor is able to locate a novel mutant gene in a virus where no mutations at all are known to occur in nature, thus predictably making a the single-mutant gene eligible subject matter in the context of an attenuated-

spondence concerning §101, and further noting that while examiners may not rely on USPTO’s published examples to make rejections (which must be based on case law), applicants are free to cite examples in support of their eligibility examples). If for no other reason, this makes the examples worth careful study.

²⁴⁸ See The Boston Patent Law Association (BPLA), Comment Letter on the USPTO 2014 Interim Guidance on Patent Subject Matter Eligibility 2-4 (Mar. 16, 2016), archived at <https://perma.cc/2VJY-HT6F> (arguing that, as concern over tying up other uses of the judicial exceptions lies at the heart of the case law, significant preemption should be considered a necessary precursor to further eligibility analysis, i.e. absent significant preemption of the judicial exception that a composition or method would automatically be eligible subject matter).

²⁴⁹ See *Subject Matter Eligibility Examples: Life Sciences*, USPTO (May 2016), archived at <https://perma.cc/6NBX-U5KT> [hereinafter *Life Sciences Examples – May 2016*] (providing six further example specifications, claims, and analyses loosely based around life science subject matter, augmenting the examples provided in the *Nature-Based Products Examples*, supra note 118).

²⁵⁰ See *id.* at 23-31 (offering three examples drawn from real patents, holding out the promise of scenarios relevant to current practice, as opposed to contrived and simplified hypotheticals).

²⁵¹ See *id.* at 28-31 (providing a summary of the claims at issue in *Eibel Process Co. v. Minnesota & Ontario Paper Co.*, 261 U.S. 45 (1923) interpreted in the light of post-Mayo USPTO policy, and comparing the Supreme Court’s analysis of *Tilghman v. Proctor*, 102 U.S. 707 (1881) to current day USPTO policy concerning “streamlined” analysis of §101 eligibility).

²⁵² See *id.* at 28-31 (discussing *U.S. Patent 845,224* – a paper making machine and *U.S. Patent 11,766* – the hydrolysis of fats, neither of which offer insight into substantive issues relating to contemporary biotechnology patenting).

virus vaccine claim. However, USPTO declines to address the more realistic problems of whether a *novel* mutant in the context of a gene known to have *other* mutations in nature, maybe with and without comparable phenotypic effects, might be eligible.²⁵³ Two other examples make pedestrian points; one is a diagnostic-serology-and-treatment invention that covers the same ground as *Mayo*.²⁵⁴ However, counter to the actual *Mayo* patent, the example illustrates how an applicant might transform the judicial exception (correlation between diagnostic marker and disease) into a patent eligible diagnose-and-treat method.²⁵⁵ In the example, this is done by reciting limitations *without* a high level of generality and adding limitations that are unconventional and/or go beyond what is simply well understood, routine and conventional extra-solution activity.²⁵⁶ The other example is an explicit recapitulation of *Myriad* and *Ambry* (as extensively discussed above), but crafts a counter-factual ending to the BRCA saga by positing hypothetical additional claims in which non-novel but unconventional analytical methods were utilized to detect the BRCA mutants, thus rendering claims incorporating them eligible subject matter.²⁵⁷

The May 2016 move by the USPTO closes with an open-ended invitation to interested parties to continue to submit comments

²⁵³ See *Life Sciences Examples – May 2016*, *supra* note 249, at 1-4 (outlining the implausible but easy to interpret scenario where a gene has no naturally-occurring variants, the same device used in the *Nature-Based Products Examples*, *supra* note 118); see also *supra* notes 209, 210, 211, 213, & 214 and accompanying text (where a gene has no mutations, no human antibodies exist to a species of *Staphylococcus* and the Fc region of an antibody is without variants with an antibody class).

²⁵⁴ See *Life Sciences Examples – May 2016* *supra* note 249, at 9-16 (providing an example similar to the facts in *Mayo* but with patent eligible claims as a result of the use of unconventional technology and narrower scope of claiming).

²⁵⁵ See *id.* (illustrating how *Mayo* step 2, the ‘significantly more’ analysis rescues impermissible monopolization of biomedical phenomena by addition of inventive limitations).

²⁵⁶ See *id.* (spelling out the lessons in the *Mayo* opinion). While there is nothing facially objectionable about this example, there is nothing here that could not already have easily been gleaned from *Mayo*. See also *Mayo*, 132 S. Ct. at 1294 (explaining that “an inventive concept [suffices] to ensure that the patent in practice amounts to significantly more than the patent upon the natural law itself”).

²⁵⁷ See *Life Sciences Examples – May 2016* *supra* note 249, at 23-28 (recapitulating BRCA mutant detection with and without additional limitations specifying the inventive use of unconventional detection methods).

to the Office concerning the various eligibility guidances.²⁵⁸ No doubt the details of the USPTO guidance will continue to be debated, but judging by the lower volume and more moderate tone of the recent commentary submitted to the USPTO, it appears that the principle parameters of the issue are now settled.²⁵⁹

V. CONCLUSION

A period of disruption, occasioned by the lack of clarity amongst applicants and examiners in how Supreme Court precedent relating to the patent eligibility of important intellectual property products of the biotechnology field should be applied, has now come to a close. Unsupported eligibility guidance issued by the USPTO has been superseded by guidance that more closely comports with the precedent cases. During 2014, important cases such as *Alice* and *Ambry* further explained and settled what was decided in 2012 (*Mayo*) and 2013 (*Myriad*). Genes and disease states are not, in themselves, eligible for broad patent protection. However, the courts have indicated that these judicial exceptions are to be framed as narrowly as is consistent with preventing the undue monopolization of phenomena of nature or natural principles, so that both minor differences from products of nature and inventive applications of natural principles that do not generally seek to monopolize the natural principle itself, remain patent eligible subject matter.

While the *de minimus* structural or functional difference required to distinguish a composition of matter is well understood and illustrated by precedent, the more nebulous concept of what constitutes “significantly more” than a judicially-recognized exception to eligibility remains sparsely illustrated by precedent, and the USPTO also seems reticent to discuss it. In general, this area of law has been

²⁵⁸ See *May 2016 Guidance*, *supra* note 2, at 27382 (indicating that the USPTO intends to continue soliciting comments for an indefinite period). There was also one additional example given concerning a natural sweetener, but as it does not fall directly within the biotechnology focus of this note, further analysis of this example is omitted.

²⁵⁹ See *Comments on 2014 Interim Guidance on Patent Subject Matter Eligibility – March 2015*, USPTO, archived at <https://perma.cc/28YX-S6FA> (indexing comments received by USPTO between December 2014 and March 2015, in addition to a small number of comments received after the March 2015 deadline for this comment round).

well served by pared down and broadly applicable rules such as those articulated in *Alice* and the Scalia concurrence in *Myriad*.

The recommendation emerging from this review is that the USPTO would do well to avoid extraneous generalizations, analogies, and hypothetical illustrations that are neither called for by statute nor clearly based on precedent. To the extent that USPTO needs to issue guidance, it should be confined to clearly stated principles, and then applied to the immediate facts of real patent prosecutions without the hypotheticals.

To the extent that *actual* patent prosecutions are at least grounded in real facts, the USPTO might better serve the examining corps and the other interested parties by fostering debate based on *actual* patent prosecutions as they unfold, or shortly thereafter, if this can be disentangled from the legal and commercial interests of the parties. As for inventors and their patent counsel who are looking to prosecute patents for biotechnology implementations of natural or near-natural phenomena or natural principles – while undoubtedly some confusion will continue, there is firm ground to be found in the two-part *Mayo* test, and few questions that cannot be answered by applying the Scalia criterion from *Myriad* and the *Alice* explanation of the *Mayo* test to any drug, molecule, or biology-reciting claim that could be subject to a §101 analysis, while keeping a close eye on USPTO actions that appear to derive from elements of their own Guidances that step outside the controlling precedent.