STEM CELLS & THE TRAJECTORY OF SECTION 101 JURISPRUDENCE AFTER *MYRIAD*

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ABSTRACT

Many patents have issued that claim either human embryonic stem cells (ES cells) or induced pluripotent stem cells (iPS cells). Yet it is unclear, given the U.S. Supreme Court's bewildering recast of the product of nature doctrine in *Association for Molecular Pathology v. Myriad Genetics, Inc.*, whether innovations that employ either stem cell type will remain eligible subject matter under section 101 of the Patent Act. In this essay, I first trace the trajectory of the Court's precedents on section 101, following those that address laws of nature and products of nature. I characterize the Court's approach in early section 101 precedents as organic because it respects the complexity of individual characteristics of the invention claimed in a given patent by assigning a proper degree of salience for purposes of determining the subject matter eligibility of patent on the whole.

What is more, early precedents respect the unified whole of these individual characteristics through consideration of the extent to which the design and intent of the claimed invention accords with fundamental norms around what does and does not warrant patent protection. An artificial approach, in contrast, assigns disproportionate salience to certain features, which has the effect of mischaracterizing the invention on the whole for purposes of distinguishing between natural (ineligible) and non-natural (eligible) subject matter. I contend that the Court appears increasingly willing to jettison its prior organic approach

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for a more artificial one that mischaracterizes and disproportionately weights individual features of claimed inventions based largely on the intuitive appeal of certain similarities and differences between natural and non-natural characteristics. I argue that this tendency may engender difficulties for the subject matter eligibility of innovations that utilize ES cells, but likely not for those that utilize iPS cells.

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I. INTRODUCTION

Association for Molecular Pathology v. Myriad Genetics, Inc.[2] stands as the most recent iteration of a long and circuitous line of cases addressing the limits of subject matter eligibility under section 101 of the Patent Act.[3] Myriad's patents concerned the precise location and sequence of the BRCA1 and BRCA2 genes.[4] Mutations in these genes carry very real health risks. The risk associated with developing breast or ovarian cancer for women with certain genetic mutations climbs to between 50 and 80 percent for breast cancer, and between 20 and 50 percent for ovarian cancer.[5] By discerning the location and sequence of the BRCA1 and BRCA2 genes, Myriad determined their typical

[2] 133 S. Ct. 2107 (2013).

[3] 35 U.S.C. § 101 (West, Westlaw through P.L. 114-49 approved Aug. 7, 2015); *see infra* notes 27–40 and accompanying text (discussing judicially created exceptions to subject matter eligibility under section 101).

[4] *Myriad*, 133 S. Ct. at 2112.

[5] *Id.*

nucleotide sequence and thereby developed diagnostic tests to detect for mutations in these genes.[6] Myriad's efforts, therefore, carry great therapeutic promise and stand to serve an important preventive health function.[7]

Stem cells have been similarly lauded for their therapeutic promise.[8] Some stem cell therapies have been successfully and widely adopted. Successful bone marrow transplantation, for instance, dates to the late 1960s.[9] As a further example, successful transplantation utilizing umbilical cord blood, another source of stem cells, dates to 1988.[10] Other stem cell therapies, such as those that rely on human embryonic stem cells (ES cells[11]), have witnessed less success.[12] The therapeutic promise of ES cells has, nonetheless, been touted since derivation of the first stable human ES cell line in 1998.[13] ES cells have the potential to treat, among other conditions, Parkinson's disease, heart disease, spinal cord injuries, diabetes, and amyotrophic lateral sclerosis.[14] With generation of induced pluripotent stem cells (iPS cells) in 2006[15] came still greater therapeutic promise, particularly

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[6] *Id.* at 2112–13.

[7] *See* Robert L. Dorit, *Brave New Worlds*, AM. SCIENTIST (2015) (reviewing SHOBITA PARTHASARATHY, BUILDING GENETIC MEDICINE: BREAST CANCER, TECHNOLOGY, AND THE COMPARATIVE POLITICS OF HEALTH CARE (2007)), *available at* http://www.americanscientist.org/bookshelf/pub/brave-new-worlds (discussing the importance of BRCA testing in the medical community).

[8] *E.g.,* Tracy Thompson, *What is the Promise of Embryonic Stem Cell Research?* 93 J. NAT'L. CANCER INST. 1445 (2001) (discussing embryonic stem cell research).

[9] Mortimer M. Bortin, *A Compendium of Reported Human Bone Marrow Transplants*, 9 TRANSPLANTATION no. 6, 1970, at 571.

[10] Elaine Gluckman et al., *Hematopoietic Reconstitution in a Patient with Fanconi's Anemia by Means of Umbilical-Cord Blood from an HLA-Identical Sibling*, 2 CELLULAR THERAPY & TRANSPLANTATION no. 7, 2010, at 2, *originally printed in* N. ENGL. J. MED., Oct. 26, 1989 at 1174.

[11] I use 'ES cells' throughout to denote human embryonic stem cells, as opposed to embryonic stem cells derived from animals.

[12] John A. Robertson, *Embryo Stem Cell Research: Ten Years of Controversy*, J. OF L. MED. & ETHICS, Summer 2010, at 194–96.

[13] *See* James A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCI., 1145, 1145 (1998) (discussing the progress of stem cell research); *see also* Michael J. Shamblott et al., *Derivation of Pluripotent Stem Cells from Cultured Human Primordial Germ Cells*, 95 PROC. NAT'L ACAD. SCI., 13726, 13726 (1998) (discussing the pluripotent nature of stem cells *in vitro* and *in vivo*).

[14] Daisy A. Robinton & George Q. Daley, *The Promise of Induced Pluripotent Stem Cells in Research and Therapy*, 481 NATURE 295, 295–305.

[15] iPS cells were first generated utilizing mouse models. *See* Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from*

around developing the capability to tailor therapies to specific patients.[16]

Many patents have issued for innovations that employ either ES or iPS cells.[17] Yet it is unclear, given the *Myriad* Court's bewildering recast of the product of nature doctrine,[18] whether technologies that employ either stem cell type will remain eligible subject matter under section 101. Absent the exclusivity rights that attend patent protection,[19] investment in therapies that endeavor to realize the potential of stem cells may decelerate. In this essay, I evaluate whether patents claiming either ES cells or iPS cells remain eligible subject matter under section 101 after *Myriad*. I first trace the trajectory of the Court's section 101 precedents, following those that address laws of nature and products of nature. While *Myriad* falls under the latter category,[20] as I will demonstrate, the Court has and continues to conflate both categories. Commenters have rightly criticized the Court for this poor organization of its own precedents,[21] which no doubt contributes to a persistent inability

Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors, 126 CELL 663, 663 (2006) (discussing the process). One year after Takahashi and Yamanaka had success with mouse models, two separate laboratories reported successful generation of iPS cells by utilizing human cells. Kazutoshi Takahashi et al., *Induction of Pluripotent Stem Cells from Adult Human Fibroblast by Defined Factors*, 131 CELL 861, 861 (2007); Junying Yu et al., *Induced Pluripotent Stem Cell Lines Derived From Human Somatic Cells*, 318 SCI. 1917, 1917 (2007).

[16] *E.g.,* Robinton & Daley, *supra* note 13, at 295–305. (noting one instance of further therapeutic promise).

[17] *See infra* notes 155–66, Parts III.a, III.b, IV, V, 167–94 and accompanying text (discussing the various patents using ES and iPS cells).

[18] *See infra* notes 122–29, 136–37 and accompanying text (discussing the *Myriad* decision).

[19] *See* U.S. CONST. art. I, § 8, cl. 8. ("To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries"); *see also* Christopher R. Leslie, *Monopolization Through Patent Theft*, 103 GEO. L.J. 47, 48 (2014) (explaining that "[t]he patent system encourages innovators to invest in research and development . . . by granting an inventor a significant period of exclusivity during which no one else can make or sell a product (or use a process) that infringes the inventor's patent. Without this period of exclusivity, innovators may worry that their inventions could be copied and sold by competitors who have not invested the time and money to create the product or process.").

[20] Ass'n for Molecular Pathology v. Myriad Genetics, 133 S. Ct. 2107, 2111 (2013).

[21] Dan L. Burk, *The Curious Incident of the Supreme Court in* Myriad Genetics, 90 NOTRE DAME L. REV. 505, 506 (2014).

to hew a cohesive jurisprudence from the longstanding judicially created exceptions to section 101.[22] I argue, however, that continued focus on this misstep only obfuscates efforts to define the emerging contours of the product of nature doctrine.

I characterize the Court's approach in early section 101 precedents, whether concerning a law or product of nature, as organic. Early precedents reflect an organic approach because they respect the complexity of individual characteristics of the invention claimed in a given patent by assigning a proper degree of salience for purposes of determining the subject matter eligibility of the patent. What is more, early precedents respect the unified whole of these individual characteristics through consideration of the extent to which the design and intent of the claimed invention accords with fundamental norms around what does and does not warrant patent protection. An artificial approach, in contrast, assigns disproportionate salience to certain features, which has the effect of mischaracterizing the invention on the whole for purposes of distinguishing between natural and non-natural subject matter.

Mayo Collaborative Services v. Prometheus Laboratories, Inc.,[23] decided two years before *Myriad*, narrowed the Court's prior organic approach through reliance on an ambiguous and artificial threshold for subject matter eligibility,[24] which presaged the Court's wholesale departure in *Myriad* from its approach in earlier precedents.[25] I contend that the Court appears increasingly willing to jettison this organic approach for a more artificial one that mischaracterizes and disproportionately weights individual features of claimed inventions based largely on the intuitive appeal of certain similarities and differences between natural and non-natural characteristics. I argue that this tendency may engender difficulties for the subject matter eligibility of innovations that utilize ES cells, but likely not those that utilize iPS cells.

In section II, I first provide an overview of section 101, making special note of the motivation for judicially created subject matter exceptions and intimating at resultant difficulties for the

[22] *See id*. at 508–09 (discussing the lack of guidance the *Myriad* opinion offered with respect to patent eligibility under section 101).

[23] 132 S. Ct. 1289 (2012).

[24] *Id.* at 1293–94.

[25] *See infra* note 71 and accompanying text (discussing pre-*Myriad* court cases).

judiciary in determining the bounds of these exceptions. I then discuss how two notable exceptions to subject matter eligibility, for laws of nature and products of nature, have evolved in the Court. In particular, I focus on the frequent conflation of these two doctrines and, notwithstanding this judicial misstep, endeavor to characterize the uncertain trajectory of section 101 jurisprudence. This analysis closes with a discussion of *Myriad* and its defining role in charting such a trajectory. In section III, I provide an overview of the science of both ES and iPS cells and, in section IV, I query whether the arc of section 101 jurisprudence augurs ill for the subject matter eligibility of either ES or iPS cells.

II. SECTION 101 JURISPRUDENCE

A. Section 101

Any discussion of subject matter eligibility begins with section 101. It defines patent-eligible subject matter as follows.

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title."[26]

Unlike the history of section 101 jurisprudence, the language of the provision itself has benefitted from consistent interpretation and application. Apart from the insertion of "process" in place of "art" in the 1952 revisions to the Act,[27] its language has remained unchanged since promulgation in 1793.[28] What is more, the judiciary has consistently cast operative terms in section 101, such as "manufacture" and "composition of matter", in accordance with their basic dictionary definitions.[29] The judiciary has, moreover, interpreted the modifier "any" as indicative of

[26] 35 U.S.C. § 101 (West, Westlaw through P.L. 114-49 approved Aug. 7, 2015).

[27] S. REP. NO. 82-1979 (1952), *reprinted in* 1952 U.S.C.C.A.N. 2394, 2398 (Westlaw).

[28] *See id*. at 2397, 2409 (discussing that the first patent law remained in effect and relatively unchanged until revisions in 1836 and 1952, with section 101 continuing to track previous wording from prior amendments).

[29] Diamond v. Chakrabarty, 447 U.S. 303, 308 (1980); *see also* Perrin v. United States, 444 U.S. 37, 42 (1979) (explaining that "unless otherwise defined, words will be interpreted as taking their ordinary, contemporary common meaning").

Congressional intent that the section have wide scope.[30] To this end, section 101 is considered to sweep broadly enough to "include anything under the sun that is made by man."[31]

The breadth of section 101 is not, however, without some limits. While section 101 does not set out any subject matter exclusions, the judiciary has carved out notable exceptions.[32] Since the 1850s, the U.S. Supreme Court has recognized[33] an exception to patentable subject matter under section 101 for "laws of nature, physical phenomena, and abstract ideas"[34] The Court has justified its exception of these subject matters chiefly through the role that they play in the inventive process.[35] As example, the Court has called laws of nature, physical phenomena, and abstract ideas "the basic tools of scientific and technological work."[36] Similarly, in *Funk Brothers Seed Co. v.*

[30] *Chakrabarty*, 447 U.S. at 308; *see also* In re Bilski, 545 F.3d 943, 977 (2008) ("From the first United States patent act in 1790, the subject matter of the 'useful arts' has been stated broadly, lest advance restraints inhibit the unknown future.").

[31] *Patent Law Codification and Revisions: Hearings on H.R. 3760 Before Subcomm. No. 3 of the H. Comm. on the Judiciary,* 82d Cong. 37 (1951) (statement of P.J. Federico, Examiner in Chief, U.S. Patent Office), *quoted in Chakrabarty*, 447 U.S. at 309 n. 6; *see also* Gregory Dolin, *Exclusivity Without Patents: The New Frontier of FDA Regulation for Genetic Materials*, 98 IOWA L. REV. 1399, 1418 n.149 (2013) (discussing varying interpretations of the meaning of the quoted text).

[32] Christopher Beauchamp, *Patenting Nature: A Problem of History*, 16 STAN. TECH. L. REV. 257, 264 (2013) (arguing that these judiciary creations engender difficulties in interpreting precedent). While the 1952 revision to the Patent Act divides the requirements for patentability into discrete conditions, Beauchamp argues, cases prior to 1952 "tangled, merged, and overlapped" these conditions. *Id.* As a result, courts could invalidate a claim related to, for instance, a phenomena of nature for nonobviousness under section 103; whereas, such a claim would today be evaluated under section 101. *Id.* According to Beauchamp, before 1952 courts were not inclined to separate the requirements for patentability in the manner codified in 1952. *Id.* Because many leading cases come from the pre-1952 period, the true contours of section 101 are difficult to define. *Id.*

[33] *See e.g.,* Le Roy v. Tatham, 55 U.S. 156, 159–60 (1853); O'Reilly v. Morse, 56 U.S. 62, 116 (1854) (for examples of how the court in the late nineteenth century handled early patent cases).

[34] *Chakrabarty*, 447 U.S. at 309–10; *see also* Douglas L. Rogers, *After* Prometheus*, Are Human Genes Patentable Subject Matter?* 11 DUKE L. & TECH. REV. 434, 508 n.24 (2013) ("The Court has used those terms—physical phenomena and natural phenomena—interchangeably.").

[35] *See* Dolin, *supra* note 30, at 1420 ("This dividing line, though not explicit in either the constitutional or statutory text, is not arbitrary but rather stems directly from the underlying purposes of patent law.").

[36] Gottschalk v. Benson, 409 U.S. 63, 67 (1972).

Kalo Inoculant Co.,[37] Justice Douglas referred to phenomena of nature as "part of the storehouse of knowledge of all men."[38] More narrowly, the Court has connected the fundamental role of these subject matter to the basic tenet of patent law that grant of a patent confers an exclusive right.[39] As Justice Breyer wrote in *Mayo*, "monopolization of [phenomena of nature, mental processes, and abstract intellectual concepts] through the grant of a patent might tend to impede innovation more than it would tend to promote it."[40]

The Court has stated, however, that this exception reflects certain intrinsic limits.[41] As Justice Stewart recognized in *Parker v. Flook*,[42] a patent does not fail to satisfy section 101 simply because it contains a law of nature.[43] Indeed, as the Court wrote in 1852, it is the processes employed to "extract, modify, and concentrate natural agencies" that comprise the invention.[44] Similarly, as Justice Stone observed in 1939, "a novel and useful structure created with the aid of [unpatentable] knowledge of scientific truth may be [patentable]."[45] Later precedents likewise echo this emphasis on how nature has been applied, and thereby claimed in a patent, in the process of discovery.[46] As the Court admonished in *Mayo*, application requires more than a perfunctory recitation of a particular law or product of nature employed with the addition of "'apply it.'"[47] Not surprisingly, pre-1952 precedents sometimes interweaved issues now addressed under nonobviousness or novelty into analyses of the type and

[37] 333 U.S. 127 (1948).

[38] *Id.* at 130.

[39] Mayo Collaborative Servs. v. Prometheus Labs. Inc., 132 S. Ct. 1289, 1305 (2012).

[40] *Id.* at 1293.

[41] *See, e.g., id.* at 1293 ("The Court has recognized . . . that too broad an interpretation of this exclusionary principle could eviscerate patent law.").

[42] 437 U.S. 584 (1978).

[43] *Id.* at 590.

[44] Le Roy v. Tatham, 55 U.S. 156, 175 (1852).

[45] Mackay Radio & Tel. Co. v. Radio Corp., 306 U.S. 86, 94 (1939).

[46] *See, e.g.*, Mayo Collaborative Servs. v. Prometheus Labs., Inc., 132 S. Ct. 1289, 1294 (2012) ("While a scientific truth, or mathematical expression of it, is not a patentable invention, a novel and useful structure created with the aid of knowledge of scientific truth may be.").

[47] *Id.* (citing Gottschalk v. Benson, 409 U.S. 63, 71–72 (1972)); *see* Diamond v. Diehr, 450 U.S. 175, 192 (1981) ("To hold otherwise would allow a competent draftsman to evade the recognized limitations on the type of subject matter eligible for patent protection.").

extent of application in a section 101 inquiry.[48] In *Funk Brothers*, for instance, Justice Douglas wrote that mere discovery of a law of nature does not constitute patentable subject matter; rather, patentable subject matter requires application "to a new and useful end."[49]

B. Laws of Nature

The laws of nature doctrine factored prominently in the Court's 1948 decision in *Funk Brothers*, but not without shades of grey.[50] While *Funk Brothers* was ostensibly a product of nature case—it concerned a patent for an inoculant comprised of naturally occurring bacteria with salient agricultural applicability—the Court focused on the extent to which the inoculant exhibited a law of nature.[51] The Court conceived of the inoculant as no more than an aggregation of select strains of bacteria from several species, in which case it was properly an invention only insofar as it "borrowed invention from the discovery of the natural principle itself."[52] While the *Myriad* Court would later rely heavily on *Funk Brothers*,[53] the decision in *Funk Brothers* reflects an organic approach to evaluating subject matter eligibility uncommon in later precedents.[54] Rather than giving short shrift to certain characteristics in favor of others with perceived though unsubstantiated salience to determining subject matter

[48] *See e.g.*, *Mayo*, 132 S. Ct. at 1303 (discussing the court's analysis in *Funk Bros.* in determining patent eligibility under section 101).

[49] Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948); O'Reilly v. Morse, 56 U.S. 62, 132–33 ("The mere discovery of a new element, or law, or principle of nature, without any valuable application of it to the arts, is not the subject of a patent. But he who takes this new element or power, as yet useless, from the laboratory of the philosopher, and makes it the servant of man; who applies it to the perfecting of a new and useful art, or to the improvement of one already known, is the benefactor to whom the patent law tenders its protection.").

[50] *See Funk Bros.*, 333 U.S. at 131–32 (finding that the inoculant fell short of invention); *see also* Burk, *supra* note 20, at 511–12 (arguing that *Funk Brothers* is in fact a case about invention, not subject matter eligibility).

[51] *Ass'n for Molecular Pathology*, 133 S. Ct. at 2117 (noting that the product claim in *Funk Bros. Seed Co.* "fell squarely within the law of nature exception").

[52] *Funk Bros.*, 333 U.S. at 132.

[53] *See Myriad*, 133 S. Ct. at 2117 (noting similarities between the situation in *Funk Bros. Seed Co.* and *Myriad*).

[54] *Compare Funk Bros.*, 333 U.S. at 131 *with Myriad*, 133 S. Ct. at 2117–18 (comparing the analysis of the cases to show how the courts have shifted from an organic examination of subject matter to a more rigid application of the patent requirements).

eligibility, as later precedents would do,[55] the *Funk Brothers* court looked to the whole of the inoculant to characterize its relation to nature.[56] While a more generous reading of the disputed patent might suggest that the inoculant exhibited a degree of invention beyond mere aggregation, the Court's approach took care to evaluate all characteristics of the invention equally and consider the resultant whole—that is, the invention itself—in view of the purpose of section 101.[57]

In the post-1952 era, the Court considered the validity of a process claim for a mathematical algorithm that would convert binary-coded decimal numerals into pure binary numerals.[58] The Court's 1972 decision in *Gottschalk v. Benson*[59] represents the first computer-related case concerning subject matter eligibility to come before the Court.[60] The Court invalidated the patent on the grounds that the algorithm "ha[d] no substantial practical application except in connection with a digital computer,"[61] meaning that allowing the patent to stand "would wholly pre-empt the mathematical formula and in practical effect would be a patent on the algorithm itself."[62] Here, the Court's reasoning reflects an organic approach to evaluating subject matter eligibility because it could have, in the alternative, relied on the bare criteria in *Funk Brothers*—"application of the law of nature to a new and useful end"[63]—in conjunction with prior case law supporting the patent-eligibility of process claims,[64] to uphold the challenged patent.[65] Instead, the Court queried whether the process claimed by the patent, taken in the wider context of the algorithm's limited applicability outside of the disputed patent, accorded with the sort of invention that the patent system should feasibly protect.[66]

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[55] *See infra* notes 119–120 and accompanying text.

[56] *See Funk Bros.*, 333 U.S. at 132 (looking at how the discovery of the inoculant discovered a new rule of nature, but did not create a new way of using the bacterium).

[57] *See id.* at 131 (characterizing the lower court's ruling as "f[alling] short of invention within the meaning of the patent statutes").

[58] Gottschalk v. Benson, 409 U.S. 63, 64 (1972).

[59] 409 U.S. 63 (1972).

[60] *Id.* at 64.

[61] *Id.* at 71–72.

[62] *Id.* at 72.

[63] Funk Bros. Seed Co. v. Kalo Inoculant Co., 333 U.S. 127, 130 (1948).

[64] *See Benson*, 409 U.S. at 68–71 (discussing prior cases).

[65] *Id.* at 71–72, 73.

[66] *Id.* at 71–72.

The 1970s saw one more decision concerning the law of a nature doctrine. In *Flook*, the Court invalidated a patent on a method for updating alarm limits during catalytic conversion processes on the grounds that the only novel feature, a mathematical algorithm, did not constitute patentable subject matter.[67] *Flook* evinces a salient distinction in evaluating section 101 challenges that speaks to the organic approach taken up by the Court during these earlier precedents. In *Flook*, the Court stressed the need to look to the patent as a whole, rather than piecemeal, in determining subject matter eligibility.[68] Rather than stressing the fact that the disputed process claim contained an otherwise unpatentable algorithm as a means to negate subject matter eligibility, the Court considered its role in the invention to find the patent invalid under section 101 "not because it contain[ed] a[n algorithm] as one component, but because once that algorithm is assumed to be within the prior art, the application, considered as a whole, contain[ed] no patentable invention."[69] The distinction, therefore, is not whether a challenged patent employs a law of nature, but whether the patent as a whole evinces an "inventive application".[70]

The Court would revisit the laws of nature doctrine just three years after *Flook*. The Court's 1981 decision in *Diamond v. Diehr*[71] stands out not least for its outcome. Contrary to *Benson* and *Flook*, which both invalidated a patent under the laws of nature doctrine, in *Diehr* the Court upheld as patentable subject matter a process for curing synthetic rubber that relied upon a mathematical formula and programmed computer.[72] *Diehr* stands out for another significant reason. In the term just prior to *Diehr*, the Court handed down its influential product of nature decision in *Diamond v. Chakrabarty*.[73] Although a product of nature case, the *Diehr* Court envisioned at least some degree of relationship to the law of nature case at issue because it relied upon *Chakrabarty* for more than mere background information,[74] which notably differs from how the *Myriad* Court would later

[67] Parker v. Flook, 437 U.S. 584, 594–95 (1978).
[68] *Id.* at 594.
[69] *Id.*
[70] *Id.*
[71] 450 U.S. 175 (1981).
[72] *Id.* at 187, 191, 192–93.
[73] 447 U.S. 303 (1980).
[74] *Diehr*, 450 U.S. at 181, 182, 185.

treat its recent decision in *Mayo*.[75]

Yet, more importantly, the *Diehr* Court presented a more comprehensive approach to assessing subject matter eligibility for the first time in either a law of nature or product of nature case.[76] First, the Court sought to marry *Chakrabarty* with *Flook* and *Benson* by asserting that the two computer cases "stand for no more than the[] long-established principles" articulated in *Chakrabarty*.[77] Second, the Court folded these more recent precedents into a comprehensive framework that stretched to early section 101 precedents including, among others, *Funk Brothers* and *Mackay Radio & Tel. Co. v. Radio Corp. of America*.[78] As Justice Stone distinguished in *Mackay Radio*,[79] a mathematical expression of a scientific truth does not constitute patentable subject matter,[80] but "a novel and useful structure created with the aid of knowledge of scientific truth may be."[81] Justice Rehnquist, writing for the majority in *Diehr*, employed this language to craft a fundamentally equal distinction, namely, that Diehr and Lutton's patent on a process for curing synthetic rubber could be upheld because it clearly had not sought to patent the underlying mathematical equation.[82]

Justice Rehnquist likewise offered instructive dicta that, in contrast to earlier precedents, endeavored to pr. . .cis an approach to evaluating section 101 challenges.

We recognize, of course, that when a claim recites a mathematical formula (or scientific principle or phenomenon of nature), an inquiry must be made into whether the claim is seeking patent protection for that formula in the abstract . . . On the other hand, when a claim containing a mathematical formula implements or applies that formula in a structure or process which, *when considered as a whole*, is performing a function which the patent laws were designed to protect (e.g.,

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[75] *See infra* note 122 and accompanying text (noting how the *Myriad* Court conspicuously relied on *Mayo* for mere background).

[76] *See* Rebecca S. Eisenberg, *Wisdom of the Ages or Dead-Hand Control? Patentable Subject Matter for Diagnostic Methods After In Re Bilski*, 3 CASE W. RESERVE J. L. TECH. & INTERNET 1, 10 (2012) (discussing the holdings in *Dier* and *Chakrabarty* cases).

[77] *Diehr*, 450 U.S. at 185, 187.

[78] *Id.* at 185, 187–88.

[79] 306 U.S. 86 (1939).

[80] *Id.* at 94.

[81] *Id.*

[82] *Diehr*, 450 U.S. at 191–93.

transforming or reducing an article *to a different state or thing*), then the claim satisfies the requirements of § 101.[83]

Justice Rehnquist's focus on evaluation of the totality of a challenged patent, as opposed to according those features that state a law of nature a greater degree of attention, approaches a cogent global method for determining subject matter eligibility more so than in any other section 101 precedent. That Justice Rehnquist articulates this global method in such a way as to yoke together law and product of nature cases without offending their subtle differences is telling. There can no sooner be a more organic approach to determining subject matter eligibility than one that looks equally upon the bare components of a patent without disturbing their individual significance to the whole.

Over two decades elapsed between *Diehr* and the Court's notable 2012 law of nature decision in *Mayo*. In *Mayo*,[84] the Court invalidated two patents involving the use of thiopurine drugs in the treatment of autoimmune disease.[85] Together, the two patents described processes that, based on the way in which the human body metabolizes thiopurine compounds, indicate whether a dosage is likely too low or too high.[86] Prometheus, the owner of the patents, sold diagnostic tests embodying the processes described in the two patents.[87] Mayo purchased and used these tests, but in 2004 announced that it would begin using and selling its own test, which differed as to the metabolite levels used.[88]

Justice Breyer, writing for the Court, cast the issue as whether the two patent claims "add *enough* to . . . the processes they describe to qualify as patent-eligible process that *apply* natural laws."[89] As to what may constitute "enough," the Court focused on whether the process claimed in the patent exhibited "additional features" to distinguish it from, for instance, a clever drafting effort to render patentable an otherwise unpatentable law of nature.[90] As to Prometheus' patents, the Court reasoned that the "additional features" described in the patent were insufficient to

[83] *Id.* at 191–92 (emphasis added).
[84] 132 S. Ct. 1289 (2012).
[85] *Id.* at 1294–95.
[86] *Id.* at 1295.
[87] *Id.*
[88] *Id.* at 1295–96.
[89] *Id.* at 1297 (emphasis in original).
[90] *Mayo*, 132 S. Ct. at 1297.

confer subject matter eligibility. In particular, the Court found that the additional steps set out in the patent were merely "well-understood, routine, and conventional activit[ies]" already known to an informed community.[91] In this sense, "when viewed as a whole, [those steps] add nothing significant beyond the sum of their parts taken separately."[92]

Whether the *Mayo* Court sufficiently respects the organic approach embodied by *Diehr* remains questionable. The *Mayo* Court seemed to take up the spirit of this approach through consideration of the full spectrum of processes in both challenged patents, but not without some struggle.[93] For instance, its addition of the need for an indeterminate further quality to separate it from obviously unpatentable subject matter has the effect of narrowing the organic approach set out in earlier precedents through consideration of a metric that is quite artificial, namely, an appeal to unspecified "additional features."[94] Viewed in this manner, the *Mayo* Court's not insubstantial efforts to situate the strength of the claim in *Mayo* in relation to those in *Diehr* and *Flook* appears more artificial still.[95] Consideration of the strength of a claim in relation to others implies a calculus for classifying and weighing otherwise distinguishable subject matter that not only moves afield of an organic approach, but also interjects, save explanation, a deliberative dimension that the Court had theretofore not taken up in prior section 101 jurisprudence.

C. Products of Nature

Perhaps fittingly for the disorderly history of section 101, the product of nature doctrine originated not in the U.S. Supreme Court—or any court, for that matter—but in an opinion authored by the Commissioner of Patents ("Commissioner").[96] The 1889 opinion in *Ex parte Latimer*[97] concerned a patent for the product

91 *Id.* at 1298.

92 *Id.*

93 *Id.* at 1296–98.

94 *Id.* at 1297.

95 *Id.* at 1299 ("The claim before us presents a case for patentability that is weaker than the (patent-eligible) claim in *Diehr* and no stronger than the (unpatentable) claim in *Flook*.").

96 Daniel J. Kevles, *Of Mice and Money: The Story of the World's First Animal Patent*, 131 DAEDALUS, no. 2, Spring 2002, at 79.

97 46 O.G. 1638 (Comm'r of Patents 123 1889).

and process for extracting long fibers from the pine needles of an Australian pine tree.[98] While the Commissioner found that Latimer's procured fiber differed from other naturally occurring fibers in, for instance, length and strength, these variances were due to nature's efforts, rather than his method for extracting them.[99] Accordingly, the Commissioner found that the procured fibers lacked material alteration to differentiate it from what was already found in nature.[100] Confusingly, the decision had but limited reach. Around that time, patents regularly issued for products that were unaltered or merely slightly altered from their natural state.[101] What is more, the decision did not appear in any of the major patent treatises published in its era and it was not until well into the twentieth century before it would be cited in a published opinion.[102]

Early product of nature cases after *Ex parte Latimer* established the original bounds of the doctrine, specifically, carving out an exception for purified and isolated natural substances.[103] Notably, these precedents originated in lower federal court holdings, rather than in the U.S. Supreme Court.[104] In *Kuehmsted v. Farbenfabriken of Elberfeld Co.*,[105] for instance, the Seventh Circuit upheld a patent on "substantially pure" aspirin, despite having the same chemical formulae as its impure form, because it had different therapeutic uses.[106] Judge Learned Hand echoed this reasoning one year later in the influential 1911 decision in *Parke-Davis & Co. v. H.K. Mulford Co.*[107] Judge Hand differentiated the product at issue, purified adrenaline, from its natural form because the former both possessed new properties

98 *Id.* at 125.

99 *Id.*

100 *Id.* at 125–27.

101 Beauchamp, *supra* note 31, at 274.

102 *Id.* at 275.

103 *See, e.g.,* Kuehmsted v. Farbenfabriken of Elberfeld Co., 179 F. 701, 705 (7th Cir. 1910) (holding Aspirin was patentable as a purified natural product); *see also* Parke-Davis & Co. v. H. K. Mulford Co., 189 F. 95, 113–14 (S.D.N.Y. 1911) (holding that the isolation of a salt from its principle compound was patentable as a new product).

104 *See, e.g., Kuehmsted*, 179 F. at 705 (noting one instance where precedent was created outside the Supreme Court); *see also Parke-Davis*, 189 F. at 113–14 (noting another example of the court allowing patents for isolated natural substances, which originated in the Circuit Court for the Southern District of New York).

105 179 F. 701 (7th Cir. 1910).

106 *Id.* at 703–05.

107 189 F. 95 (S.D.N.Y. 1911).

not otherwise found in its native counterpart and constituted "a new thing commercially and therapeutically."[108] While *Parke-Davis* lay dormant for many years, including a noticeable absence from the Court's 1948 opinion in *Funk Brothers*, it would be resurrected by the Fourth Circuit in its 1958 decision in *Merck & Co. v. Olin Mathieson Chemical Corp.*,[109] which upheld a patent on a purified form of vitamin B_{12} obtained through fermentation of fungi.[110] In contrast to natural fermentates, which were "quite useless" on their own, vitamin B_{12}, as a purification of the active principle in natural fermentates, had "great therapeutic and commercial worth."[111] It was, as the court wrote, "a new and useful composition[]" entitled to patent protection.[112]

Not until 1980 did the Court finally address the product of nature doctrine. *Chakrabarty* stands as the first significant product of nature precedent in the Court during the post-1952 era. The dispute in *Chakrabarty* dates to a 1972 patent application asserting 36 claims related to the invention of "human-made, genetically engineered" bacterium with commercial value for their ability to treat oil spills.[113] Writing for the Court in *Chakrabarty*, Chief Justice Burger clarified the scope of *Flook*—decided just two years prior—stating that its holding did not announce a new principle that inventions must be contemplated by Congress at the time of enactment of the patent laws in order to satisfy section 101.[114] Accordingly, the Court rejected the Commissioner of Patents and Trademarks' argument that the 1930 Plant Patent Act[115] and 1970 Plant Variety Protection Act,[116] which excluded bacterium from their protections,[117] evinced Congressional understanding that section

[108] *Id.* at 103.

[109] 253 F.2d 156 (4th Cir. 1958); *see* Beauchamp, *supra* note 31, at 304 ("*Merck* marked the arrival of *Parke-Davis* as a standard reference in the case law. At the same time, the *Merck* opinion became the source for the 'cannon' of standard historical references on product-of-nature patents.").

[110] *Merck*, 253 F.2d at 164.

[111] *Id.*

[112] *Id.*

[113] *Id.* at 305.

[114] *Id.* at 314–15.

[115] 35 U.S.C. § 161 (West, Westlaw through P.L. 114-49 approved Aug. 7, 2015).

[116] *See generally* 7 U.S.C. § 2321 *et seq.* (West, Westlaw through P.L. 114-49 approved Aug. 7, 2015) (for all statutes contained within the chapter).

[117] Diamond v. Chakrabarty, 447 U.S. 303, 310–11 (1980).

101 did not contemplate living things.[118] In particular, citing to Congressional testimony regarding the Plant Patent Act, Chief Justice Burger wrote that "Congress . . . recognized that the relevant distinction was not between living and inanimate things, but between products of nature, whether living or not, and human-made inventions."[119] Chakrabarty's micro-organism, which was the "result of human ingenuity and research," fell under the latter category,[120] as "a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility."[121]

Chakrabarty is at once salient precedent and emblematic of the uncertain trajectory of the Court's section 101 jurisprudence. Its significance derives chiefly from its unique position as the first product of nature case to come out of the Court in post-1952 era. It also stands as the Court's opening act with regard to section 101 challenges in the biotechnology age.[122] Its influence can be witnessed in, for instance, the *Myriad* Court's reliance on its reasoning over other, more recent, section 101 precedents, chiefly *Mayo*.[123] What is more, *Chakrabarty* had an immediate and significant effect on United States Patent and Trademark Office (USPTO) practice. After *Chakrabarty*, the USPTO began granting gene patents, as well as patents on isolated and purified proteins and on cell lines,[124] under the rationale that isolated and purified naturally occurring substances differed significantly from the cellular components of their native counterparts.[125]

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118 *Id.* at 310–11.

119 *Id.* at 313.

120 *Id.*

121 *Id.* at 310.

122 Tup Ingram, *Association for Molecular Pathology v. Myriad Genetics, Inc.: The Product of Nature Doctrine Revisited*, 29 BERKELEY TECH. L. J. 394, 395 (2014).

123 *See* Z. Peter Sawicki et al., *Patenting Biologicals Myriad Issues and Options in the Wake of Myriad*, BENCH & B. MINN., Sept. 9, 2013, *available at* http://mnbenchbar.com/2013/09/patenting-biologicals/ (discussing the Court's reliance on *Chakrabarty* rather than *Mayo*).

124 *See* Ingram, *supra note* 121, at 395 (discussing how the interpretation of *Chakrabarty* spurred the issuance of gene patents).

125 Samantak Ghosh, *Gene Patents: Balancing the* Myriad *Issues Concerning the Patenting of Natural Products*, 27 BERKELEY TECH. L. J. 241, 250 (2012); *see* Andrew Chin, *Artful Prior Art and the Quality of DNA Patents*, 57 ALA. L. REV. 975, 986 (2006) ("Since *Chakrabarty*, the scope of patentable subject matter under § 101 has been extended to cover an ever-widening range of biological materials that have been genetically altered, purified, or otherwise changed through human intervention into forms not found in nature."); *see also* Rebecca

As influential as *Chakrabarty* has been for section 101 jurisprudence, it admits a few weaknesses. Much as the Court would later do in *Myriad*,[126] *Chakrabarty* conflates laws of nature and product of nature precedents.[127] For instance, the Court relies on *Funk Brothers* for much of its reasoning,[128] without acknowledging either that each addressed distinctly different subject matter or that it pre-dates promulgation of the 1952 Patent Act. Moreover, the Court clearly envisaged a relationship between its recent holding in *Flook*, a laws of nature case, and the issue in *Chakrabarty* because in 1978 it had instructed the Court of Customs and Patent Appeals (now the Federal Circuit) to reconsider the dispute in view of *Flook*.[129] The *Chakrabarty* Court would devote significant attention to discussing *Flook*.[130] Despite what at least appears to be some evidence of the Court's belief that product and law of nature cases are sufficiently similar to be treated under a unified juridical approach, *Chakrabarty* affords no insights into why the Court would advance such a view.

By the time the Roberts Court considered *Myriad*, section 101 jurisprudence could arguably not have been more muddied. The patents at issue in *Myriad* concern the exact location of the BRCA1 and BRCA2 genes on chromosomes seventeen and thirteen.[131] Mutations in these two genes may significantly

S. Eisenberg, *Wisdom of the Ages or Dead-Hand Control? Patentable Subject Matter for Diagnostic Methods After In re Bilski*, 3 CASE W. RESERVE J. L. TECH. & INTERNET 1, 10 (2012) (noting that after *Chakrabarty* and *Diehr*, "the Court seemed to retire from policing the subject matter boundaries of the patent system following the creation of the Court of Appeals for the Federal Circuit in 1982"); *see* Lauren M. Nowierski, *A Defense of Patenting Human Gene Sequences Under U.S. Law: Support for the Patenting of Isolated and Purified Substances*, 26 CARDOZO ARTS & ENT. L. J. 473, 502 (2008) (stating that *Chakrabarty* "is the decision most frequently relied upon to suggest that biotechnology patents do, in fact, meet the subject matter requirements of [section] 101").

[126] *See* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2119 (2013) (examining the issue with a combined product of nature and laws of nature approach).

[127] *See* Diamond v. Chakrabarty, 447 U.S. 303, 313 (1980) (noting that the invention in *Chakrabarty*, was a mixture of nature and human ingenuity).

[128] *See id.* at 309–10 (distinguishing the facts in *Funk Bros.* from the facts of *Chakrabarty* to assist the Court in reaching its conclusion).

[129] *See* Parker v. Bergy, 438 U.S. 902, 902 (1978) (remanding the case for consideration in light of Parker v. Flook).

[130] *See Chakrabarty*, 447 U.S. at 314–15 (discussing the *Flook* holding in great detail).

[131] *Myriad*, 133 S. Ct. at 2112.

increase an individual's risk of developing either breast or ovarian cancer.[132] By ascertaining the location of these two genes, Myriad could determine their typical nucleotide sequence, thereby facilitating development of medical tests to detect mutations that may be associated with a patient's heightened risk of cancer.[133] Following location and sequence of the two genes, Myriad sought and obtained a number of patents, of which nine composition claims from three of those patents were at issue in *Myriad*.[134] If valid, Myriad's patents would afford exclusive rights to isolate an individual's BRCA1 and BRCA2 genes, or any strand of at least fifteen nucleotides within those genes, and synthetically create BRCA cDNA.[135]

Writing for the Court, Justice Thomas relied chiefly on *Chakrabarty*, noticeably employing the Court's more recent opinion in *Mayo* solely for background information.[136] Justice Thomas focused on *Chakrabarty*'s concern for the presence of an inventive quality, "with markedly different characteristics from any found in nature,"[137] in assessing the validity of Myriad's patents.[138] Granting that Myriad had found an important and useful gene—yet noting that this alone does not satisfy section 101[139]—Justice Thomas concluded that Myriad had "not create[d] anything".[140] More narrowly, "separating [the BRCA1 and BRCA2] genes from [their] surrounding genetic material is not an act of invention."[141] What Myriad had done, Justice Thomas wrote, was "detail the 'iterative process' of discovery" and "import these extensive research efforts" for purposes of eligibility under section 101.[142] In contrast, cDNA satisfied section 101 because

132 *Id.*
133 *Id.* at 2112–13.
134 *Id.* at 2113.
135 *Id.*
136 *See* Sawicki et al., *supra* note 122 ("The *Myriad* Court relied heavily on *Diamond v. Chakrabarty* and only mentioned the *Mayo* case in passing, primarily for background and a historical perspective. As such, the *Myriad* holding suggests that the Court may have been reluctant to issue another all-encompassing decision in the wake of the controversy surrounding *Bilski* and *Diamond v. Diehr*, such as further elaborating abstractly on one of their previous tests on patent-eligible subject matter or giving us another broad test to contemplate and criticize; nor apparently did it want to elaborate on *Mayo*.").
137 Diamond v. Chakrabarty, 447 U.S. 303, 310 (1980).
138 *Myriad*, 133 S. Ct. at 2117.
139 *Id.*
140 *Id.*
141 *Id.*
142 *Id.* at 2118.

cDNA is the result of laboratory efforts—"the lab technician unquestionably creates something new"—that distinguish it from the DNA from which it had been derived.[143]

Myriad exhibits a number of flaws. First, the Court's assertion that Myriad had "not create[d] anything"[144] reflects an indefensibly parochial interpretation of the inventive process that discounts the extensive steps taken by Myriad to locate the BRCA1 and BRCA2 genes. In pertinent part, Myriad connected these genes with a predisposition to certain types of cancer—a testing process that required significant monitoring and data collection—which enables more accurate cancer diagnosis and prognosis determinations.[145] To be sure, the Court acknowledges the efforts of Myriad in locating the two genes,[146] yet its approach preferentially weights a singular similarity—namely, the location of naturally occurring genes—over associated processes that reflect various non-natural differences. As example, the Court points to the "'iterative' process of discovery" claimed in a number of the disputed patents, but confusingly reduces this process to a matter of effort, concluding plainly that "extensive effort alone" does not satisfy section 101.[147]

I note this misstep because it is emblematic of the *Myriad* Court's fragmentary analysis of subject matter eligibility. In analyzing section 101 challenges with regard to the invention for which patent protection has been sought, the Court tends to accord greater determinative importance to certain characteristics, typically those that exhibit on their face similarity to naturally occurring subject matter.[148] The Court deploys this preferential weighting without either clear guidance on why one feature warrants greater determinative importance than another or, at minimum, why the deliberative process should entail preferential weighting in the first place.[149] To some degree, as the Court's determination that Myriad had not created anything intimates, this preferential weighting may be

143 *Id.* at 2119.

144 *Myriad*, 133 S. Ct. at 2117.

145 Jill M. Fraley, *The Jurisprudence of Nature: The Importance of Defining What is "Natural,"* 63 CATH. U. L. REV. 917, 925–26 (2014).

146 *See Myriad*, 133 S. Ct. at 2118 (characterizing Myriad's work as an "extensive effort").

147 *Id.*

148 *See* Fraley, *supra* note 144, at 922–23 (detailing the non-patentability of natural phenomena in the Section 101 context).

149 *Id.* at 925.

attributable to the intuitive appeal of certain overly simplified analytic approaches to the subject matter of the underlying invention.[150] While Justice Thomas chose to view Myriad's invention as nothing more than an attempt to patent the discovery process of locating the BRCA1 and BRCA2 genes,[151] others applied a more nuanced metric that identified fundamental differences in the chemical structures between gDNA and its native counterpart.[152]

The *Myriad* Court's arbitrary preferential weighting can be acutely witnessed in how it arrives at the tipping point, as it were, for subject matter eligibility.[153] While the Court concedes that the act of isolating gDNA "severs chemical bonds and thereby creates a nonnaturally [sic] occurring molecule," it chooses instead to focus on the similarity between the nucleotide sequence in the isolated gDNA and its native counterpart.[154] This similarity, the Court reasons, matters most for purposes of subject matter eligibility, without explaining why, for instance, fundamental differences in the chemical structures should not be afforded more—or at least equal—weight in determining subject

[150] *See* Burk, *supra* note 20, at 513, 514 (assessing the laws of nature doctrine as it pertains to the *Myriad* decision).

[151] *Myriad*, 133 S. Ct. at 2112.

[152] *See* Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d. 1303, 1330 (Fed. Cir. 2012) ("Plaintiffs argue that because the claimed isolated DNAs retain the same nucleotide sequence as native DNAs, they do not have any "markedly different" characteristics. This approach, however, looks not at whether isolated DNAs are markedly different—have a distinctive characteristic—from naturally occurring DNAs, as the Supreme Court has directed, but at one similarity, albeit a key one: the information content contained in isolated and native DNAs' nucleotide sequences. Adopting this approach, the district court disparaged the patent eligibility of isolated DNA molecules because their genetic function is to transmit information. We disagree, as it is the distinctive nature of DNA molecules as isolated compositions of matter that determines their patent eligibility rather than their physiological use or benefit. Uses of chemical substances may be relevant to the nonobviousness [sic] of these substances or to method claims embodying those uses, but the patent eligibility of an isolated DNA is not negated because it has similar informational properties to a different, more complex natural material. The claimed isolated DNA molecules are distinct from their natural existence as portions of larger entities, and their informational content is irrelevant to that fact. We recognize that biologists may think of molecules in terms of their uses, but genes are in fact materials having a chemical nature and, as such, are best described in patents by their structures rather than by their functions.").

[153] *See* Fraley, *supra* note 144, at 924–25 (discussing the Court's analysis of the law of nature exception in patent law as applied to *Myriad*).

[154] *Myriad*, 133 S. Ct. at 2118.

matter eligibility.[155] This approach is more confusing still when the Court, in finding cDNA patent-eligible subject matter, chooses instead to stress the import of differences in the chemical structures of cDNA and its native counterpart.[156]

The Federal Circuit recently employed *Myriad*'s approach, with a view to the intuitive appeal of natural versus non-natural comparisons, in *In re Roslin Institute*,[157] which considered the patent-eligibility of Dolly, the famous cloned sheep.[158] In applying *Myriad*, the Court relied on language in *Chakrabarty*—whether the claimed invention possesses "markedly different characteristics from any found in nature"[159]—much as the *Myriad* Court had done,[160] despite that this language is arguably dicta.[161] Accordingly, the Court concluded "Dolly herself is an exact genetic replica of another sheep."[162] This similarity, the Court found, rendered Dolly ineligible subject matter under section 101.[163] The reasoning in *Myriad* almost forces such an outcome, never mind that a clone, as Roslin had argued unsuccessfully, is by its fundamental nature very clearly the opposite of "nature's handiwork."[164]

The ramifications of the *Myriad* Court's approach touch a variety of issues. As a practical matter, the arbitrariness of the characteristics that the Court selects as deserving of more weight stands to frustrate USPTO and practitioner efforts to identify eligible subject matter. This uncertainly also likely engenders downstream biotechnological innovation ramifications. For instance, because the availability of patent protection helps to inform whether certain innovations are deserving of the significant capital investment required to take a new biotechnological product to market, uncertainty with regard to

155 *Id.*

156 *Id.* at 2119; *see* Burk, *supra* note 20, at 508 ("[O]ne is therefore forced to conclude that molecules that differ structurally from a native molecule are both excluded from and included within patentable matter, while molecules with the same coding information as a native molecule are *also* both excluded from and included within patentable subject matter.") (emphasis added).

157 750 F.3d 1333 (Fed. Cir. 2014).

158 *Id.* at 1334.

159 Diamond v. Chakrabarty, 447 U.S. 303, 310 (1980).

160 *Myriad*, 133 S. Ct. at 2117.

161 Burk, *supra* note 20, at 511.

162 *In re Roslin*, 750 F.3d at 1337.

163 *See id.* at 1337–39 (outlining the Court's reasoning on why Dolly is not patentable subject matter).

164 *Id.*

the boundaries of section 101 stands to inhibit biotechnological companies, researchers, and investors from setting and executing investment strategies.

Myriad also further arcs the trajectory of section 101 jurisprudence afield of the organic approach employed in earlier precedents. It does so through a continuation of the *Mayo* Court's narrowing of the Court's early approach to subject matter eligibility challenges. Rather than focusing on the indeterminate "additional features" threshold in *Mayo*, *Myriad* constricted the Court's evaluative approach by hinging subject matter eligibility on an even more narrow calculus, namely, specific similarities or differences with unsubstantiated importance to the distinction between natural and non-natural subject matter.[165] More troubling still, *Myriad*'s effect on the arc of section 101 jurisprudence is not accompanied by a greater degree of clarity around either the law or product of nature doctrine. While the *Myriad* Court continued the habit of conflating law of nature and product of nature precedents, it did not endeavor to clarify why and to what extent it envisages such an overlap; in fact, contrary to the Court in *Chakrabarty*, which afforded attention to its recent law of nature decision in *Flook*, the *Myriad* Court largely ignored its recent decision in *Mayo*.[166] Here, the Court missed a valuable opportunity to imbue a measure of clarity to section 101 jurisprudence that had been noticeably absent in the *Mayo* Court's use of the artificial "additional features" threshold.[167]

III. AN OVERVIEW OF THE SCIENCE OF ES CELLS & IPS CELLS

What follows is a brief overview of the science behind ES cells and iPS cells. Rather than offering a rich explication of the science, the overview below is meant simply to sketch the foundational science that informs germane biotechnological innovations, the patents for which claim either ES cells or iPS cells, and may generate complications for subject matter eligibility under section 101, in view of *Myriad*.

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[165] *See Myriad*, 133 S. Ct. at 2116 (briefly setting out the Court's section 101 distinction between natural and non-natural subject matter).

[166] *Id.* at 2114, 2116.

[167] *See supra* notes 88–94 and accompanying text (explaining the Mayo Court's "additional features" threshold and why it is problematic).

A. ES cells

The process for deriving ES cells is, at bottom, the same human fertilization process that occurs in nature, except replicated under laboratory conditions.[168] To enable this process, scientists rely on human embryos developed through in-vitro fertilization (IVF) procedures that have been donated for clinical research purposes.[169] Early cell development occurs under laboratory conditions in the same manner that it does in nature. Following successful fertilization of a human oocyte, which yields a zygote (i.e., fertilized egg), the embryo begins a doubling process.[170] It first divides into two cells, then again into four cells, and so on.[171] Eventually, the embryo will have doubled enough times to contain approximately one hundred cells, at which time it forms a blastocoel and inner cell mass (ICM).[172] At this stage, the embryo is called a "blastocyst".[173]

Importantly, blastocyst cells are undifferentiated, meaning that they have not yet developed into specialized cells—ones destined to become the crucial building blocks for myriad functions in the human body—and, therefore, have the potential to become any cell.[174] Blastocyst cells do not remain undifferentiated for long, however. At approximately five days

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168 PAUL KNOEPFLER, STEM CELLS: AN INSIDER'S GUIDE 33 (2013).

169 *Id.* at 32. It must be noted, however, that scientists have had success in recent years deriving ES cells through processes that do not rely on discarded embryos from IVF procedures. In 2013, a team in the U.S. derived ES cells through a process called somatic cell nuclear transfer (SCNT). *See* Masahito Tachibana et al., *Human Embryonic Stem Cells Derived by Somatic Cell Nuclear Transfer*, CELL, Jun. 6, 2013, at 1228. SCNT holds the promise of developing personalized ES cells through patients' somatic cells, from which cell-based therapies could ultimately be developed. *Id*. ES cells derived through SCNT were recently shown to resemble iPS cells with respect to similar gene expression and DNA methylation patterns, as well as similar amounts of DNA mutations. *See* Bjarki Johannesson et al., *Comparable Frequencies of Coding Mutations and Loss of Imprinting in Human Pluripotent Cells Derived by Nuclear Transfer and Defined Factors*, CELL STEM CELL, Nov. 6, 2014, at 634 (discussing how iPS cells drawn through SCNT methods resemble other types of cells). SCNT is also the method utilized to clone Dolly the sheep, the patent for which the Federal Circuit recently invalidated under *Myriad*. *See supra* notes 119–125 and accompanying text (discussing the Federal Circuit's decision in *In re Roslin Institute*).

170 KNOEPFLER, *supra* note 167, at 33.

171 *Id.*

172 *Id.*

173 *Id.*

174 Junying Yu & James A. Thomson, *Embryonic Stem Cells*, *in* REGENERATIVE MEDICINE 1, 1 (2006).

after fertilization, the differentiation process begins.[175] Initially, an outer layer of cells separates from the ICM, but many cells still remain in the ICM.[176] Derivation of ES cells begins with removal of the remaining ICM cells from the blastocyst before further differentiation occurs.[177] After removal, scientists culture the derived cells, so that they can establish cell lines and continue to multiply indefinitely.[178] Because ES cells have been removed before differentiation can occur, they are pluripotent, meaning that have the potential, under appropriate laboratory conditions, to develop into any type of cell in the human body.[179] While ES cells may seem similar to or share the same origin as ICM cells, they do not exist naturally in the embryo; rather, they are the fruit of laboratory creation.[180]

B. iPS cells

Put simply, iPS cells are the result of reprogramming somatic cells to act like ES cells.[181] iPS cells express stem cell markers and form tumors that include cells from all three germ layers.[182] These germ layers are the precursors of all cell types, meaning that iPS cells can potentially become any cell in the human body.[183] Early generation of iPS cells focused on identifying "inducers" of pluripotency that could change ordinary human cells, such as fibroblasts, such that they would resemble ES cells.[184] Importantly, unlike ES cells, which rely on the scarce resource of donated human embryos to enable derivation,[185] fibroblasts are abundant in the human body.[186]

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175 *Id.*

176 *Id.*

177 *See id.* at 1–3 (discussing the removal of ICM cells and the potential benefits of culturing ICM cells under the right circumstances).

178 *Id.* at 3.

179 KNOEPFLER, *supra* note 167, at 35.

180 *Id.*

181 MARIA BOROWSKI & GARY S. STEIN, INTRODUCTION TO PLURIPOTENT STEM CELLS: BIOLOGY AND APPLICATIONS, *in* HUMAN STEM CELL TECHNOLOGY AND BIOLOGY: A RESEARCH GUIDE AND LABORATORY MANUAL 6 (Gary S. Stein et al. eds. 2011).

182 *Id.*

183 *Id.*

184 *See* KNOEPFLER, *supra* note 167, at 42 (explaining the process of "reprogramming," where ordinary cells, such as fibroblasts, are changed into pluripotent stem cells).

185 *See id.* (explaining that the derivation of iPS cells do not require human blastocyst embryos, while embryonic stem cell cultures do).

186 *Id.* at 44.

Early research identified four inducing factors—Sox2, Oct4, c-Myc, and Klf4—which, when combined, would transform fibroblasts into cells that resembled ES cells.[187] By forcing these combined inducing factors into fibroblasts through infecting, or transducing, the cells with four retroviruses, it causes fibroblasts to express the ribonucleic acid of each inducing factor.[188] Accordingly, fibroblasts express the proteins for these four inducing factors, all of which are transcription factors.[189] A transcription factor binds DNA at genes and determines whether a gene is on or off.[190] During development of iPS cells, the inducing factors turn off specific genes through transcription.[191] By turning off specific genes, the cells are in essence told at the molecular level that they are no longer differentiated, which in turn enables them to resemble (undifferentiated and pluripotent) ES cells.[192] While initial development of iPS cells relied upon the abovementioned cocktail of inducing factors, other methods exist for generation of iPS cells, such as adjusting the inducing factors utilized in the cocktail.[193]

IV. ES CELLS AFTER *MYRIAD*

Patents that specifically claim ES cells have issued since Thomson and colleagues' original 2001 patent concerning derivation of the first stable human ES cell line.[194] Since 2001, patents claiming methods of using, maintaining, or inducing differentiation of ES cells, or to the resultant modified or differentiated cells themselves, have not been uncommon.[195] USPTO data from 2004 indicates that approximately 300 patents across both human and animal ES cells had issued since

187 *Id.* at 42.
188 *Id.*
189 *Id.*
190 KNOEPFLER, *supra* note 167, at 42.
191 *Id.* at 44.
192 *Id.* at 42.
193 *Id.* at 43; s*ee, e.g.,* Junying Yu ET AL., *Induced Pluripotent Stem Cells Derived from Human Somatic Cells*, SCI., Dec. 21, 2007, at 1917–18, 1919 (documenting early success with utilizing the inducing factors Oct4, Sox2, Nanog, and Lin28).
194 Mark L. Rohrbaugh, *Intellectual Property of Human Pluripotent Stem Cells, in* REGENERATIVE MEDICINE 53 (U.S. Dep't of Health & Human Servs. 2006); *see also supra*, note 12 and accompanying text (discussing the promise of ES cells since 1998).
195 *See* Rohrbaugh, *supra* note 193, at 53 (discussing the rise of patent claims since Thomson).

Thomson and colleagues' original patent, with approximately thirty-eight that encompass human ES cells.[196] Data published in 2007 demonstrate 1,724 patents issued for uses, methods, compositions involving human or animal ES cells.[197] However, application and issue of such patents have declined globally since 2008.[198]

Despite a steady stream of issued patents, the subject matter eligibility of ES cells under section 101 has received increased attention as of late, chiefly due to the perceived ramifications of the decisions in *Mayo* and *Myriad*. In particular, much attention has focused on a recent decision out of the Federal Circuit, *Consumer Watchdog v. Wisconsin Alumni Research Foundation*,[199] decided in 2014. The dispute in *Consumer Watchdog* turned on a patent owned by the Wisconsin Alumni Research Foundation ("WARF") directed to ES cell cultures.[200] Consumer Watchdog alleged that "broad and aggressive assertion of the [WARF patent] has put a severe burden on taxpayer-funded research in [California]."[201] Without alleging any involvement in either research or commercial activities involving ES cells, or alleging that it is an actual or prospective competitor of WARF or licensee of the WARF patent, the Federal Circuit unsurprisingly dismissed Consumer Watchdog's complaint for a lack of standing.[202]

While the Federal Circuit did not reach the merits in *Consumer Watchdog*, the issue of whether the WARF patent, which claimed ES cells, constituted eligible subject matter under section 101 was argued in the briefs.[203] In its brief, Consumer Watchdog argued that *Myriad*, which had come down just one month before, would invalidate the WARF patent.[204] Consumer

196 *Id.*

197 Karl Bergman & Gregory D. Graff, *The Global Stem Cell Patent Landscape: Implications for Efficient Technology Transfer and Commercial Development*, 25 NATURE BIOTECH., no. 4, Apr. 2007, at 420.

198 Debra J.H. Mathews et al., *Patents and Misplaced Angst: Lessons for Translational Stem Cell Research From Genomics*, CELL STEM CELL, May 2, 2013, at 508.

199 753 F.3d 1258 (Fed. Cir. 2014).

200 *Id.* at 1260.

201 *Id.*

202 *Id.* at 1261–62, 1263.

203 Opening Brief of Appellant at 15–18, Consumer Watchdog v. Wis. Alumni Res. Found., No. 2013-1377 (Fed. Cir. Jul. 2, 2013)

204 *See id.* at 13–15 (characterizing the holding in *Myriad* as applying to "a product that occurs in nature").

Watchdog's argument in favor of invalidating the WARF patent is, however, far too thin. It first assigns a mistakenly expansive scope of applicability to the holding in *Myriad* by stating that it applies to all products of nature.[205] This stance contradicts the *Myriad* Court's explicit confinement of its holding by, for instance, stating that it spoke only to genes.[206] While such an expansive reading of *Myriad* may in fact become its enduring meaning, due to application in subsequent cases, it is surely not what the Court had plainly expressed.

Consumer Watchdog also attempted to fashion like comparisons between genes and ES cells—fundamentally different biological units—in an effort to demonstrate that the WARF patent suffered from similar subject matter eligibility flaws to Myriad's patents. Such a comparison ignores weaknesses in the Court's analysis of Myriad's patents, as discussed above.[207] What is more, as WARF counters in its brief, Consumer Watchdog relied on an unsubstantiated view of the science, which had the effect of intimating that the WARF patent, in claiming ES cells, ran afoul of section 101 by not differentiating ES cells created in culture from cells in the embryo.[208] Among other relevant distinctions, WARF identified evidence that ES cells in culture are chemically distinct from those in the embryo and that the properties of the ES cells claimed in the WARF patent had been altered in the laboratory such that they exhibited properties dissimilar from their natural counterparts.[209]

While counterarguments presented by WARF demonstrate how ES cells differ from naturally occurring cells in the embryo to such a degree as to render them eligible under section 101, this leaves open the issue of whether the arc of section 101 jurisprudence following *Myriad* likewise augurs in favor of subject matter eligibility. As the briefs in *Consumer Watchdog* suggest,[210] section 101 jurisprudence remains burdened by an

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[205] *Id.* at 15–16.

[206] *See Ass'n for Molecular Pathology*, 133 S. Ct. at 2119–20 (discussing the patentability of genetic material).

[207] *See supra* notes 143–46, 151 and accompanying text (discussing the flaws in the *Myriad* decision*)*.

[208] Brief for Appellee at 36–37, Consumer Watchdog v. Wis. Alumni Research Found., 753 F.3d 1258 (Fed. Cir. 2014), (No. 2013–1377).

[209] *Id.* at 37; *see supra* notes 176–177 and accompanying text (explaining that ES cells exhibit properties not found in their native counterparts).

[210] *See* Brief for Appellee, *supra* note 207, at 48–49 (noting that the

inadequate understanding of the underlying science that attends biotechnological patents. The arc of section 101 jurisprudence, most notably as shaped by *Myriad*, seems to embrace the existence of such a flawed understanding. The *Myriad* Court's turn away from the organic approach of earlier precedents, in favor of preferentially weighting certain characteristics based on perceived salience to determining subject matter eligibility, suggests that ES cells may be confronted with fundamentally similar problems to *Myriad*'s genes. It is not difficult to imagine a court, operating under an inadequate scientific understanding, following *Myriad*'s lead and affording greater salience to characteristics of an invention claiming ES cells that exhibit a perceived similarity to cells in the embryo, rather than properly accounting for more important differences that better speak to a determination of subject matter eligibility.

V. iPS CELLS AFTER *MYRIAD*

iPS cells have been a part of the global patent landscape since Takahashi and Yamanaka's first successful generation utilizing mouse models in 2006.[211] Patents claiming iPS cells can be bifurcated into two types: 1) patents concerning the production of iPS cells; and 2) patents concerning downstream differentiation technologies.[212] Patents concerning the production of iPS cells include, among others, culture technologies and growth factors utilized in reprogramming somatic cells.[213] Among so-called differentiation patents, iPS cells play varying roles, whether central or merely ancillary to the ultimate invention.[214] Overall, patent filings for iPS technologies globally have increased year-on-year since 2006.[215] Patent applications globally nearly doubled from 2009 to 2010, and reached an apex in 2012.[216] Between 2006

appellant's statements are unsupported and introducing expert testimony to show the science behind the patent claim).

[211] MacKenna Roberts et al., *The Global Intellectual Property Landscape of Induced Pluripotent Stem Cell Technologies*, 32 NATURE BIOTECH., no. 8 Aug. 2014, at 744; *see also* David Cyranoski & Brian Owens, *First US Patent for iPS Cells*, *News & Comments*, *News Blog*, NATURE.COM, (Aug. 16, 2011), *available at* http://blogs.nature.com/news/2011/08/first_us_patent_for_ips_cells.html (noting that the first U.S. patent for iPS cell technology was issued in 2011).

[212] Roberts et al., *supra* note 210, at 743.

[213] *Id.*

[214] *Id.*

[215] *Id.* at 744.

[216] *Id.*

and 2013, approximately 650 patents were filed globally concerning the generation of iPS cells and approximately 1,300–1,400 patents concerning iPS cell differentiation technologies.[217] However, only approximately 11 percent of filed patents globally have actually been granted, with as low as 8 percent granted in each the U.S. and Japan, and as high as 35 percent granted in Korea.[218]

Owing to the process of generation, iPS cells present few, if any, subject matter eligibility worries compared with ES cells. Unlike ES cells, which to some may resemble other cells in the embryo, iPS cells do not have any native counterparts.[219] Moreover, the process for generating iPS cells relies only minimally on naturally occurring units.[220] While generation of iPS cells relies initially on (naturally occurring) somatic cells, for instance, subsequent steps in the generation process dramatically alter these cells such that the resultant products, iPS cells, reflect a distinctly human-made quality not otherwise found in nature. Even given the arc of section 101 jurisprudence following *Myriad*, it is difficult to imagine that iPS cells would run afoul of subject matter eligibility. While *Myriad* manifests a worryingly parochial way of thinking about parsing the salient details of the underlying science for purposes of determining subject matter eligibility, the process of generating iPS cells simply does not afford enough opportunities to collapse non-natural into natural. For a court to invalidate a patent claiming iPS cells based solely on section 101—assuming adept drafting of the patent—it would have to both preferentially weight the importance of somatic cells in the generation process, and ignore fundamental differences between somatic cells and iPS cells.

VI. LOOKING FORWARD

Myriad has the effect of layering ambiguity atop an already circuitous line of section 101 precedents. Worryingly, *Mayo* and *Myriad* have *in toto* shifted section 101 jurisprudence so far afield of the organic approach to evaluating law and product of

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[217] *Id.* at 743.

[218] Roberts et al., *supra* note 210, at 746.

[219] *Cf.* Robin Feldman & Deborah Furth, *The Intellectual Property Landscape for iPS Cells*, 3 STAN. J.L., SCI., & POL'Y 16, 24–25 (2010) (discussing the authority under which iPS cells are patentable giving way for the argument that there are no native counterparts in iPS cells).

[220] *See id.* at 18 (discussing the generation process for iPS cells).

nature challenges of early precedents that it has become uncertain how future challenges to, for instance, patents that claim either ES or iPS cells are likely to play out. For an industry that relies on the exclusivity rights that attend patent protection to garner sufficient research funding—research that, importantly, endeavors to generate therapeutic advancements—this shift should be particularly troubling.