The Impact of Uncertainty Regarding Patent Eligible Subject Matter for Investment in U.S. Medical Diagnostic Technologies

A. Sasha Hoyt

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I. Introduction

> *"Why would anyone in their right mind risk millions if not billions of dollars to develop a product when they have no idea if they're eligible for protection? From a business perspective, it simply isn't worth the risk for many endeavors."*[1]

Have you been swabbed to check for COVID-19? Has a doctor analyzed your blood or urine when assessing your health? If you answered "yes" to either of these questions, you have experienced the benefits of medical diagnostic testing. Most obviously, medical diagnostics enable physicians to identify conditions and diseases in their patients from the mundane—such as a blood typing test—to those serious, concerning conditions requiring further treatment—such as COVID-19 and various cancers.[2] Diagnostics are especially important for patients with rare diseases and conditions such as Philadelphia-chromosome-positive (Ph+) chronic myeloid leukemia (CML), an aggressive cancer that has become increasingly treatable due to the discovery of its genetic biomarker.[3] Physicians also use medical diagnostic testing preventatively, enabling the diagnosis of

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[1] *The State of Patent Eligibility in America, Part I*, 116th Cong. 3:32–47 (2019) (opening statement of Sen. Thom Tillis).

[2] *See* PERSONALIZED MEDICINE COALITION, THE PERSONALIZED MEDICINE REPORT: OPPORTUNITY, CHALLENGES, AND THE FUTURE 5 (2017) [hereinafter PMC REPORT], *available at* http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The_PM_Report.pdf (PDF) (detailing the use of diagnostic tests by physicians to "identify specific biological markers, often genetic, that help determine which medical treatments and procedures will work best for each patient").

[3] See *infra* Part III for a detailed discussion of the diagnostic testing for this cancer.

diseases and conditions at earlier stages of severity and thus improving patient outcomes. [4] But these benefits often come at a great cost, from twenty to over one hundred million dollars to develop diagnostic tests for rare diseases according to a survey in 2013.[5]

Patent protection has historically offered an incentive for the up-front expenditures required to create new diagnostic methods. Indeed, for many start-ups that develop new, cutting-edge technologies, patent rights are a lifeline in the quest to obtain venture capital investment, to survive in competitive markets, and to commercialize their products.[6] However, this incentive has become less powerful in recent years because of increasing uncertainty regarding the scope of patent-eligible subject matter.

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[4] *See* PMC REPORT, *supra* note 2, at 5 ("By combining this information with an individual's medical records, circumstances, and values, personalized medicine allows doctors and patients to develop targeted treatment and prevention plans.").

[5] *See* PETER KEELING ET AL., DIACEUTICS, MYSTERY SOLVED! WHAT IS THE COST TO DEVELOP AND LAUNCH A DIAGNOSTIC? 1 (Jan. 15, 2013), *available at* https://diaceutics-website.s3.eu-west-1.amazonaws.com/stxore/2e17552089662dafc17a2597f44463dc.pdf (PDF) (reporting in 2013 that "on average the cost of developing and commercializing a diagnostic properly in the US is $50 million to $75 million").

[6] *See* Stuart J. H. Graham & Ted Sichelman, *Why Do Start-Ups Patent*, 23 BERKELEY TECH. L.J. 1063, 1078 (2008) ("[I]ncreased patenting by venture-backed companies in the software and biotech industries is significantly correlated with total investment, total number of financing rounds, and firm longevity . . . .").

Scholars and practitioners studying recent changes in standards of patent eligibility seem to agree that "[p]atent law is in a state of crisis."[7] Even Andrei Iancu, the recently-departed Director of the USPTO, has expressed concern about murky patent eligibility jurisprudence.[8] In particular, Supreme Court and Federal Circuit cases have effectively turned 35 U.S.C. § 101,[9] the statute governing patentable subject matter, into a brick wall rather than a sieve when applying it to medical diagnostic methods. Scholars and practitioners have expressed alarm about the "remarkably complex" analysis required "[f]or a simple 'threshold' eligibility test."[10]

This Note presents the first study that empirically examines venture capital investments to determine the impact on investment in medical diagnostic technologies following the Supreme Court's decisions restricting patent eligible subject matter in *Bilski*

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7 David O. Taylor, *The Crisis of Patent Eligibility in America*, 4 CRITERION J. ON INNOVATION 733, 733 (2019).

8 *See* Kevin Stawicki, *Iancu Says Congress May Be Up For Patent Eligibility Reform*, LAW360 (Sept. 1, 2020, 10:34 PM), https://www.law360.com/articles/1149185? (quoting Andrei Iancu as stating, "[T]he current state of Section 101 is a problem").

9 35 U.S.C. § 101.

10 Paul Michel & John Battaglia, *New Enablement-Like Requirements for 101 Eligibility:* AAM v. Neapco *Takes the Case Law Out of Context, and Too Far—Part I,* IP WATCHDOG (Aug. 19, 2020), https://www.ipwatchdog.com/2020/08/19/new-enablement-like-requirements-101-eligibility-aam-v-neapco-takes-case-law-context-far-part/id=124433/.

v. Kappos[11] and *Mayo Collaborative Services v. Prometheus Laboratories*.[12] In particular, this Note demonstrates that there has been a modest but significant adverse effect to venture capital investment in medical diagnostics following these cases.[13]

In order to reach that conclusion, Part II of this Note examines the relationship between patents and innovation.[14] Part III then examines the importance of medical diagnostics to modern personalized medicine and discusses the impact of medical diagnostic testing on individuals with rare diseases and conditions.[15] Part IV dissects the Supreme Court and Federal Circuit's contemporary decisions regarding the judicial exclusions to § 101.[16] Part IV concludes with an analysis of what patent protection remains for medical diagnostic methods in the wake of caselaw that renders most diagnostics patent ineligible.[17] Part V transitions to the discussion of venture capital investment perspectives and the impact of uncertainty on investment-making decisions and innovation as it relates to medical diagnostics and § 101.[18] Part VI outlines the experimental methodology for this project—a difference-in-difference analysis measuring the impact of *Bilski* and *Mayo* on

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11 561 U.S. 593 (2010).

12 566 U.S. 66 (2012).

13 *See infra* Part VII.

14 *See infra* Part II.

15 *See infra* Part III.

16 *See infra* Part IV.

17 *See infra* Part IV.D.

18 *See infra* Part V.

venture capital investment rates in disease diagnosis technologies versus all technologies.[19] Part VII discusses the results of the difference-in-difference analysis, ultimately finding that *Bilski* and *Mayo* have had a negative impact on venture capital investment rates in disease diagnosis technologies.[20] Lastly, Part VIII presents several important implications of this finding as it relates to § 101 doctrine and the development of new medical diagnostic technologies.[21]

II. Patents and Innovation

Intellectual property, by its nature, is "non-rivalrous," with large up-front transaction costs to produce and little to no transaction costs to duplicate.[22] The patent system restores rivalrousness to intellectual property by granting a limited monopoly on the right to exclude others from using said property, thereby incentivizing investment in innovation.[23] Stemming from the right to exclude, economic incentives of patents include the ability to charge "monopoly rent" for use of a patented technology (e.g., issuing a

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19 *See infra* Part VI.

20 *See infra* Part VII.

21 *See infra* Part VIII.

22 *See* David W. Barnes, *Congestible Intellectual Property and Impure Public Goods*, 9 NW. J. TECH. & INTELL. PROP. 533, 533–34 (2011) (explaining the property as information theory); Maureen K. Ohlhausen, *Patent Rights in a Climate of Intellectual Property Rights Skepticism*, 30 HARV. J.L. & TECH. 103, 116 (2016) ("A basic economic premise underlies the patent system: technologies are expensive to invent but easy to copy.").

23 *See* Ohlhausen, *supra* note 22, at 116–17 (arguing that, absent the patent rights scheme, "positive externalities will cause suboptimal investment in innovation").

license).[24] Proponents of the patent system thus believe that stronger patent rights correlate with willingness to invest in the research and development (R&D) of new technologies.[25] Further, the disclosure requirements of the patent system "increase[] the flow of ideas and stimulate[] innovation" by improving the public knowledge of science and other technical fields.[26] And because of the patentholder's right to exclude public uses of her technology, patents "incentivize ingenuity by encouraging the public to design around and improve upon existing patented technology."[27]

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[24] *See* Michele Boldrin & David K. Levine, *The Case Against Patents*, 27 J. ECON. PERSPS. 3, 17 (2013) (discussing the argument that patentholders utilize patents for monopoly rent rather than to increase societal welfare); 35 U.S.C. § 154(a)(1) (enumerating the patentee's right to exclude third parties from selling, manufacturing, or making use of the patent in the United States).

[25] *See, e.g.*, Brief for National Venture Capital Association as Amicus Curiae Supporting Respondent at 9–10, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150) ("[I]n biotechnology, strong patent protection correlates with the amount of R&D investments made by companies . . . .").

[26] Philip Merksamer, Ariosa Diagnostics v. Sequenom: *Metastasis of* Mayo *and* Myriad *and the Evisceration of Patent Eligibility for Molecular Diagnostics*, 31 BERKELEY TECH. L.J. 495, 525 (2016).

[27] *Id.*

On the other side of the table, some patent skeptics, including Judge Richard Posner,[28] have argued that the patent system discourages or limits innovation.[29] These scholars argue that robust patent rights produce more costs than benefits, including the creation of greater barriers to obtain entry in certain markets and inciting needless litigation.[30] However, many of those who critique the patent system admit that "[t]here is little doubt that providing a monopoly as a reward for innovation increases the incentive to innovate."[31]

III. Medical Diagnostics Background

Medical diagnostics are socially valuable, meritorious tools that can improve public health. The medical diagnostics industry is broad and ranges from expensive research-driven testing for specific and rare diseases to routine, general testing for

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[28] Richard A. Posner, *Why There Are Too Many Patents in America*, ATLANTIC (July 12, 2012), https://www.theatlantic.com/business/archive/2012/07/why-there-are-too-many-patents-in-america/259725/ (discussing problems with the patent system, notably that patents provide different incentives across industries).

[29] *See generally* Ohlhausen, *supra* note 22, at 110–12 (discussing popular critiques of the patent system including the theory that patents provide the right to block innovation).

[30] *See* Boldrin & Levine, *supra* note 24, at 5–8 (rebutting the notion that patents encourage thoughtful innovation); Note, *Diagnostic Method Patents and Harms to Follow-on Innovation*, 126 HARV. L. REV. 1370, 1371 (2013) (arguing that "granting strong, early patent rights will result in the underdevelopment of technology[,]" particularly for "broad diagnostic method patents").

[31] Boldrin & Levine, *supra* note 24, at 7.

pregnancy and blood type.[32] Importantly, certain "diagnostic tests enable physicians to identify the most effective treatment for a patient immediately by testing for specific molecular characteristics, thus avoiding the frustrating and costly practice of trial-and-error medicine."[33] Such diagnostic tests may operate by identifying genetic mutations in a person's DNA that make the person more susceptible to an associated condition.[34]

For example, the BCR-ABL fusion gene appears in patients with certain types of leukemia.[35] Physicians most often use a BCR-ABL genetic test to "diagnose or rule out"

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[32] *See* WORLD HEALTH ORG., WHO TECH. REP. SERIES, NO. 1031, THE SELECTION AND USE OF ESSENTIAL IN VITRO DIAGNOSTICS 277–89 (2021) (listing essential disease-specific *in vitro* diagnostic tests such as tests to diagnose diabetes, HIV, COVID-19, and influenza); *see id.* at 275–76 (listing essential in vitro diagnostic tests for general use, such as tests to diagnose blood type, kidney disease, urinary tract infections, and pregnancy).

[33] *See* PMC REPORT, *supra* note 2, at 10.

[34] *See, e.g.*, *BCR ABL Genetic Test*, NAT'L LIBR. MED.: MEDLINEPLUS (July 30, 2020), https://medlineplus.gov/lab-tests/bcr-abl-genetic-test/ (describing BCR-ABL genetic test used to identify certain types of leukemia and to examine efficacy of cancer treatment).

[35] *See* BLUECROSS BLUESHIELD N.C., CORPORATE MEDICAL POLICY: BCR-ABL 1 TESTING AHS – M2027 1 (July 2020) [hereinafter BCR-ABL BLUE CROSS], *available at* https://www.bluecrossnc.com/sites/default/files/document/attachment/services/public/pdfs/medicalpolicy/bcr_abl_1_testing.pdf (PDF) (describing the BCR-ABL 1 mutation as resulting "from a reciprocal translocation that joins the ABL 1 gene from chromosome 9 to the BCR gene on chromosome 22, . . . necessary for the development of CML").

chronic myeloid leukemia (CML) or Ph-positive acute lymphoblastic leukemia (ALL).[36] CML, "a slowly-progressing cancer," comprises fifteen percent of leukemias in adults.[37] Ph-positive ALL, an "aggressive form of cancer," predominantly affects children.[38] A polymerase-chain-reaction (PCR) diagnostic test can detect *one* cell expressing the BCR-ABL mutation in "10^5 to 10^6" healthy cells—enabling physicians to diagnose CML or Ph-positive ALL early on and improve patient prognoses.[39] Significantly, diagnosis of CML in a patient through the identification of the BCR-ABL mutation can revolutionize her care, as treatments that target the mutation produce fewer side effects than other cancer treatments.[40] The drug imatinib mesylate by Novartis, for example, directly targets the BCR-ABL kinase and "drastically improves [a CML patient's] overall survival . . . rate to 88% after 5 years versus 57% from nonspecific treatment with hydroxyurea and interferon, with fewer side effects."[41]

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36 *See BCR ABL Genetic Test*, *supra* note 34 and accompanying text.

37 BCR-ABL BLUE CROSS, *supra* note 35, at 1.

38 BCR-ABL BLUE CROSS, *supra* note 35, at 1.

39 Charles L. Sawyers, *Chronic Myeloid Leukemia*, 340 N. ENG. J. MED. 1330, 1332 (1999).

40 *Id.*; *see Leukemia - Chronic Myeloid - CML: Types of Treatment*, CANCER.NET (Mar. 2018), https://www.cancer.net/cancer-types/leukemia-chronic-myeloid-cml/types-treatment (describing targeted therapy using tyrosine kinase inhibitor drugs to treat CML, which "blocks the growth and spread of cancer cells while limiting damage to healthy cells").

41 *See* BCR-ABL BLUE CROSS, *supra* note 35, at 2.

With the rise in development of precision medicine, physicians are better equipped to diagnose and treat rare conditions and diseases. Approximately sixty-six percent of all medical treatment decisions are based on the results of in vitro diagnostic testing,[42] a subset of diagnostic tests used for detection of disease and other conditions.[43] Importantly, in vitro diagnostic tests "may be used in precision medicine to identify patients who are likely to benefit from specific treatments or therapies."[44]

The precision medicine movement reflects a growing acknowledgement that society benefits from the development of diagnostic tests and treatments for rare conditions and diseases affecting fewer (but still numerous) lives[45] than conditions to which medicine has

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[42] *See* Ulrich-Peter Rohr, et al., *The Value of In Vitro Diagnostic Testing in Medical Practice: A Status Report*, 11 PLOS ONE 1, 2, 11, 13 (2016), *available at* https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4778800/pdf/pone.0149856.pdf (PDF) (analyzing the role of in vitro diagnostics in healthcare worldwide).

[43] *See In Vitro Diagnostics*, U.S. FOOD & DRUG ADMIN. (Oct. 25, 2019), https://www.fda.gov/medical-devices/products-and-medical-procedures/vitro-diagnostics ("In vitro diagnostics can detect diseases or other conditions, and can be used to monitor a person's overall health to help cure, treat, or prevent diseases.").

[44] *Id.*

[45] *See, e.g.*, Soley Bayraktar & Mark Goodman, *Detection of BCR-ABL Positive Cells in an Asymptomatic Patient: A Case Report and Literature Review*, 2010 CASE REPS. MED. 1, 2 (2010) (estimating that physicians diagnose about 4,000 new cases of CML annually in the United States); *Rare Cancers*, DEP'T OF DEF.: CONGRESSIONALLY DIRECTED MED. RSCH. PROGRAMS (Mar. 15, 2021), https://cdmrp.army.mil/rcrp/default ("[A]round *200 forms* of

traditionally given focus.[46] However, as with drug development,[47] the development of medical diagnostic tests requires hefty up-front investment[48] and firms may weigh heavily the possibility of patent protection in determining whether to move forward with R&D for a given test.[49] Additionally, from the innovation standpoint, weighing the cost of development

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rare cancer compose around 20–25% of all U.S. cancer diagnosis, which affect more than 400,000 Americans per year." (emphasis added)).

[46] *See, e.g.*, Rebecca L. Siegel et al., *Cancer Statistics, 2020*, 70 CA: CANCER J. FOR Clinicians 7, 18 (2020) ("The progress against cancer reflects large declines in mortality for the 4 major cancers (lung, breast, prostate, and colorectum) . . . .").

[47] *See* Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 505 (2009) (describing financial incentives including patent protection that companies look for prior to developing a new drug and noting that firms "regularly screen their drugs in R&D and discard ones with weak patent protection").

[48] *See* Liddicoat et al., *The Effects of Myriad and Mayo on Molecular-Test Development in the United States and Europe: Interviews from the Frontline*, 22 VAND. J. ENT. & TECH. L. 785, 800 (2020) ("[D]iagnostic executives estimate the cost to fully develop a test, including clinical education, [to be] between $20.1 and $106 million in the United States alone.").

[49] *See* Roin, *supra* note 47, at 505 ("Given the immense investment needed to fund clinical trials on drugs and the ability of generic manufacturers to rely on those tests to secure regulatory approval for their own products, pharmaceutical companies are rarely willing to develop drugs without patent protection."); Taylor, *supra* note 60, at 2156–57 (discussing the "prevailing view that, because of the non-statutory exceptions to patent

versus the commercial potential of a diagnostic test for a rare condition or disease presents significant challenges—especially if patent rights are unavailable.[50] Recent Supreme Court and Federal Circuit jurisprudence, however, has dramatically affected the scope and availability of patent rights for medical diagnostic technologies, as discussed in the next Part.

IV. Medical Diagnostics and § 101

A. Judicial Exclusions to § 101

Congress has defined patent eligible subject matter broadly to comprise "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof."[51] This definition of patent eligible subject matter remains largely unchanged from the eighteenth century, when Congress enacted the Patent Act of 1793.[52]

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eligibility, patents will not be available to protect worthy inventions, and as a result individuals and companies may not invest efficiently in research and development").

[50] *Cf.* Brief for Association of University Technology Managers as Amicus Curiae Supporting Respondent at 3–4, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150) ("Patent rights are the currency of the tech transfer process, allowing early-stage research to be moved from universities and research institutions to the private sector for development and commercialization.").

[51] 35 U.S.C. § 101.

[52] Act of Feb. 21, 1793, ch. 11, § 1, 1 Stat. 318; *see* Diamond v. Chakrabarty, 447 U.S. 303, 308–09 (1980) (describing the history of the modern § 101, with the sole change since 1793 being the replacement of the word "art" in the 1793 Act with the word "process" in 1952).

When assessing the bounds of this definition, the Supreme Court in *Diamond v. Chakrabarty*[53] noted that,"[i]n choosing such expansive terms . . . modified by the comprehensive 'any,' Congress plainly contemplated that the patent laws would be given wide scope."[54] However, despite the statutory language, the Supreme Court crafted several broad judicial exclusions to § 101. The three broad categories of patent ineligible subject matter are "laws of nature, natural phenomena, and abstract ideas."[55] The Supreme Court created these exclusions to preserve "the basic tools of scientific and technological work"[56] and to ensure that patents do not impede innovation.[57] Indeed, the Supreme Court in *Mayo*

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53 447 U.S. 303 (1980).

54 *Id.* at 308.

55 Diamond v. Diehr, 450 U.S. 175, 185 (1981) (teaching, as well, that although laws of nature, natural phenomena, and abstract ideas cannot be patented, "an *application* of a law of nature or mathematical formula to a known structure or process may well be deserving of patent protection"); *see* Gottschalk v. Benson, 409 U.S. 63, 67 (1972) (stating that "mental processes[] and abstract intellectual concepts are not patentable").

56 *Benson*, 409 U.S. at 67.

57 *See* Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 71 (2012) (positing that "monopolization of" scientific principles and tools "through the grant of a patent might tend to impede innovation more than it would tend to promote it").

recognized "that too broad an interpretation of this exclusionary principle could eviscerate patent law."[58]

Some scholars have critiqued these judicial exclusions—particularly the abstract ideas and natural laws exclusions—as lacking proper definition by the Supreme Court.[59] Likewise, Professor David O. Taylor has argued that the Supreme Court steps out of its Article III shoes and into those of Congress when it creates patent law through judicial exceptions to eligibility.[60] Moreover, judges on the Federal Circuit have opined that other

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[58] *Mayo*, 566 U.S. at 71; *see id.* (asserting that interpretation should not be too broad because "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas").

[59] *See* Rebecca S. Eisenberg, *Diagnostics Need Not Apply*, 21 B.U. J. SCI. & TECH. L. 256, 274 (2015) ("[N]one of these terms has been clearly defined, [so] there is likely some redundancy in the list of exclusions."); Michael Clancy, Note, *Intellectual Property Law—The Future of Patent Eligibility Analysis on Medical Diagnostics and Its Effects on Healthcare Innovation*—Ariosa Diagnostics Inc. v. Sequenom Inc., 12 J. HEALTH & BIOMEDICAL L. 319, 332 (2016) ("The strict interpretation of section 101 may be attributable to the ambiguity left by the failure of the Supreme Court and Federal Circuit Court of Appeals to provide definitions of a law of nature, natural phenomena, abstract idea, or an inventive concept.").

[60] *See* David O. Taylor, *Amending Patent Eligibility*, 50 U.C. DAVIS L. REV. 2149, 2155 (2017) ("In short, given the existing statutory patent law doctrines, the Court has identified no policy-based justification for an independent, non-statutory patent eligibility requirement. In the process, the Court has usurped Congress's role of crafting statutory

statutes adequately filter out unpatentable technologies during examination and that the Supreme Court's interpretation of § 101 is too limiting.[61] They also attribute uncertainty in the existing doctrine to the Supreme Court not providing enough clarity about the boundaries of § 101.[62] In light of these critiques, this Note explores the recent Supreme Court doctrine impacting the boundaries of § 101 and the subsequent deterioration of patent rights to medical diagnostic technology.[63] This Note also examines the Federal Circuit's application of § 101 doctrine to meritorious diagnostic patents in the face of societal and investment interests.[64]

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patentability requirements."); *see also* Ohlhausen, *supra* note 22, at 107 (noting patentable subject matter as an area of rights that "the U.S. Supreme Court has recently diluted").

61 *See* Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1335 (Fed. Cir. 2019) (Lourie, J., concurring in the denial of the petition for rehearing en banc)

> If I could write on a clean slate, I would write as an exception to patent eligibility, as respects natural laws, only claims directed to the natural law itself, *e.g.*, $E=mc^2$, F=ma, Boyle's Law, Maxwell's Equations, etc. I would not exclude uses or detection of natural laws. The laws of anticipation, obviousness, indefiniteness, and written description provide other filters to determine what is patentable.

62 *See* Berkheimer v. HP Inc., 890 F.3d 1369, 1380 (Fed. Cir. 2018) (per curiam) (Reyna, J., dissenting from the denial of the petition for rehearing en banc) ("Unlike prior art for purposes of §§ 102 and 103, we have no established parameters or guidance for what evidence we can and should consider for inventive concept purposes [at Step Two of the *Mayo-Alice* test].").

63 *See infra* Part IV.B.

64 *See infra* Part IV.C.

B. Modern Era of § 101: Chipping Away at Patent Rights

1. Bilski *and the Court's Foreshadowing of a Restrictive § 101 Analysis*

Since the Federal Circuit's creation in 1982 and until 2010, it took an expansive view of patent eligibility, reading the judicial exceptions to § 101 narrowly.[65] For example, in *State Street Bank v. Signature Financial Group*,[66] the Federal Circuit held that business methods are patent eligible[67] and adopted the lenient "useful, concrete, and tangible result" test to determine statutory patent eligibility.[68] In 2008, the Federal Circuit overruled its "useful, concrete, and tangible result" test from *State Street* and adopted the

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[65] *See* Christopher B. Seaman & Sheena X. Wang, *An Inside History of the Burger Court's Patent Eligibility Jurisprudence*, 53 AKRON L. REV. 915, 973 (2019) ("[T]he Federal Circuit's decisions in the 1980s and 1990s seemingly eviscerated any meaningful limits on patent eligibility. The broad conception of patent eligibility adopted by the Court in *Chakrabarty* and *Diehr* had apparently won out . . . .").

[66] 149 F.3d 1368 (Fed. Cir. 1998), *abrogated by In re* Bilski, 545 F.3d 9433 (Fed. Cir. 2008).

[67] *See State Street*, 149 F.3d at 1375–76 (rejecting a "business method exception" to patent eligibility and holding that "[s]ince the 1952 Patent Act, business methods have been, and should have been, subject to the same legal requirements for patentability as applied to any other process or method").

[68] *See State Street*, 149 F.3d at 1373–75 (holding patent eligible the appellant's claims for a machine-implemented data processing system that operated using mathematical algorithms because the algorithms produced a "useful, concrete, and tangible result").

machine-or-transformation test to discern patent eligibility of a process claim.[69] Under that test, "[a] claimed process is . . . patent-eligible under § 101 if: (1) it is tied to a particular machine or apparatus, or (2) it transforms a particular article into a different state or thing."[70]

The first major contemporary Supreme Court case regarding patent eligibility is *Bilski v. Kappos.*[71] In that case, the Court reviewed the petitioner's claims for the "concept of hedging risk and the application of that concept to energy markets."[72] In the decision below, *In re Bilski*,[73] the Federal Circuit declared the machine-or-transformation test to be the "sole" test for determining patent eligibility of a process claim.[74] Applying this test, the Federal Circuit rejected the patent claims because "[p]urported transformations or manipulations simply of public or private legal obligations or relationships, business risks,

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69 *In re* Bilski, 545 F.3d 943, 959–60 (Fed. Cir. 2008), *aff'd but criticized sub nom.* Bilski v. Kappos*,* 561 U.S. 593 (2010) ("[W]e . . . conclude that the 'useful, concrete and tangible result' inquiry is inadequate and reaffirm that the machine-or-transformation test outlined by the Supreme Court is the proper test to apply.").

70 *Id.* at 954.

71 561 U.S. 593 (2010).

72 *Bilski*, 561 U.S. at 609.

73 545 F.3d 943, (Fed. Cir. 2008), *aff'd but criticized sub nom.* Bilski v. Kappos*,* 561 U.S. 593 (2010).

74 *In re* Bilski, 545 F.3d at 955.

or other such abstractions" do not tangibly "transform any article to a different state or thing."[75]

On appeal, the Supreme Court addressed the boundaries of patent eligible subject matter for the first time in the almost thirty years since *Diamond v. Diehr*.[76] Affirming the ruling of the Federal Circuit, the Court determined that the claims in the petitioner's application were recitations of abstract ideas rather than patentable processes.[77] Specifically, the Court noted that risk hedging is a foundational economic concept "taught in any introductory finance class."[78] Moreover, the Court was concerned that allowing the petitioner to retain a patent for risk hedging "would pre-empt use of [the] approach in all fields, and would effectively grant a monopoly over an abstract idea."[79] The Court likewise emphasized that "limiting an abstract idea to one field of use" does not make it patentable.[80]

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75 *Id.* at 963.

76 450 U.S. 175 (1981); *see* Seaman & Wang, *supra* note 65, at 970 ("[T]he Supreme Court [had] retreated from the issue of patent eligibility after *Diehr* for over 25 years . . . .").

77 *See Bilski*, 561 U.S. at 611–12 ("In light of . . . [our] precedent[], it is clear that petitioners' application is not a patentable 'process.'").

78 *Id.* at 611 (quoting *In re* Bilski, 545 F.3d 943, 1013 (Fed. Cir. 2008) (Rader, J., dissenting)).

79 *Id.* at 612.

80 *Id.*

As foreshadowed by the Federal Circuit's ruling[81] in *In re Bilski*, the Court rejected the machine-or-transformation test as "the sole test governing § 101 analyses"[82] for process claims. The Court held that the machine-or-transformation test "is an important and useful clue, an investigative tool," in the patent eligibility analysis.[83] In making this decision, the Court acknowledged concerns of *amici curiae* regarding an expansive application of the machine-or-transformation test: "As numerous amicus briefs argue, the machine-or-transformation test would create uncertainty as to the patentability of software, advanced diagnostic medical techniques," and other advanced technical inventions.[84] Here, the Court suggested that emerging diagnostic methods may "raise new difficulties for the patent law."[85] However, the Court stepped away from stating a

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81 *See In re* Bilski, 545 F.3d at 957 (recognizing "that the Supreme Court may ultimately decide to alter or perhaps even set aside this test to accommodate emerging technologies").

82 *Id.* at 955.

83 Bilski v. Kappos, 561 U.S. 593, 605 (2010).

84 *Id.*

85 *Id.* at 607.

bright-line rule regarding subject matter eligibility under § 101.[86] The "great challenge,"[87] stated the Court, would be in "striking the balance between protecting inventors and not granting monopolies over procedures that others would discover by independent, creative application of general principles."[88]

This "great challenge" about the patent eligibility of medical diagnostic patents was foreshadowed in *Laboratory Corporation of America Holdings v. Metabolite Laboratories*.[89] In that case, the disputed claim comprised the steps of "assaying" bodily fluid to detect homocysteine levels and "correlating" the homocysteine levels with a vitamin B deficiency.[90] At trial, the District of Colorado held that the claim was patent eligible, and the Federal Circuit affirmed.[91]

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86 *See id.* at 606 ("Section 101 is a 'dynamic provision designed to encompass new and unforeseen inventions.' A categorical rule denying patent protection for 'inventions in areas not contemplated by Congress . . . would frustrate the purposes of the patent law.'" (citing J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int'l, Inc. 534 U.S. 124, 125 (2001); Diamond v. Chakrabarty, 447 U.S. 303, 315 (1980)) (internal citations omitted)).

87 *Id.*

88 *Id.*

89 *Id.*; 548 U.S. 124 (2006).

90 U.S. Pat. No. 4,940,658 at col. 41, ll. 61, 63.

91 *See* Lab. Corp. of Am. Holdings v. Metabolite Lab'ys., Inc., 548 U.S. at 125 (Breyer, J., dissenting) (discussing procedural history).

The Supreme Court granted petitioner's writ of certiorari but then issued a per curiam opinion dismissing the writ "as improvidently granted."[92] Justice Breyer, joined by Justices Stevens and Souter, dissented, arguing that the question at issue—"whether the patent claim is invalid on the ground that it improperly seeks to 'claim a monopoly over a basic scientific relationship'"—could have, and *should* have, been decided then.[93] Examining the purpose of the patent system itself—to "promote the Progress of Science and useful Arts"[94]—Justice Breyer's dissent emphasized that an overly protective system can stymy scientific progress by "impeding the free exchange of information."[95] Excluding fundamental scientific and technological principles from patentability constitutes "[o]ne way in which patent law seeks to sail between [the] opposing and risky shoals" of under-protection and overprotection.[96] Justice Breyer viewed with "little doubt" that "[t]he correlation between homocysteine and vitamin deficiency set forth" in the disputed claim was an unpatentable

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92 *Lab. Corp.*, 548 U.S. at 125.

93 *Id.* at 125–26 (Breyer, J., dissenting).

94 U.S. CONST. art. I, § 8, cl. 8.

95 *Lab. Corp.*, 548 U.S. at 127 (Breyer, J., dissenting); *see id.* (enumerating examples of the impediment, including "forcing researchers to avoid the use of potentially patented ideas, . . . leading them to conduct costly and time-consuming searches of existing or pending patents, and . . . raising the costs of using the patented information, sometimes prohibitively so").

96 *Id.* at 127; *see id.* at 128 (specifying that the exclusion "reflects a basic judgment that protection" of "manifestations of laws of nature" would "too often severely interfere with, or discourage, development and the further spread of useful knowledge itself").

"natural phenomenon."[97] Justice Breyer concluded by addressing the value of deciding the case even if his analysis regarding patentability "[was] wrong."[98] First, the Supreme Court's decision "would help diminish legal uncertainty" surrounding § 101.[99] Second, the decision would enable medical professionals to "better understand the nature of their legal obligations" and avoid directly infringing on patents by performing medical diagnoses or procedures disclosed therein.[100]

2. Mayo *and* Alice: *A New Age for Diagnostic Patents*

Another opportunity for the Court to address the "great challenge"[101] came in 2010. The Supreme Court granted Mayo Collaborative Services' first petition for writ of certiorari[102] after the Federal Circuit ruled that Prometheus Laboratories' claims for "calibrating the proper dosage of thiopurine drugs" for patients with certain autoimmune diseases were patent eligible under § 101.[103] However, the Court declined the opportunity to

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97 *Id.* at 135.

98 *Id.* at 138.

99 *Id.*

100 Lab. Corp. of Am. Holdings v. Metabolite Lab'ys., Inc., 548 U.S. 124, 138 (2006).

101 Bilski v. Kappos, 561 U.S. 593, 606 (2010).

102 *See* Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 561 U.S. 1040, 1040 (2010) (granting writ of certiorari).

103 Prometheus Lab'ys., Inc. v. Mayo Collaborative Servs., 581 F.3d 1336, 1339, 1345 (Fed. Cir. 2009), *cert. granted*, *judgment vacated*, 561 U.S. 1040 (2010).

rule on the bounds of § 101 and instead vacated the Federal Circuit's judgment and remanded the case "for further consideration in light of *Bilski*."[104]

When the Court granted Mayo Collaborative Services' second petition for writ of certiorari and ruled on the case in 2012, Justice Breyer penned the Court's opinion.[105] In *Mayo*, Prometheus Laboratories brought an action against Mayo, alleging that its technique to calibrate dosages of thiopurine drugs infringed Prometheus' own patented techniques.[106] Specifically, the patents at issue embodied correlations between levels of certain metabolites including 6-thioguanine, and the likelihood that a dose of a thiopurine drug will be too high and harm the patient, or too low and thus ineffective.[107] Although the district court found that Mayo's technique infringed claim seven of Prometheus' '623 patent,[108] the court granted summary judgment in Mayo's favor because it further found that the asserted patents "recite[d] a natural phenomenon" and thus were ineligible for patenting under § 101.[109] The Federal Circuit ultimately reversed—twice—based on finding the claimed

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104 561 U.S. at 1040.

105 *See* Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (Breyer, J.) (writing unanimously for the Court).

106 *See Mayo*, 566 U.S. at 75–76 (stating procedural history).

107 *See id.* at 73–74 (discussing the use of thiopurine drugs to treat Crohn's disease and other autoimmune diseases).

108 U.S. Pat. No. 6,355,623 (2002).

109 Prometheus Lab'ys., Inc. v. Mayo Collaborative Servs., No. CIV. 04CV1200JAHRBB, 2008 WL 878910, at *14 (S.D. Cal. Mar. 28, 2008), *rev'd*, 581 F.3d 1336 (Fed. Cir. 2009),

methods patent eligible under § 101.[110] The Federal Circuit found that, apart from the natural correlations, "the claims recite[d] specific treatment steps" involving "a particular application of the natural correlations."[111] Likewise, the court found that the claimed treatment methods "satisf[ied] the transformation prong of the machine-or-transformation test" because they "transform[ed] an article into a different state or thing."[112]

In reviewing the case, the Court considered claim one of the '623 patent as "typical" of the claims at issue and examined its patent eligibility under § 101.[113] Claim one, "[a] method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder," comprised three steps: "(a) administering a drug" containing 6-thioguanine to the patient, "(b) determining the level of 6-thioguanine" in the patient, and

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cert. granted, *judgment vacated*, 561 U.S. 1040 (2010), and *rev'd*, 628 F.3d 1347 (Fed. Cir. 2010).

110 The Federal Circuit held for the second time that the disputed treatment method claims were patent eligible because they "recite[d] a patent-eligible *application* of naturally occurring correlations between metabolite levels and efficacy or toxicity" rather than "just the correlations themselves." Prometheus Lab'ys., Inc. v. Mayo Collaborative Servs., 628 F.3d 1347, 1355 (Fed. Cir. 2010) (emphasis added). Further, stated the court, the claims "satisf[ied] the transformation prong of the machine-or-transformation test" under *Bilski*. *Id.*; *see id.* ("The transformation is of the human body and of its components following the administration of a specific class of drugs . . . .").

111 *Prometheus Lab'ys.*, 628 F.3d at 1355.

112 *Id.* at 1355 (quoting *In re* Bilski, 545 F.3d 943, 962 (Fed. Cir. 2008)).

113 *Mayo*, 566 U.S. at 74.

(c) "wherein" the physician determines, based on claimed thresholds for concentration of 6-thiopurine in the patient's blood, whether to increase or decrease subsequent doses of the drug to the patient.[114] Notably, as emphasized by the Court, scientists "already understood" these correlations "[a]t the time the discoveries embodied in the patents were made" but without the precision set forth in the patents.[115] The Court inquired, thus, whether the claims "add[ed] *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws."[116]

In its analysis, the Court first identified that the claims were directed to a "law of nature," a judicial exclusion to § 101.[117] Then, the Court analyzed the individual elements of the claimed processes to ascertain whether they had "additional features that provide practical assurance that the process is more than a drafting effort designed to monopolize the law of nature itself."[118] First discussing the "administering" step, the Court stated that it simply referred to the "pre-existing audience" of physicians that utilized thiopurine drugs to treat patients with autoimmune disorders "long before anyone asserted [the] claims" at

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114 *Id.* at 74–75; U.S. Patent No. 6,355,623, col. 20, ll. 10–25.

115 *Mayo*, 566 U.S. at 73–74.

116 Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 77 (2012).

117 *Id.*

118 *Id.*

issue.[119] However, as the Court noted, targeting the use of an abstract idea to a limited technological area does not render a claim patent eligible under § 101.[120]

Second, the Court examined the "wherein" clauses which told physicians how to adjust dosages of thiopurine drugs depending on blood levels of 6-thioguanine.[121] The Court opined that these clauses, rather than applying the natural law, "simply tell a doctor about the relevant natural laws . . . while trusting them to use those laws appropriately where they are relevant to their decisionmaking."[122] A claim which recites a law of nature or abstract idea and appends an instruction to the tune of "apply the law" is patent ineligible under § 101.[123]

Third, the Court assessed the "determining" step. That step instructed physicians to determine blood levels of the relevant thiopurine metabolite.[124] However, as the Court emphasized, the methods to measure metabolite levels in blood "were well known in the

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119 *Id.* at 78.

120 *See id.* ("In any event, the 'prohibition against patenting abstract ideas cannot be circumvented by attempting to limit the use of the formula to a particular technological environment.'" (quoting Bilski v. Kappos, 561 U.S. 593, 610–11 (2010))).

121 *See id.* (interpreting the claim element).

122 *Id.*; *see id.* (comparing the "wherein" step to "Einstein telling linear accelerator operators about his basic law and then trusting them to use it where relevant;" in other words, simply telling the relevant audience to apply a natural law).

123 *Id.*

124 *Id.* at 79 (describing the claim element).

art."[125] Scientists also "routinely measured" metabolites when investigating the correlations claimed.[126] Therefore, the step directed physicians to perform "well-understood, routine, conventional" activities already engaged in by others in the field.[127] Such activity, as explained by the Court, "is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law."[128]

Lastly, looking at the claim holistically, the Court stated that "the steps are not sufficient to transform unpatentable natural correlations into patentable applications" thereof.[129] Rather, taken in their sum, the claim elements "add[ed] nothing significant beyond the sum of their parts taken separately."[130]

When considering the broader issue of patent eligibility of claims embodying a law of nature, the Court showed particular concern "that patent law not inhibit further discovery by improperly tying up the future use of laws of nature."[131] Likewise, the Court worried that even a diagnostic patent claiming "limited applications" of natural laws would "threaten to inhibit the development of more refined treatment recommendations" combining "later discovered features of metabolites, human physiology or individual patient

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125 *Id.*

126 *Id.*

127 Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 79 (2012).

128 *Id.*

129 *Id.* at 80.

130 *Id.*

131 *Id.* at 85.

characteristics."[132] Though the Court recognized the utility of the diagnostic patent at issue, it stepped away from determining "whether, from a policy perspective, increased protection for discoveries of diagnostic laws of nature is desirable."[133]

Following *Mayo*, diagnostic patents were largely considered unpatentable.[134] Two years later in *Alice Corporation v. CLS Bank International*,[135] the Court clarified that *Mayo* applies to all three categories of judicial exclusions—not just to laws of nature as discussed in *Mayo*.[136] The Court further refined *Mayo* in establishing its holding as a two-step test governing the patent eligibility analysis under § 101.[137] At "Step One," a court must determine whether the claims at issue are directed towards a law of nature, abstract idea, or natural phenomenon.[138] Then, at "Step Two," the court must examine the elements of the

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132 *Id.* at 86–87.

133 *Mayo*, 566 U.S. at 92.

134 *See* Rebecca S. Eisenberg, *Diagnostics Need Not Apply*, 21 B.U. J. SCI. & TECH. L. 256, 257 (2015) (arguing that "diagnostic applications are not patent eligible").

135 573 U.S. 208 (2014).

136 *See Alice*, 573 U.S. at 217–18 (describing the Court's analysis in *Mayo* as "a framework for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts").

137 *See id.* at 217–18 (setting forth the two-part test).

138 *See* Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 77 (2012) ("If a law of nature is not patentable, then neither is a process reciting a law of nature . . . ."); *Alice*, 573 U.S. at 217 ("First, we determine whether the claims at issue are directed to . . . [a] patent-ineligible concept[].").

claims to ascertain whether they "add *enough* to their statements of" a judicial exclusion to transform the claim into a patentable application of the otherwise patent-ineligible subject matter.[139] The *Mayo-Alice* test remains the controlling test for determining patent eligible subject matter under § 101.

In *Alice*, the Court examined Alice Corporation's claims pertaining to a computerized method to mitigate "settlement risk," "the risk that only one party to an agreed-upon financial exchange will satisfy its obligation."[140] At trial, the district court found that all claims were patent ineligible under § 101 as being directed to an abstract idea.[141] The Federal Circuit reversed, but during an en banc rehearing the court vacated its prior judgment and a plurality of judges affirmed the judgment of the district court.[142] The

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139 *Mayo*, 566 U.S. at 77 (2012); *see Alice*, 573 U.S. at 217–18 (answering the inquiry requires consideration of claim elements individually and holistically to determine whether those elements sufficiently "'transform the nature of the claim' into a patent-eligible application" (quoting *Mayo*, 566 U.S. at 78)).

140 *Alice*, 573 U.S. at 213.

141 *See* CLS Bank Int'l v. Alice Corp. Pty., 768 F. Supp. 2d 221, 252, 243 (D.D.C. 2011) (finding that the claims were directed to the abstract idea of "employing a neutral intermediary to ensure that parties to an exchange can honor a proposed transaction"), *rev'd*, 685 F.3d 1341 (Fed. Cir. 2012), *reh'g en banc granted*, *opinion vacated*, 484 F. App'x 559 (Fed. Cir. 2012), and *aff'd*, 717 F.3d 1269 (Fed. Cir. 2013), *aff'd*, 573 U.S. 208 (2014).

142 *See Alice*, 573 U.S. at 214–15 ("The plurality concluded that petitioner's claims 'draw on the abstract idea of reducing settlement risk by effecting trades through a third-party intermediary,' and that the use of a computer to maintain, adjust, and reconcile shadow

Supreme Court granted Alice's writ of certiorari and affirmed, utilizing the *Mayo* framework to guide its analysis.

First, the Court found that the claims were directed to the "abstract idea of intermediated settlement."[143] Like in *Bilski*, the Court emphasized that the abstract idea at issue was a foundational economic practice existent prior to the claims at issue.[144] Second, the Court looked at the claim elements to determine whether it contained enough "additional features"[145] to transform the abstract idea "into a patent-eligible application" thereof.[146] At Step Two, the Court stressed that "the mere recitation of a generic computer cannot transform a patent-ineligible abstract idea into a patent-eligible invention" and likened such a recitation to "[s]tating an abstract idea while adding the words 'apply it with a computer.'"[147] Ultimately, following consideration of the claim elements individually and holistically, all claims at issue—method, system, and media claims—were held patent

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accounts added nothing of substance to that abstract idea." (quoting CLS Bank Int'l v. Alice Corp. Pty., 717 F.3d 1269 (Fed. Cir. 2013))).

143 *Id.* at 218.

144 *See id.* at 219–20 (comparing the concept of intermediated settlement to the risk hedging in *Bilski*).

145 *Id.* at 221 (quoting *Mayo*, 566 U.S. at 77).

146 Alice Corp. v. CLS Bank Int'l, 572 U.S. 208, 221 (2014).

147 *Id.* at 223.

ineligible under this principle.[148] Following *Mayo* and *Alice*, some practitioners and scholars asserted that medical diagnostics were no longer patentable.[149]

C. Mayo-Alice *Aftermath: Questionable Patent Eligibility for Diagnostics*

The Court in *Mayo* pointed out that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas."[150] This statement applies with special force to medical diagnostic technologies, which may depend on utilizing a correlation found in nature, for example, between presence of a specific gene mutation to diagnose likelihood of future cancer[151] or levels of certain metabolites or

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148 *See id.* at 225–27 (finding that the claims "add nothing of substance to the underlying abstract idea").

149 *See* Gene Quinn, *It May Be Time to Abolish the Federal Circuit*, IPWATCHDOG (July 9, 2019), https://www.ipwatchdog.com/2019/07/09/may-time-abolish-federal-circuit/id=111122/ ("It would be easy to distinguish both *Mayo* and *Alice*, but rather than recognize the peculiar facts of these cases as representing the most trivial of innovations, the Federal Circuit has used *Mayo* to destroy medical diagnostics . . . .").

150 Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 71 (2012).

151 *See supra* notes 35–39 (discussing testing for BCR-ABL fusion gene mutation to diagnose certain types of leukemia); Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 579–83, 595 (2013) (holding that patents for the isolated location and sequence of the BRCA1 and BRCA2 genes on chromosomes 13 and 17, "mutations of which can substantially increase the risks of breast and ovarian cancer," were not patent eligible under § 101).

enzymes in a patient's body to ascertain a condition.[152] Because such naturally occurring correlations may be necessary *per se* in the development of diagnostics, *Mayo* injected significant uncertainty into decisions of claim drafting and whether to pursue a diagnostic patent in the first place.[153] However, evidence from practitioners, companies, and technology transfer officers intent on patenting new diagnostic technologies demonstrates that molecular diagnostic tests are still patent eligible in the United States following *Mayo*—at least, according to the standards of the USPTO.[154] A different story emerges when those patents are subject to judicial review.

When establishing the *Mayo* test as governing all judicial exclusions to § 101, the *Alice* Court recognized that they must "tread carefully in construing . . . exclusionary

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152 *See, e.g.*, Cleveland Clinic Found. v. True Health Diagnostics LLC, 760 F. App'x 1013, 1015, 1019 (Fed. Cir. 2019) (discussing method claims for a diagnostic test utilizing the correlation between levels of the blood myeloperixodase enzyme and having—or developing—certain cardiovascular diseases, ultimately finding the claims ineligible under § 101 as "us[ing] a known technique in a standard way to observe a natural law").

153 *See* Liddicoat et al., *supra* note 48, at 828–29 (2020).

> Uncertainty was a recurrent theme in interviews when discussing *Mayo*. Respondents raised three issues in particular: (i) whether claims could be drafted that were *Mayo*-compliant (and valuable); (ii) how USPTO examiners would apply *Mayo* to a patent application; and (iii) whether granted papers would survive judicial review, which also applied to patents granted *before* the decision.

154 *See id.* at 828 (arguing that interview data from companies, technology transfer offices, and patent practitioners in the United States and Europe demonstrate that molecular diagnostic tests are still patent eligible in the United States following *Mayo* as "many interviewees described a variety of ways to draft valuable claims").

principle[s] lest [they] swallow all of patent law."[155] However, as evidenced by subsequent cases in the Federal Circuit, the *Alice-Mayo* framework operates restrictively when applied to diagnostic patents.[156]

1. The Federal Circuit Begrudgingly Declares Patent Ineligible Diagnostic Methods in Ariosa *and* Athena

In *Ariosa Diagnostics v. Sequenom*,[157] the Federal Circuit examined claims of Sequenom's '540 patent,[158] which taught methods for non-invasive prenatal testing to diagnose "certain fetal characteristics based on the detection of paternally inherited cffDNA."[159] Following a letter from Sequenom threatening to bring an action for infringing the '540 patent, Ariosa Diagnostics filed a declaratory action alleging non-infringement.[160]

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155 *Id.* at 217.

156 Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1352 (Fed. Cir. 2019) (per curiam) (Moore, J., dissenting from the denial of rehearing en banc) ("Since *Mayo*, we have held every single diagnostic claim in every case before us ineligible."); *see id.* at 1354 ("We have turned *Mayo* into a per se rule that diagnostic kits and techniques are ineligible. That per se rule is 'too broad an interpretation of this exclusionary principle [which] could eviscerate patent law.'" (quoting *Mayo*, 566 U.S. at 71)) (alteration in original).

157 788 F.3d 1371 (Fed. Cir. 2015).

158 U.S. Pat. No. 6,258,540 (2001).

159 Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d at 1373.

160 *See id.* at 1374 (describing the infringement action; Sequenom counterclaimed alleging that Ariosa's Harmony Test infringed the '540 patent).

In denying Sequenom's motion to "preliminarily enjoin Ariosa from selling the accused Harmony Prenatal Test," the district court found that "there was a substantial question over whether the subject matter of the asserted claims" was patent eligible under § 101.[161] Sequenom appealed to the Federal Circuit, which vacated and remanded the case "for the district court to examine subject matter eligibility . . . in light of"[162] *Association for Molecular Pathology v. Myriad*.[163]

On remand, the district court held that the asserted claims were patent ineligible under § 101 as being "directed to the natural phenomenon of paternally inherited cffDNA and that the claims did not add enough to the natural phenomenon to make the claims

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161 *Id.* at 1374.

162 *Id.* at 1375 (quoting Aria Diagnostics, Inc. v. Sequenom, Inc., 726 F.3d 1296, 1305 (Fed. Cir. 2013).

163 569 U.S. 576 (2013). In *Myriad*, the Court examined patents for the location and sequence of mutations of the BRCA1 and BRCA2 genes in a person's DNA. *See id.* at 583–84 (describing the disputed claims). The Court found the disputed claims patent ineligible, narrowly holding that "genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material." *Id.* at 589–94, 595. Unlike *Mayo*, *Myriad* did not implicate method claims and moreover does not encompass a large swathe of medical diagnostics. *See id.* at 595 (discussing the limitations to the Court's holding); Christopher M. Holman, *Mayo, Myriad, and the Future of Innovation in Molecular Diagnostics and Personalized Medicine*, 15 N.C. J.L. & TECH. 639, 647–61 (2014) (arguing that, unlike *Mayo*, *Myriad* will not heavily impact the patenting of medical diagnostics).

patent eligible."[164] Sequenom appealed the ruling, and the Federal Circuit affirmed, finding that the claims were directed toward a natural phenomenon[165] and lacked sufficient "new and useful" "additional features."[166]

In its analysis, the Federal Circuit examined three independent claims of the '540 patent. Claim one, a method to detect paternally-inherited nucleic acids in maternal plasma or serum, comprised two steps: (a) "amplifying a paternally inherited nucleic acid" from a maternal serum or plasma sample, and (b) "detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample."[167] Claim twenty-four, a method to detect paternally inherited nucleic acids in a maternal blood sample, comprised three steps: (a) "removing" specified "cell populations from the blood sample," (b) "amplifying a paternally inherited nucleic acid from the remaining fluid," and (c) "subjecting the amplified nucleic acid" to tests to detect the paternally inherited nucleic acids.[168] Lastly, claim twenty-five, a method "for performing a prenatal diagnosis on a maternal blood sample," comprised three steps: (a) "obtaining a non-cellular fraction of the blood sample," (b) "amplifying a paternally inherited nucleic acid" from that sample, and (c) "performing nucleic acid analysis on the amplified nucleic acid to detect paternally inherited fetal nucleic acid."[169]

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164 *Id.* at 1375.

165 *Ariosa*, 788 F.3d at 1376 (conducting *Mayo-Alice* Step One analysis).

166 *Id.* at 1377.

167 U.S. Pat. No. 6,258,540, at col. 23, ll. 61–67.

168 *Id.* at col. 26, ll. 20–28.

169 *Id.* at col. 26, ll. 29–36.

The court analyzed collectively the patent-eligibility of the three claims and utilized the two-step framework as set forth in *Mayo* and *Alice* to guide its analysis.

First, the court asked "whether the claims at issue [were] directed to a patent-ineligible concept."[170] The claims each comprised multiple steps, starting with cffDNA[171] sourced from "a sample of maternal plasma or serum."[172] Notably, the location of cffDNA "existed in nature" before its precise discovery by the inventors of the '540 patent.[173] The court also stressed that the methods ended with a natural phenomenon—paternally inherited cffDNA.[174] According to the court, the claims were thus directed to a natural phenomenon.[175]

Turning to Step Two, the court examined the elements of the method claims "to determine whether the claim contains an inventive concept sufficient to 'transform' the

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170 Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1375 (Fed. Cir. 2015).

171 cffDNA is "a naturally occurring non-cellular fetal DNA that circulates freely in the blood stream of a pregnant woman." *Id.* at 1376.

172 *Id.*

173 *Id.; see id.* ("It is undisputed that the existence of cffDNA in maternal blood is a natural phenomenon.").

174 *See id.* (stating that Sequenom did not argue that the inventors "created or altered any of the genetic information encoded in the cffDNA").

175 *See id.* (emphasizing the finding that the methods "begin[] and end[] with a natural phenomenon," and noting further support for the finding in the patent's written description).

claimed naturally occurring phenomenon into a patent eligible application."[176] *Mayo* alternatively labeled the search as one for "additional features" within the claims to achieve the transformation.[177] "For [method] claims that encompass natural phenomenon[s]" the Federal Circuit stated that the "steps [of the method] are the additional features that must be new and useful."[178] The court focused on the "amplifying" and detection steps present in each of the claims at issue.

Comparing Sequenom's claims to those at issue in *Mayo*, the court articulated that, like in *Mayo*, the claims instructed physicians to conduct "routine, conventional techniques" at each step.[179] Specifically, "[u]sing methods like PCR to amplify and detect cffDNA [were] well-understood, routine, and conventional activity" at the time the application for the '540 patent was filed.[180] Drawing further from the '540 patent's specification and from expert testimony, the court concluded that the methods at issue "amount[ed] to a general instruction to doctors to apply routine, conventional techniques when seeking to detect

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176 *Id.* at 1376 (quoting Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 72 (2012)).

177 *Id.* at 1377 (quoting *Mayo*, 566 U.S. at 77).

178 *Id.*

179 *Id.*; *see id.* (comparing the claims at issue to those in *Mayo*, which instructed physicians to apply well-understood scientific correlation utilizing known methods of measuring specified metabolites).

180 *Id.*; *see id.* at 1378 (providing excepts from the specification of the '540 patent, the patent's prosecution history, expert testimony, and testimony of the inventors).

cffDNA," and were thus "not new and useful."[181] Therefore, the court held that the claims at issue were patent ineligible.[182]

Judge Linn concurred with the court's judgment, albeit with a distinct qualifier and critique of *Mayo*:

> I join the court's opinion invalidating the claims of the '540 patent *only because* I am bound by the sweeping language of the test set out in [*Mayo*]. In my view, the breadth of the second part of the test was unnecessary to the decision reached in *Mayo*. This case represents the consequence—perhaps unintended—of that broad language in excluding a meritorious invention from the patent protection it deserves and should have been entitled to retain. [183]

Judge Linn highlighted the evident frustration at the Federal Circuit following that case. Moreover, Judge Linn specifically called out the *Mayo* Court's "blanket dismissal of conventional post-solution steps" as "leav[ing] no room to distinguish *Mayo* from [*Ariosa*]," despite significant factual differences between the "conventional" steps required to perform the methods of the asserted claims.[184] In *Mayo*, the Court noted that physicians understood and utilized the scientific correlations embodied in Prometheus' patents long before the patent was granted, and likewise routinely measured blood levels of metabolites to investigate the claimed correlations.[185] By contrast, Judge Linn stressed that "*no one* was amplifying and detecting paternally-inherited cffDNA using the plasma or serum of

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181 *Id.* at 1377.

182 *See* Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1378 (Fed. Cir. 2015) ("The claims of the '540 patent at issue in this appeal are not directed to patent eligible subject matter and are, therefore, invalid.").

183 *Id.* at 1380 (Linn, J., concurring) (emphasis added).

184 *Id.* at 1381.

185 *See supra* notes 119–127 and accompanying text.

pregnant mothers."[186] Rather, "the maternal plasma used to be routinely discarded because . . . nobody thought that fetal cell-free DNA would be present."[187] To that same point, Judge Linn also emphasized the merits of Sequenom's invention and advances over prior art—asserting that Sequenom's '540 patent taught a *new method*[188] rather than "appending conventional steps" to an existing method.[189]

Four years later in *Athena Diagnostics v. Mayo Collaborative Services*,[190] the Federal Circuit examined claims of Athena's '820 patent,[191] which taught a method of diagnosing certain neurological disorders, including a rare form of *Myasthenia Gravis* (MG) through detection of antibodies to the muscle-specific tyrosine kinase (MuSK) protein.[192] Prior to the discoveries by the '820 patent's inventors of the association between MG and MuSK autoantibodies, "no disease had been associated with MuSK."[193] Athena developed and

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186 *Ariosa*, 788 F.3d at 1381 (Linn, J., concurring) (emphasis added).

187 *Id.* (internal citations omitted).

188 *See id.* (highlighting that prior methods for prenatal diagnoses "required invasive methods," were less accurate, and presented greater risks than the claimed method).

189 Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 82 (2012).

190 915 F.3d 743 (Fed. Cir. 2019), *cert. denied,* 140 S. Ct. 855 (2020).

191 U.S. Pat. No. 7,267,820 (2007).

192 *See Athena*, 915 F.3d at 746–47 (discussing the discovery that, while "80% of patients with MG produce acetylcholine receptors autoantibodies," some of the other 20% which do not produce those autoantibodies "instead generate autoantibodies to a membrane protein called MuSK").

193 *Id.* at 747 (citing U.S. Pat. No. 7,267,820 at col. 2, ll. 35–37).

marketed a test called FMUSK to diagnose MuSK-related neurological disorders.[194] When Athena discovered that Mayo "developed two competing tests," Athena brought an infringement action against Mayo.[195] Mayo moved to dismiss the action, arguing that the patent effectively "patent[ed] a law of nature" and that "it use[d] techniques standard in the art."[196] The district court granted that motion, finding that the claims were directed to ineligible subject matter.[197] On appeal, the Federal Circuit examined whether dependent claims 6–9 were patent eligible under § 101.[198]

The court analyzed claims 7–9, then briefly discussed claim six as "Athena did not present any arguments specific to claim six."[199] The court honed in on claim nine as representative of the claims at issue, summarizing it as comprising: "(1) contacting MuSK or an epitope thereof having a 125I label, with bodily fluid; (2) immunoprecipitating any

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194 *See id.* at 746–47 (discussing the diagnostic test and methods).

195 *Id.* at 746 (discussing procedural history).

196 Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 275 F. Supp. 3d 306, 308 (D. Mass. 2017), *aff'd*, 915 F.3d 743 (Fed. Cir. 2019).

197 *See Athena Diagnostics*, 275 F. Supp. 3d at 311–13 (granting Mayo's motion to dismiss after finding that the claims were directed to a natural law and that the claims lacked an "inventive concept" so as to make the claims patent eligible under § 101 (quoting Alice Corp. v. CLS Bank Int'l, 572 U.S. 208, 218 (2014))).

198 *See Athena*, 915 F.3d 743, 747 (focusing on claim 9, "the most specific one at issue").

199 *Id.* at 748. Accordingly, this section focuses on the court's analysis of claims 7–9. For the text of claims 7–9, see U.S. Pat. No. 7,267,820 at col. 12, *l.* 62–col. 13, *l.* 5 (claim 7); *id.* at col. 13, ll. 6–7 (claim 8); *id.* at col. 13, ll. 8–9 (claim 9).

antibody/MuSK complex; and (3) monitoring for the label on the complex, wherein the presence of the label indicates the presence of a MuSK-related disorder."[200] The court noted that "[i]t is undisputed that iodination and immunoprecipitation were known techniques at the time of the invention."[201] Likewise, techniques to perform autoantibody detection, including radioimmunoassays as utilized in the claimed methods, were "known per se in the art."[202]

Examining the claims under the *Mayo*/*Alice* framework, the court first assessed whether the claims were "directed to a law of nature."[203] Whereas Athena contended that the claims were "directed to a new laboratory technique," Mayo argued that the claims were instead "directed to a natural law: the correlation between naturally-occurring MuSK autoantibodies and MuSK-related neurological diseases."[204] Ultimately, the court agreed with Mayo's interpretation of the asserted claims,[205] finding that there could "be no dispute that [the correlation] is an ineligible natural law" because it "exists in nature apart from

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200 *Athena*, 915 F.3d at 747.

201 Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743, 748 (Fed. Cir. 2019), *cert. denied,* 140 S. Ct. 855 (2020).

202 *Athena*, 915 F.3d at 748 (quoting U.S. Pat. No. 7,267,820 at col. 3, *l.* 35)).

203 *Id.* at 749.

204 *Id.* at 750.

205 *See id.* ("We ultimately agree with Mayo that, under *Mayo*, the claims are directed to a natural law. . . . Here, it is the correlation between the presence of naturally-occurring MuSK autoantibodies in bodily fluid and MuSK-related neurological diseases like MG.").

any human action."[206] Addressing Athena's arguments, the court stated that, rather than "harness[ing] a natural law to produce a technological improvement," claims 7–9 "are directed to a natural law because the claimed advance was only in the discovery of a natural law, and that the additional steps recited only apply conventional techniques to detect that natural law."[207] Although the court acknowledged that the claims also involved "certain concrete steps to observe its operation,"[208] the court rejected Athena's contention that the claims were directed to an "innovative laboratory technique"[209] because the steps were not "meaningful non-routine steps."[210]

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206 *Id.*

207 *Id.* at 751 (likening the claims at issue to those in *Ariosa*).

208 *Id.*

209 *Id.*; *see id.* at 750–52 (distinguishing the claims at issue from those in *Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc.* which recited a new, patent eligible method of producing preserved hepatocyte cells for subsequent use rather than "an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles" (quoting Rapid Litig. Mgmt, Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1048 (Fed. Cir. 2016)).

210 *Id.* at 751 (quoting Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352, 1361 (Fed. Cir. 2017)); *see id.* at 751–52 (comparing the claims at issue to those in *Cleveland Clinic*, wherein the Federal Circuit found patent ineligible under § 101 claims which "recited detecting [myeloperoxidase (MPO)] or other MPO-related products in a patient sample and then predicting a patient's risk of having or developing cardiovascular disease").

Having concluded that claims 7–9 were directed to a natural law, the court turned to Step Two. At Step Two, the court examined the elements of the claims individually and holistically "to determine whether the additional elements 'transform the nature of the claim' into a patent eligible application."[211] In line with its discussion at Step One, the court held that "the claims fail[ed] to provide an inventive concept" because "the specification defines the individual immunoprecipitation and iodination steps and the overall radioimmunoassay as conventional techniques."[212] Discussing Athena's argument that "the claimed steps were unconventional because they had not been applied to detect MuSK autoantibodies prior to [the] discovery of the correlation between MuSK autoantibodies and MG," the Court stated that it "cannot hold that performing standard techniques in a standard way to observe a newly discovered natural law provides an inventive concept" as required by *Mayo*.[213]

Notably, though the court rejected all of Athena's arguments for eligibility, the court acknowledged the validity of the policy positions taken by the dissent and opined that under *Mayo* and Federal Circuit precedent it could not rule in any other direction:

> The dissent states much that one can agree with from the standpoint of policy, and history, including that "the public interest is poorly served by adding disincentive to the development of new diagnostic methods." . . . But, whether or not we as individual judges might agree or not that these claims only recite

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211 *Athena*, 915 F.3d at 753 (quoting Alice Corp. v. CLS Bank Int'l, 572 U.S. 208, 217 (2014)).

212 Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743, 754 (Fed. Cir. 2019), *cert. denied,* 140 S. Ct. 855 (2020).

213 *Athena*, 915 F.3d at 754.

> a natural law, . . . [Supreme Court] precedent leaves no room for a different outcome here.[214]

Judge Newman dissented from the judgment, demonstrating that—even five years later—applying the *Mayo-Alice* framework to diagnostic technologies remained highly contentious.[215] In particular, *Athena* highlights how the Federal Circuit, rather than heeding the Supreme Court's instruction to apply cautiously the exclusions to § 101,[216] has further constrained the *Mayo-Alice* framework.[217] For instance, though the court in *Athena* stated that "[t]he step one 'directed to' inquiry focuses on the claim as a whole," part of the court's rationale for concluding that the asserted claims were directed to a natural law was "because . . . the additional recited steps [in the claims] only apply conventional techniques

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214 *Athena*, 915 F.3d at 753 n.4 (internal citations omitted).

215 *See Athena*, 915 F.3d at 757 (Newman, J., dissenting) ("This court's decisions on the patent-ineligibility of diagnostic methods are not consistent, and my colleagues today enlarge the inconsistencies and exacerbate the judge-made disincentives to development of new diagnostic methods, with no public benefit.").

216 *See* Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 71 (2012) ("[T]oo broad an interpretation of [judicial exclusions to § 101] could eviscerate patent law.").

217 *See Athena*, 915 F.3d at 757 (Newman, J., dissenting) ("The court again departs from the cautious restraints in the Supreme Court's *Mayo/Alice* application of laws of nature and abstract ideas.").

to detect that natural law."[218] Here, the court arguably inserted Step Two requirements into its analysis at Step One.[219]

Likewise, Judge Newman argued in her dissent that, in breaking down the asserted claims but not considering *all* limitations and elements thereof, the court departed from Supreme Court precedent regarding claim interpretation.[220] Specifically, the Federal Circuit erred at Step One when it ignored significant "chemical and biological steps" taught by the claims which were not known or standard in the art[221] and instead "excise[d] from the claims . . . steps performed by conventional procedures."[222] Only as a whole did the

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218 *Athena*, 915 F.3d at 750, 751.

219 *See id.* at 761 (Newman, J., dissenting)

> The majority does not distinguish between the question of whether the claimed method as a whole is eligible, and the question of whether the separate steps use conventional procedures. Instead, my colleagues hold that since the separate procedures are conventional, it is irrelevant that the method as a whole is a new method.

220 *See id.* at 758 (Newman, J., dissenting) ("In determining the eligibility of respondents' claimed process for patent protection under § 101, their claims must be considered as a whole. It is inappropriate to dissect the claims into old and new elements and then to ignore the presence of the old elements in the analysis." (quoting Diamond v. Diehr, 450 U.S. 175, 188 (1981))).

221 *Id.* at 758; *see id.* ("The reaction between the antibody and the MuSK protein was not previously known, nor was it known to form a labeled MuSK or its epitope, nor to form the antibody/MuSK complex, immunoprecipitate the complex, and monitor for radioactivity, thereby diagnosing these previously undiagnosable neurotransmission disorders.").

222 *Id.* at 758–59.

claims enable physicians to diagnose MG: the inventors claimed "a new multi-step diagnostic method[,] . . . a man-made reaction sequence employing new components in a new combination to perform a new diagnostic procedure."[223]

Judge Newman also acknowledged concerns of many *amici curiae*—from life sciences organizations to groups of law professors—that inconsistency in judge-made law disincentivizes the development of diagnostic methods.[224] In that situation, Judge Newman asserted, "[t]he loser is the afflicted public, for diagnostic methods that are not developed benefit no one."[225]

2. Following Ariosa *and* Athena*, Judges Asks for Reform of § 101*

Following the Federal Circuit's decisions in *Ariosa* and *Athena*, the patentees in both cases petitioned for rehearing en banc. In both instances—notably four years apart—the

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[223] Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743, 759 (Fed. Cir. 2019), *cert. denied,* 140 S. Ct. 855 (2020).

[224] *See Athena*, 915 F.3d at 762–63 (discussing disincentives to innovation brought about by "unabated uncertainty about the patent-eligibility of many biotechnological inventions, with diagnostic and prognostic methods being particularly affected" (quoting Brief for Biotechnology Innovation Organization et al. as Amici Curiae Supporting Appellants at 2, Athena Diagnostics, Inc. v. Mayo Collaborative Servs., Inc., 915 F.3d 743 (Fed. Cir. 2019) (No. 2017-2508), 2019 WL 189542)).

[225] *Id.* at 763.

Federal Circuit denied the petition,[226] albeit with individual judges remarking that the decision was required by *Mayo*.

Indeed, the varying concurring and dissenting opinions accompanying the denials of en banc rehearing in both cases—especially considering Judge Linn's concurring opinion in *Ariosa* and Judge Newman's dissent in *Athena*—suggest the need for reform of § 101, particularly regarding diagnostic technologies.[227] For instance, in his opinion concurring in the denial of Athena's petition for rehearing en banc, Judge Hughes expressed that "the bottom line for diagnostics is problematic" and invited the Supreme Court or Congress to

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[226] *See* Ariosa Diagnostics, Inc. v. Sequenom, Inc., 809 F.3d 1282, 1284 (Fed. Cir. 2015) (denying Sequenom's petition); Athena Diagnostics, Inc. v. Mayo Collaborative Servs., Inc., 927 F.3d 1333 (Fed. Cir. 2019) (denying Athena's petition).

[227] *See Ariosa*, 809 F.3d 1282, 1287 (Fed. Cir. 2015) (Lourie, J., concurring in the denial of rehearing en banc)

> In sum, it is unsound to have a rule that takes inventions of this nature out of the realm of patent-eligibility on grounds that they only claim a natural phenomenon plus conventional steps, or that they claim abstract concepts. But I agree that the panel did not err in its conclusion that under Supreme Court precedent it had no option other than to affirm the district court.

id. at 1287 (Dyk, J., concurring in the denial of rehearing en banc)

> In my view the framework of *Mayo* and *Alice* is an essential ingredient of a healthy patent system, allowing the invalidation of improperly issued and highly anticompetitive patents without the need for protracted and expensive litigation. Yet I share the concerns of some of my colleagues that a too restrictive test for patent eligibility under 35 U.S.C. § 101 with respect to laws of nature (reflected in some of the language in *Mayo*) may discourage development and disclosure of new diagnostic and therapeutic methods in the life sciences, which are often driven by discovery of new natural laws and phenomena.

issue "further explication of eligibility standards in the area of diagnostic patents."[228] Likewise, Judge Moore, dissenting from the denial for rehearing en banc of *Athena*, went as far as to discourage patentholders for medical diagnostic methods from "wast[ing] resources with additional en banc requests" if the Federal Circuit declares their claims patent-ineligible.[229] The "only hope" to ensure patent eligibility of medical diagnostic claims "lies with the Supreme Court or Congress."[230] Part VIII further discusses the importance of the Federal Circuit's calls for reconsideration of the scope of § 101 in view of the findings of the empirical study discussed in Part VII.[231]

D. What Diagnostics Survive? And How?

As the Supreme Court has indicated, and the Federal Circuit affirmed in recent cases, diagnostic methods are largely unpatentable. By contrast, if an inventor creates a new *device* to perform a medical diagnostic test, the device is arguably patentable,[232] even if

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228 *Athena*, 927 F.3d at 1337 (Hughes, J., concurring in the denial of rehearing en banc).

229 *Athena*, 927 F.3d at 1363 (Moore, J., dissenting from the denial of rehearing en banc).

230 *Id.*

231 *See infra* Parts VII–VIII.

232 *See, e.g.*, *CardioNet, LLC v. InfoBionic, Inc.*, 955 F.3d 1358, 1368–71 (Fed. Cir. 2020) (finding that the petitioner's patent was "directed to an improved cardiac monitoring device and not to an abstract idea," especially emphasizing the technological and methodological improvements of the device over prior art); *cf* Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66, 73 (2012) (holding that the process claims at issue did not satisfy § 101 and noting "[i]n particular, the steps . . . (apart from the natural laws themselves)

the underlying biological relationship examined relates to a patent ineligible natural phenomenon or abstract idea.[233] Likewise, Judge Lourie, in concurring with the denial of en banc rehearing of *Athena*, suggested that an "unconventional combination of steps to detect the natural law" may be patentable.[234] "[U]nconventional arrangements of known laboratory techniques, even if directed to a natural law," also escape *Mayo*'s prohibition.[235] Additionally, though non-binding,[236] the USPTO's subject matter eligibility guidance

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involve[d] well-understood, routine, conventional activity previously engaged in by researchers in the field").

[233] Under the *Mayo-Alice* framework, such a device would be patentable at Step 2 provided that the elements of the claim "'transform the nature of the claim' into a patent-eligible application." Alice Corp. v. CLS Bank Int'l, 572 U.S. 208, 217 (2014) (quoting *Mayo*, 566 U.S. at 78); *see* Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576, 595 (2013) (stating that "[h]ad Myriad created an innovative method of manipulating genes while searching for the [non-patentable] BRCA1 and BRCA2 genes, it could possibly have sought a method patent. But the processes used by Myriad to isolate DNA were well understood by the geneticists at the time of Myriad's patents").

[234] *Athena*, 927 F.3d at 1336 (Lourie, J., concurring in the denial of rehearing en banc).

[235] *Id.* (citing Rapid Litig. Mgmt., Inc. v. CellzDirect, Inc., 827 F.3d 1042, 1051 (Fed. Cir. 2016)).

[236] *See* Cleveland Clinic Found. v. True Health Diagnostics, LLC, 760 F. App'x 1013, 1020 (Fed. Cir. 2019) ("While we greatly respect the PTO's expertise on all matters relating to patentability, including patent eligibility, we are not bound by its guidance.").

provides that claims for specific methods of detecting a biomarker may be patent eligible if the detection is performed via non-routine, unconventional steps.[237]

Conversely, the *Mayo* Court instructed that "simply appending conventional steps . . . to laws of nature, natural phenomena, and abstract ideas cannot make those laws, phenomena, and ideas patentable."[238] This latter scenario raises concerns for the ability of physicians to treat their patients without unknowingly infringing patented diagnostic methods.[239] The contrary argument insists that limiting the scope of patent coverage in the

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[237] *See* U.S. PAT. & TRADEMARK OFF., SUBJECT MATTER ELIGIBILITY EXAMPLES: LIFE SCIENCES 26–28 (2016) *available at* https://www.uspto.gov/sites/default/files/documents/101_examples_1to36.pdf (PDF) (providing a patent eligible examples diagnostic method claims based on *Myriad*'s BRCA1 discovery and distinguishing them from methods utilizing "routine or conventional techniques").

[238] *Mayo*, 566 U.S. at 82.

[239] *See id.* at 91 (enumerating concerns of some *amici* that allowing claims to scientific correlations concerning the body to survive scrutiny would result in "a vast thicket of exclusive rights over the use of critical scientific data that must remain widely available if physicians are to provide sound medical care" (quoting Brief for American College of Medical Genetics et al. as Amici Curiae Supporting Petitioner at 7, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150))); *see* Brief for American College of Medical Genetics et al. as Amici Curiae Supporting Petitioner at 7, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150) ("If

areas of scientific correlations "will interfere significantly with the ability of medical researchers to make valuable discoveries, particularly in the area of diagnostic research."[240] Likewise—as examined later in this Note—opponents of a more limited interpretation of § 101 argue that such interpretation will stifle innovation and lead to diminished investment in expensive research that may otherwise produce discovery of important scientific correlations and laws of nature.[241]

V. Perspectives Regarding Venture Capital, Patents, and Innovation

Although patent rights incentivize innovation, inventors typically need outside funding to help commercialize their inventions and bring them to market.[242] One form of funding is through venture capital (VC).[243] VC firms and the National Venture Capital

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these patents remain in force, any physician who measures those metabolite levels and knows about the observed correlations will unavoidably become an infringer.").

240 *Mayo*, 566 U.S. at 91.

241 *See id.* (summarizing Prometheus' argument that medical research, "which includes research leading to the discovery of laws of nature, is expensive," important for the United States to maintain its status as a world leader in diagnostic research, and thus "requires protection").

242 *See What is Venture Capital?*, NAT'L VENTURE CAP. ASS'N (last accessed Feb. 17, 2021), https://nvca.org/about-us/what-is-vc/#toggle-id-3 ("Venture capital has enabled the United States to support its entrepreneurial talent by turning ideas and basic research into products and services that have transformed the world.").

243 *See id.* ("Venture capital firms are professional, institutional managers of risk capital that enable and support the most innovative and promising companies.").

Association (NVCA) argue that strong patent protection for technologies such as medical diagnostics mitigates the risk of investing in the development of those same technologies.[244] This Note, in turn, examines the effect of *Bilski* and *Mayo* on levels of VC investment in diagnostic technologies. However, before delving into analysis of VC investment data, it is necessary to provide some context about VC firms, motivation for investment, and the connection between R&D investment and patent rights.

A. Venture Capital Firms

1. Private Investment: Distinct Motivation from Federal Investment

Private investors' motivations to invest in R&D differ from the federal government's motivations. Notably, "[t]he federal government is the nation's largest supporter of basic research . . . ."[245] As compared to private investment, federal investment in R&D is motivated by societal benefit and the idea that "the private sector will, left on its own, underinvest in basic research from a societal perspective."[246] This Note focuses on VC

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244 *See, e.g.*, Brief for National Venture Capital Association as Amicus Curiae Supporting Respondent at 9–10, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150) ("[I]n biotechnology, strong patent protection correlates with the amount of R&D investments made by companies, and weak patent laws engender poor investment in R&D, diminishing a company's probability of success.").

245 JOHN F. SARGENT, CONG. RSCH. SERV. No. R45715, FEDERAL RESEARCH AND DEVELOPMENT (R&D) FUNDING: FY2020 6 (Mar. 18, 2020), *available at* https://fas.org/sgp/crs/misc/R45715.pdf (PDF).

246 *Id.*

investment in medical diagnostic technologies because societal benefit is at best a secondary consideration for VC firms in picking their investments.[247]

The federal government supports niche, innovative medical research through robust grants in the utilitarian interest of improving and saving lives.[248] For instance, the National Institutes of Health "is the largest public funder of biomedical research in the world, investing more than $32 billion a year to enhance life, and reduce illness and disability."[249] By contrast, private investors place primary focus on creating economic value.[250]

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[247] Before addressing the societal impact of eliminating patent eligibility for scientific correlations, the National Venture Capital Association in its amicus curiae brief in *Mayo* opined about the negative effect of such a decision on investments made in reliance on patent eligibility of those correlations. *See* Brief for National Venture Capital Association as Amicus Curiae Supporting Respondent at 3, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150) ("Removing patent eligibility for diagnostic correlations . . . jeopardizes the billions of dollars venture firms have already invested in personalized medicine companies in reliance on patent protection.").

[248] *See About Grants*, NAT'L INST. HEALTH (last updated Mar. 17, 2017), https://grants.nih.gov/grants/about_grants.htm ("NIH funded research has led to breakthroughs and new treatments, helping people live longer, healthier lives, and building the research foundation that drives discovery.").

[249] *Id.*

[250] *See* Sargent, *supra* note 245, at 6 ("The usual argument for this view is that the social returns (i.e., the benefits to society at large) exceed the private returns (i.e., the

2. Cautious Investors

VC firms play a critical role in the financing of start-up companies, especially in the biotechnology industry.[251] In particular, VC firms invest in companies hoping for rapid high growth and will seek to liquidate investments if they are not sufficiently profitable over a short period of time.[252] In other words, prior to investing, venture capitalists "plan for exit."[253] When examining potential investment or acquisition targets, venture capitalists view patent protection of a company's intellectual assets as indicative of competent

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benefits accruing to the private investor, such as increased revenues or higher stock value).").

[251] *See Healthcare Innovation*, NAT'L VENTURE CAP. ASS'N (last accessed Feb. 17, 2021), https://nvca.org/healthcare-innovation/ ("For over three decades, venture capital has spurred the creation and growth of healthcare innovation, such as in the biotechnology and medical device industries. . . . For example, venture capital backed 42% of all FDA-approved drugs from 2009–2018.").

[252] In re Trados Inc. Shareholder Litigation, 73 A.3d 17, 50 (Del. Ch. 2013) (explaining theory of VC investment in emerging companies, including the motivation to invest: "VCs seek very high rates of return, usually a ten-fold return of capital over a five year period").

[253] D. Gordon Smith, *The Exit Structure of Venture Capital*, 53 UCLA L. REV. 315, 316 (2005); *see id.* ("The ability to control exit is crucial to the venture capitalist's business model of short-term funding of nascent business opportunities. Exit allows venture capitalists to reallocate funds and the nonfinancial contributions that accompany them to early stage companies.").

management,[254] ability of the company to survive in a competitive market,[255] and enhanced profitability.[256] On the other hand, venture capitalists will refrain from investing in start-up companies whose work is subject to patent demands from patent assertion entities (i.e., "patent trolls").[257] Therefore, for a venture capitalist to consider investing in a start-up company, the company's R&D endeavors should not only have the potential for patent protection, but also be distinct enough from existing innovation so as not to expose the venture capitalist to losses due to settlement or litigation of patent infringement claims.[258]

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[254] *See* Ronald J. Mann & Thomas W. Sager, *Patents, Venture Capital, and Software Start-ups*, 36 RSCH. POL'Y 193, 200 (2007) (noting that this assertion likewise holds for a start-up company's "prospect of patents").

[255] *See id.* ("Most obviously, patents can solve one of the most difficult problems for a startup: convincing the venture capitalist that the startup can sustainably differentiate itself from its competitors.").

[256] *See* Graham & Sichelman, *supra* note 6, at 1078 ("[P]atents . . . are indicators of a company's ability to maintain supernormal profits or to reduce licensing costs.").

[257] *See* Robin Feldman, *Patent Demands & Start-up Companies: The View from the Venture Capital Community*, 16 YALE J.L. & TECH. 236, 243 (2014) ("When companies spend money protecting their intellectual property position, they are not expanding; and when companies spend time thinking about patent demands, they are not inventing.").

[258] *See id.* at 243 (finding, through an empirical study of VC investment behavior with respect to start-up companies, that "100% of venture capitalists indicate that if a company had an existing patent demand against it, they might refrain from investing").

Moreover, a significant correlation exists between patenting activity of a start-up and "various proxies for strong performance: rounds of financing, total investment, exit status, reaching a late stage of financing, and longevity."[259] Researchers have also found that start-ups with early patent activity achieve "much higher rates of VC funding overall," in comparison with start-ups having lower or no patent activity.[260] Because VC firms invest so cautiously and with eyes towards exit, it follows that current § 101 jurisprudence may cause VC investors to hesitate in investing in companies developing medical diagnostics technologies that—as of *Mayo* and its progeny—appear to be patent-ineligible. Decreased investment would be concerning from a societal perspective, as "[s]mall venture-backed companies play a critical role in bringing revolutionary medical innovations and discovering groundbreaking treatments and cures aimed at diagnosing, treating, and curing the most deadly and costly diseases."[261] Accordingly, the next Section explores in greater detail the effects of uncertainty on investment in innovation.

B. Investment in R&D/Innovation and Patents

1. Investment Uncertainty and Patent Rights

Some studies have indicated that greater market uncertainty tends to reduce R&D investment.[262] For instance, in a recent empirical study about patent protection, R&D

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259 Mann & Sager, *supra* note 254, at 206.

260 Ufuk Akcigit et al., *Synergizing Ventures* 9 (Fed. Rsrv. Bank of Atlanta, Working Paper 2019-17, 2019), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3473035.

261 *Healthcare Innovation*, *supra* note 251.

262 *See* Dirk Czarnitzki & Andrew A. Toole, *Patent Protection, Market Uncertainty, and R&D Investment*, 93 REV. ECON. & STAT. 147, 157 (2011) ("Our results show that higher

investment, and market uncertainty, Czarnitzki and Toole found that patent protection tends to mitigate firms' uncertainty, thereby leading to greater R&D investment.[263] Czarnitski and Toole further found that "patent protection does not mitigate the effect of uncertainty in industries where patents are ineffective."[264] Importantly, patents are highly effective tools in the biotechnology industry as firms will heavily weigh the probability of obtaining patent protection when deciding whether to invest in developing a new drug or treatment.[265]

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levels of uncertainty reduce current R&D investment . . . ."); Andrew B. Abel et al., *Options, the Value of Capital, and Investment*, 111 Q.J. ECON. 753, 754, 776 (1996) (correlating greater uncertainty with lower incentives for investment).

[263] *See* Czarnitzki & Toole, *supra* note 262, at 147 (qualifying the finding as dependent on patents serving as an effective means for market protection).

[264] *Id.* at 147.

[265] *See* David J. Kappos & Paul R. Michel, *Supreme Court Patent Decisions Are Stifling Health Care Innovation*, MORNING CONSULT (Oct. 29, 2018, 5:00 P.M.), https://morningconsult.com/opinions/supreme-court-patent-decisions-stifling-health-care-innovation/ (finding that, absent patent protection, "investors are less interested in funding costly new biomarker diagnostic research. As a result, diseases will go undiagnosed, and patients will suffer the consequences"); Ohlhausen, *supra* note 22, at 149 ("Surveys reveal that patents contribute to incentives to invest, most acutely in the bio-pharmaceutical and medical devices fields . . . .").

2. § 101, Innovation, and Investment in R&D

Uncertainty in how to apply § 101 creates problems for the economic facets of patent law.[266] Scholars argue that uncertainty in the scope of patent eligible subject matter poses problems for companies who wish to capitalize upon the economic incentives of obtaining a patent for valuable technology.[267]

Because direct measurements regarding the rate of innovation are difficult or impossible to obtain, legal and economic scholars often use R&D data[268] and patent

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266 *See* Kevin Madigan & Adam Mossoff, *Turning Gold to Lead: How Patent Eligibility Doctrine is Undermining U.S. Leadership in Innovation*, 24 GEO. MASON. L. REV. 939, 946–47 (2017) (asserting that the recent Supreme Court cases regarding patent eligibility "have injected tremendous legal uncertainty into the U.S. patent system, undermining the ability of inventors, universities, venture capitalists, and companies to make long-term investment decisions in R&D"); Ohlhausen, *supra* note 22, at 122 ("Economic models predict that, for a given invention, expanding patent scope increases the incentive to invent. Weak patent protection may therefore lead to suboptimal investment in technological development.").

267 *See, e.g.*, Ohlhausen, *supra* note 22, at 109 ("I worry that today's calls for diluted patent rights often go beyond incremental adjustment and threaten to weaken patents systematically, which could compromise R&D investment.").

268 *See, e.g.*, Iain Cockburn & Zvi Griliches, *Industry Effects and Appropriability Measures in the Stock Market's Valuation of R&D and Patents*, 78 AM. ECON. REV. 419, 422 (1988) ("Data on R&D expenditures, where available, are stronger measures of input to the process by which firms produce technical innovation than patents are of its

counts[269] as proxies for innovation. Closely related to the inquiry central to this Note, a 2020 study on patent eligibility and investment by Professor David O. Taylor demonstrates that recent § 101 jurisprudence has negatively impacted investment-making decisions.[270] In his study, Professor Taylor interviewed 475 venture capital and other private equity investors to study the impact of the Supreme Court's recent § 101 cases on investment behaviors.[271] Professor Taylor found that seventy-four percent of investors considered patent eligibility to be an important factor when their firms decide to invest in companies developing new technology.[272] Professor Taylor further found that sixty-two percent of investors "agreed that their firms are less likely to invest [in companies developing

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'output.'"); Glynn S. Lunney Jr., *Patent and Growth: Empirical Evidence from the States*, 87 N.C. L. REV. 1467, 1498–1500 (2009) (utilizing measures of state-level R&D spending to evaluate the relationship between patents and economic growth).

269 *See, e.g.*, Madigan & Mossoff, *supra* note 266 (examining patents applications that were rejected by the USPTO but granted in the European and Chinese patent offices and using that data as a measurement of innovation).

270 *See generally* David O. Taylor, *Patent Eligibility and Investment*, 41 CARDOZO L. REV. 2019 (2020) (indicating, among other findings, that "[a]bout 40% of knowledgeable investors indicated that the Court's [eligibility] decisions have somewhat negative or very negative effects on their firms' existing investments").

271 *See id.* at 2027 (describing the participants and purpose of his 2020 study).

272 *See id.* at 2054 ("About 43% of the respondents strongly agreed that patent eligibility is an important consideration when their firms decide whether to invest in companies developing technology. Another 31% somewhat agreed with the same proposition.").

patent-ineligible technologies] given the unavailability of patents, while only twenty percent disagreed."[273] Additionally, Professor Taylor found that investors overwhelmingly would decrease investment in industries lacking patent protection, and that the effect predominated in the pharmaceutical, biotechnology, and medical devices industries.[274] Importantly, Professor Taylor's findings confirm "the idea that patents help spur investment in development of technology."[275]

Likewise, an unpublished study by Professor Arti K. Rai with Professor Colleen Chien indicates that the state of § 101 has led to a slight decline in patent application filings for medical diagnostics across small firms.[276] Filings by large firms and nonprofits, however, have grown since *Mayo*.[277] Professors Rai and Chien also found that the average

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[273] *Id.* at 2055.

[274] *See id.* at 2065–67 ("[A]ccording to these investors, on average each industry would see reduced investment as a result of the elimination of patents . . . . The industries most negatively impacted would be the pharmaceutical, biotechnology, and medical device industries.").

[275] *Id.* at 2055.

[276] *See* Arti K. Rai with Colleen Chien, *Intellectual Property in Precision Medicine* 15, fig. 4 (Feb. 15, 2018) (unpublished presentation), *available at* https://precisionmedicine.duke.edu/sites/precisionmedicine.duke.edu/files/field/attachments/GPMF_Rai_02.15.2018.pdf (PDF) (graphically depicting the decline in filings of medical diagnostic patent applications post-2014).

[277] *See id.* at 14, fig. 3 (graphically depicting growth in filings by non-profits and large firms of patent applications for medical diagnostics post-2014).

first claim length in granted patents for medical diagnostics has increased by eighteen percent in the USPTO since 2011.[278] Similarly, the average first claim length for medical diagnostics patents granted in the European Patent Office (EPO) has increased by thirteen percent since 2011.[279] These findings indicate that the scope of patent protection for medical diagnostics patents has narrowed in both the United States and in Europe following 2011, albeit to a greater degree in the United States.[280]

These professors' findings help lend credence to concerns presented by the National Venture Capital Association (NVCA) in its *amicus* brief in *Mayo*. As discussed, VC firms look to a company's assets—especially patents or patent protectable technology—and future growth potential when deciding to invest.[281] Supporting Prometheus in its *amicus* brief in *Mayo*, the NVCA argued that "[r]emoving patent eligibility for diagnostic correlations removes th[e] incentive [to invest in companies contributing to personalized medicine]."[282] This point matters because "emerging personalized medicine companies do not have access to traditional avenues of funding" for the millions of dollars necessary to transform an idea

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278 *See id.* at 19 (summarizing the study's results).

279 *See id.* at 19 (summarizing the study's results).

280 *See id.* at 20. ("Both EPO and US issued claim lengths are growing; US claim length has grown more than EPO claim length.").

281 *See supra* notes 253–256, 259 and accompanying text.

282 Brief for National Venture Capital Association as Amicus Curiae Supporting Respondent at 3, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150).

into a finished, FDA-approved diagnostic technology or treatment.[283] Professor Taylor's study demonstrates the veracity of the investment argument, having found a decrease in venture capital investors' willingness to invest in diagnostic technologies post-*Mayo*.[284]

Moreover, the NVCA asserted that that diminished protection of medical diagnostics would "jeopardize[] the billions of dollars venture firms have already invested in personalized medicine companies in reliance on patent protection."[285] Professors Rai and Chien's finding of increased claim length in U.S. diagnostic patents may relate to this concern, as one strategy to retain patent protection in the current § 101 environment could be to write increasingly narrow, specific claims.[286]

This Note presents an addition to the discussion of VC investment attitudes in light of recent § 101 jurisprudence and affirms the NVCA's cautionary prediction regarding diagnostic technologies.

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283 *Id.* at 8.

284 *See supra* notes 272–274 and accompanying text.

285 Brief for National Venture Capital Association as Amicus Curiae Supporting Respondent at 3, Mayo Collaborative Servs. v. Prometheus Lab'ys., Inc., 566 U.S. 66 (2012) (No. 10-1150).

286 Alan Douglas Miller & Brian Amos, *Successful Strategies for Diagnostic Method Patents*, 23 J. COM. BIOTECHNOLOGY 39, 42 (2017) (emphasizing the difficulty in obtaining broad diagnostic method claims, but that one possible tactic for improving patentability under § 101 is to use narrower claims).

VI. Methodology and Predictions

To assess the effects of the Court's jurisprudence on VC investment for diagnostics, this Note empirically analyzes an existing dataset of VC funding across all industries in the United States from 2006–2010 and 2013–2017. This Part recounts the study's methodology, hypothesis, and potential limitations.

A. Hypothesis

Based on anecdotal evidence and caselaw, medical diagnostics appear to be less able to gain patent protection after *Mayo*.[287] Moreover, this is widely known within the medical diagnostic and VC industries.[288]

If the judicial restrictions on patent eligibility for medical diagnostic methods cause VC investors to hesitate to invest in the development of such technology or in companies that plan to develop such technology (e.g., investment in start-ups through seed funding), then there will be a relative decrease in VC investment in medical diagnostics following *Mayo* as compared to other technological fields where patent eligibility is unchanged.

*B. Data*set

The author obtained data for overall VC investment and investment in disease diagnostic technology for the period of 2006–2017 using the Pricewater Clearinghouse (PwC) MoneyTree[289] tool. The MoneyTree tool includes data for verifiable, VC-backed

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287 *See supra* notes 149, 226–230 and accompanying text.

288 *See supra* notes 224, 282, 285 and accompanying text.

289 *See PwC Moneytree*, PRICEWATER CLEARINGHOUSE (2020), https://www.pwc.com/us/en/industries/technology/moneytree.html (reporting venture capital investment dollars according to industry, round, and deals per fiscal quarter).

equity funding of private companies.[290] PwC verifies data "via (1) various federal and state regulatory filings; (2) direct confirmation with firm or investor; (3) press release; or (4) credible media sources."[291] Notably, the MoneyTree tool excludes data for "[f]unding rounds raised by public companies," "government funding," "[v]enture debt," and various non-equity funding "arrangements."[292]

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290 *See MoneyTree™ Definitions: Report Methodology*, PRICEWATER CLEARINGHOUSE (2020), https://www.pwc.com/us/en/industries/technology/moneytree/moneytree-definitions.html ("Funding rounds raised by public companies of any kind on any exchange . . . are excluded from our numbers, even if they received investment by a venture firm[].").

291 *Id.*

292 *Id.*; *see id.* (exemplifying as excludable "business development / R&D arrangements," such as when a company forms an "R&D partnership with a larger corporation," as that situation "is not equity financing nor is it from venture capital firms"). Importantly, these "R&D arrangements" differ from the typical VC equity investments discussed in this Note. *Compare* DELOITTE, LIFE SCIENCES: ACCOUNTING AND FINANCIAL REPORTING UPDATE—INTERPRETIVE GUIDANCE ON RESEARCH AND DEVELOPMENT 2 (2018), *available at* https://www2.deloitte.com/content/dam/Deloitte/us/Documents/audit/us-audit-interpretive-guidance-2018-research-and-development.pdf (PDF) (explaining that in "R&D funding arrangements" such as "collaborations [between companies], licensing arrangements, [and] partnerships," "passive third-party investors . . . provide funds to offset the cost of R&D programs in exchange for milestone payments or other forms of consideration"), *with What is Venture Capital?*, *supra* note 242 ("Once the investment into a company has been made,

To ascertain the impact of *Bilski* and *Mayo* on investment trends, the author first summed quarterly investment totals within the PwC data to reflect an investment total for each year. Second, the author coded the yearly totals for overall VC investment and investment in disease diagnostics as a numeric variable.[293] The corresponding years were coded too.[294] Further, the author created a binary (dummy) variable corresponding to whether a specific year was pre- or post-*Mayo*.[295]

C. Analytical Method

The author conducted a difference-in-difference (DID) analysis to compare change in investment amount over time for disease diagnosis technologies against all other areas of investment (total VC investment). As compared to other analytical methods which may merely indicate a correlation between variables, the results of a DID test demonstrate

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venture capital [firms] actively engage with a company, providing strategic and operational guidance, connecting entrepreneurs with investors and customers, taking a board seat at the company, and hiring employees.").

[293] Data for overall investment and investment in disease diagnostic technologies was stacked within the same numeric variable: [dis_diagnosis].

[294] This was coded as a numeric variable: [year]. When the author performed the DID analysis in R, this variable was utilized to define a new binary variable: [post2012].

[295] This was coded as a binary variable: [dummy]. When the author performed the DID estimator analysis in R, this variable was utilized to define a new binary variable: [treatment].

causation.[296] Additionally, DID inherently "[a]ccounts for change/change due to factors other than [the] intervention."[297] Economists and legal scholars routinely utilize the DID technique to analyze the impact of a treatment—for instance, the enactment of a specific policy measure or use of a specific health intervention—on two equivalent groups.[298] The essential assumption regarding equivalence relates to the concept of causation: but-for the treatment, both groups would exhibit parallel trends over time.[299] This may be examined

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296 *See Difference-in-Difference Estimation*, COLUMBIA PUB. HEALTH: POPULATION HEALTH METHODS (last updated 2:27 PM, Nov. 23, 2020), https://www.publichealth.columbia.edu/research/population-health-methods/difference-difference-estimation ("DID is a quasi-experimental design that makes use of longitudinal data from treatment and control groups to obtain an appropriate counterfactual to estimate a causal effect.").

297 *Id.*

298 *See generally* Colleen P. Murphy et al., *Note-Taking Mode and Academic Performance in Two Law School Courses*, 68 J. LEGAL EDUC. 207 (2019) (using the DID method to calculate impact on 2L student GPA from use of varied 1L note-taking techniques); Eric M. Gaier et al., *Empirical Analysis of Causation and Damages in Off-Label Marketing Cases*, BATES WHITE ECON. CONSULTING D-7–D-8 (Apr. 2013) (describing the DID technique in the context of proving causation in FDA off-label cases).

299 *See Difference-in-Difference Estimation*, *supra* note 296 ("The parallel trend assumption . . . requires that in the absence of treatment, the difference between the 'treatment' and 'control' group is constant over time.").

visually,[300] as the author did in the present study. The author plotted the average yearly values for total VC investment and for disease diagnosis technologies as a function of time. Both investment categories exhibited a positive trend.

Utilizing 2012 (*Mayo*) as a dividing line to compare the rates of change in total VC investment and investment in disease diagnosis technologies, the author analyzed data over two four-year intervals of time: 2006–2010 (through *Bilski*) and 2013–2017 (following *Mayo*). The present analysis excludes data from 2011–2012 because, given that *Bilski* was decided in 2010 and *Mayo* was decided in 2012, VC investment decisions during that period would not have been affected by both *Bilski* and *Mayo*. Likewise, because the Court decided *Mayo* in 2012, the author contends that its effects on VC investment may not be seen in full force until the following calendar year. Prior to analyzing the data in R, the author plotted the data as a line graph to assess whether the parallel-trend assumption was met. The data met the parallel-trend assumption.[301]

D. Limitations

As with most empirical research, the methodology and data source employed in this study have limitations that may affect the results and implications discussed in the balance of this Note.[302] First, investment in research and product development comes from many

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300 *See id.* ("Although there is no statistical test for this assumption, visual inspection is useful when you have observations over many time points.").

301 See notes 299–300, *supra*, for a description of this assumption.

302 *See, e.g.*, David L. Schwartz, *Explaining the Demise of the Doctrine of Equivalents*, 26 BERKELEY TECH. L.J. 1157, 1187 (2011) ("All projects involving empirical studies of legal

sources—venture capital, contractual agreements between companies, the federal government, and private company self-funding, to name a few. This analysis only accounts for venture capital investment and must be interpreted with that limitation in mind. As previously discussed, VC firms and the federal government have differing motivations to invest[303] that may impact the volume of investment in medical diagnostic technologies following *Bilski* and *Mayo*.

Second, the author did not directly collect this data and rather found it in aggregate form. Direct collection of data from VC firms may provide more meaningful results as the investment patterns for disease diagnostics technologies could be attributed to specific firms that target primarily biotech and personalized medicine companies.[304] It is possible that firms whose investors keep up to date with the recent developments in § 101 jurisprudence will tread more lightly than more general VC firms whose investors may not be as informed about the ever-changing doctrine of patentable subject matter.[305]

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decisions have limitations . . . ."); Kathryn Zeiler, *The Future of Empirical Legal Scholarship: Where Might We Go from Here?*, 66 J.L. EDUC. 79, 81 (2016) ("The usefulness of empirical legal research, however, depends heavily on the methods employed to produce it and on the validity of the inferences drawn from reported results.").

303 *See supra* notes 246–250 and accompanying text.

304 Of course, this would be a herculean task. It is impractical to individually survey hundreds of VC firms to collect investment data independently. Utilizing PwC's dataset was a logical alternative for this Note.

305 *See, e.g.*, Taylor, *supra* note 270, at 2060 (finding that "while eligibility knowledgeable investors and eligibility unknowledgeable investors both report that patent

Third, the DID analysis—although indirectly accounting for confounding variables because of the comparison of investment trends in medical diagnostics to the counterfactual trend (i.e., other industries that are generally unaffected by *Bilski* and *Mayo*)—does not directly account for factors such as the state of the economy, productivity, poverty levels, and international affairs. A longer, larger scale project of the same nature as the current study would benefit from direct data collection—and complex econometric modeling as the methodology—in order to account for some of these potential confounding variables.

VII. Results

The author calculated the DID statistic through two avenues: manually and through an ordinary least-squares (OLS) regression. The author started by calculating the DID statistic manually. First, the author calculated the time trend in the control (all technologies) group by subtracting the average yearly investment level post-*Mayo* from the average yearly investment level pre-*Mayo*. Next, the author calculated the time trend in the "treatment" (disease diagnosis technologies) group by subtracting the average yearly investment level post-*Mayo* from the average yearly investment level pre-*Mayo*. Lastly, the author calculated the DID statistic by subtracting the time trend value in the control group from the time trend in the treatment group. Manual calculation of the DID statistic produced a negative value.[306] The negative value indicates a negative relationship between

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eligibility is an important consideration when their firms make decisions to invest in companies developing technology, eligibility knowledgeable investors place greater importance on patent eligibility").

306 The manually calculated DID statistic was -9285961000.

Mayo (the independent variable) and VC funding for medical diagnostics (the dependent variable).

The author also ran an OLS regression to confirm the manual DID estimate of the effect of *Mayo* and *Bilski* on the level of VC investment in disease diagnosis technologies and calculate the significance of that effect.[307] The coefficient estimate of the interaction between the treatment (change in § 101 jurisprudence) on the treated group (investment levels in disease diagnosis technologies) matched the manually calculated value.[308] Further, the regression data indicated that the negative relationship between *Mayo* and VC investment in medical diagnostics is statistically significant.[309] In essence, in the four years following *Mayo*, investment in disease diagnostic technologies was nearly $9.3 billion dollars lower than it would have been absent *Mayo*.[310] However, it is important to note that

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[307] The OLS regression model was coded as follows:

reg1 = lm(dis_diagnosis ~post2012 + treatment + post2012*treatment, data = mayoeffect)

[308] The coefficient estimate equaled $-9.286e^{9}$.

[309] The relationship was statistically significant, $p = 2.82e^{-14}$, $R^2 = 0.9$. In practical terms, "[s]tatistical significance helps quantify whether a result is likely due to chance or to some factor of interest." Amy Gallo, *A Refresher on Statistical Significance*, HARV. BUS. REV. (Feb. 16, 2016), https://hbr.org/2016/02/a-refresher-on-statistical-significance (quoting Tom Redman). The significance level "is usually expressed as a 'p-value,' and the lower the p-value, the less likely the results are due purely to chance." *Id.*

[310] This situation is the counterfactual (i.e., had the treated group *not* received treatment, its mean value would be the same distance from the control group in the post-treatment period as it was in the pre-treatment period).

the yearly investment totals for disease diagnostic technologies have generally increased in the years following *Mayo*—but it has increased at a lower rate compared to all other industries. Thus, another general way to conceptualize the data is that VC investment for all technologies increased much more than the increase in investment for disease diagnostic technologies over the time period analyzed.

VIII. Applying Data to Innovation Framework and § 101 Jurisprudence

This Part describes several key implications from the results discussed above. First, this Note's findings support calls to Congress for reform of § 101 following *Ariosa* and *Athena* to provide greater certainty and clarity regarding patent eligibility of medical diagnostics. As noted by one Federal Circuit judge, "[t]he multiple concurring and dissenting opinions regarding the denial[s] of en banc rehearing [of *Athena* and *Ariosa*] are illustrative of how fraught the issue of § 101 eligibility, especially as applied to medical diagnostics patents, is."[311] Moreover, Judges Hughes and Moore specifically called to Congress for further clarification about § 101.[312]

Many prominent figures in patent law have echoed the Federal Circuit's concerns about patent eligible subject matter in written testimony presented to the Senate Judiciary Committee's Subcommittee on Intellectual Property during the June 2019 Senate hearings on "The State of Patent Eligibility in America"[313] ("Patent Eligibility Hearings"). For

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311 Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1337 (Fed. Cir. 2019) (Hughes, J., concurring in the denial of rehearing en banc).

312 *See supra* notes 228, 230 and accompanying text.

313 *The State of Patent Eligibility in America: Hearing Before the S. Judiciary Comm., Subcomm. on Intellectual Property*, 116th Cong. (2019).

instance, Judge Paul Michel, a retired Chief Judge on the Federal Circuit, stated that "recent cases are unclear, inconsistent with one another and confusing. . . . That applies equally to Supreme Court and Federal Circuit cases."[314] Judge Michel specifically mentioned the *Mayo-Alice* regime, asserting that it "conflates eligibility with novelty and non-obviousness . . . creat[ing] impossible confusion."[315] This observation hits at a key point of Judge Linn's concurring opinion in *Ariosa*, in which he called out the *Mayo* Court's "blanket dismissal of conventional post-solution steps" as prohibiting future courts from distinguishing *Mayo* from other diagnostic method patents involving "conventional" steps.[316]

Similarly, a number of legal academics who study IP and innovation have called for patent eligibility reform. Professor David Taylor's testimony at the Patent Eligibility Hearings emphasized what he saw as several judges "not[ing] they were disturbed" by the Federal Circuit's denial of en banc rehearing in *Ariosa*.[317] "[A] resulting concern" stemming

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[314] *The State of Patent Eligibility in America: Part I: Hearing Before the S. Judiciary Comm., Subcomm. on Intellectual Property*, 116th Cong. (2019) (statement of Judge Paul Michel, Former C.J., United States Court of Appeals for the Federal Circuit), at 5.

[315] *Id.*

[316] Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1381 (Fed. Cir. 2015) (Linn, J., concurring).

[317] *The State of Patent Eligibility in America: Part I: Hearing Before the S. Judiciary Comm., Subcomm. on Intellectual Property*, 116th Cong. (2019) (statement of Prof. David O. Taylor, Associate Professor of Law, Southern Methodist University Dedman School of Law), at 4.

from inconsistent and confusing opinions in the judiciary "is that the current [§ 101] environment substantially reduces incentives to invest in research and development."[318] The central finding of this Note—that VC firms' investment rate in disease diagnosis technologies has slowed as a result of *Bilski* and *Mayo*—supports that concern. Professor Adam Mossoff's testimony at the Patent Eligibility Hearings in turn stressed the high rates of invalidations and rejections of medical diagnostic patents following *Mayo* and *Alice* as "revealing because the *Alice-Mayo* framework is often accused of being indeterminate and providing little predictability for inventors or lawyers in how a judge or examiner at the USPTO may choose to apply it."[319] Professor Mossoff echoed Judge Moore's dissent in the denial of en banc rehearing in *Athena*, averring that § 101 "does appear to offer some predictability: the odds of receiving or keeping a patent under § 101 are not in your favor if you are innovating new products and services in . . . medical diagnostics, medical devices, and other inventions driving the U.S. innovation economy."[320]

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318 *Id.* at 5.

319 *The State of Patent Eligibility in America: Part I: Hearing Before the S. Judiciary Comm., Subcomm. on Intellectual Property*, 116th Cong. (2019) (statement of Prof. Adam Mossoff, Professor of Law, George Mason University Antonin Scalia School of Law), at 8.

320 *Id.*; *see* Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1354 (Fed. Cir. 2019) (per curiam) (Moore, J., dissenting from the denial of rehearing en banc) ("Since *Mayo*, we have held every single diagnostic claim in every case before us ineligible."); *see id.* at 1354 ("We have turned *Mayo* into a per se rule that diagnostic kits and techniques are ineligible.").

Moreover, Professor Mark Lemley—who is generally supportive of retaining the "two hundred years of rules that have prevented patent law from locking up the fundamental building blocks of nature"[321]—asserted that any reform to § 101 should "focus narrowly on identified problems in the medical diagnostics business."[322] Congress should answer these calls for reform of § 101 in a manner that "target[s] the effect of *Mayo* on medical diagnostics"[323] and reinstates incentives to invest in the development of new medical diagnostic technologies.

Second, the present study provides empirical evidence that complements and further supports some of the key findings in Professor Taylor's recent study about investment behavior following *Mayo* and *Alice*. For instance, Professor Taylor found a statistically significant correlation between investors' familiarity with Supreme Court patent eligibility cases and the consideration of patent eligibility as important when making investment decisions.[324] Moreover, he posited that the correlation between investor knowledge of § 101 doctrine and importance of patent eligibility as an investment consideration "may indicate that the more an investor learns about the Supreme Court's eligibility cases, the more that

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321 *The State of Patent Eligibility in America: Part I: Hearing Before the S. Judiciary Comm., Subcomm. on Intellectual Property*, 116th Cong. (2019) (statement of Prof. Mark A. Lemley, Professor of Law, Stanford Law School), at 2.

322 *Id.*

323 *Id.*

324 *See* Taylor, *supra* note 270, at 2060 ("Those with this familiarity reported greater agreement that patent eligibility is an important consideration when their firms decide whether to invest in companies developing technology.").

knowledge (here, eligibility) impacts investment decisions."[325] Although the empirical study discussed in this Note did not directly measure VC knowledge of § 101 jurisprudence, the NVCA has indicated through its *amicus* brief in *Mayo* that VC firms closely follow—and regard as important—the Supreme Court's precedential decisions impacting patent eligibility of medical diagnostics.[326] And indeed, the NVCA indicated that the decline in rate of VC investment in disease diagnostic technologies would follow restrictive interpretations of § 101 as it applies to medical diagnostics.[327]

The current project also complements Professor Taylor's findings that the Supreme Court's patent eligibility cases caused an overall decrease in investment among forty-nine percent of firms.[328] This finding could help explain the decline in rate of investment in disease diagnosis technologies exemplified through the present study. Although some firms will proceed more cautiously following *Mayo*, *Bilski*, and *Alice*, other firms may continue their investment patterns prior to those cases or even increase investment.[329]

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325 *Id.*

326 *See supra* notes 244, 282–283 and accompanying text.

327 *See supra* notes 244, 282–283 and accompanying text.

328 *See* Taylor, *supra* note 270, at 2074 (noting as well that "the percentage of these investors who reported increasing investments as a result of the Supreme Court's known eligibility decisions stood at 8%, significantly below the percentage indicating decreased investments at 49%").

329 *See* Taylor, *supra* note 270, at 2074 (highlighting that nine percent of representatives from firms responded "other" to the question of how particular Supreme Court cases affected firm investment decisions).

Third, while the DID analysis shows a relative decrease in VC investment for disease diagnosis technologies as compared to all technologies,[330] the raw data indicates that VC investment for disease diagnosis technologies continues to increase. The author also plotted yearly investment totals for the disease diagnosis technologies through 2019, and that data demonstrates a continued increase in investment for disease diagnosis technologies. This finding suggests that even if patent rights for medical diagnostics are unavailable, there will still be some innovation in that space.[331] The question remains, however, if "some" innovation will be enough given the medical field's emphasis on personalized medicine.[332]

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330 *See supra* Part VII.

331 *See* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1586–87, 1588 (2003) (discussing ex post rewards and ex ante subsidies for successful innovation and noting that "there is every reason to believe that achieving optimal innovation in different industries will require greater or lesser measures of legal incentive"—and not necessarily patent rights as the legal incentive); Daniel J. Hemel & Lisa Larrimore Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303, 317–19 (2013) (describing the historical use of performance-based prizes to incentivize innovation, and contemporary use of private and U.S. government agency performance-based prize funds to spur developments in STEM); *see generally id.* at 322–26 (discussing provisions of the Internal Revenue Code that permit "the expensing of research and experimental expenditures (Section 174) and the credit for increasing research activities (Section 41)").

332 *See* PMC REPORT, *supra* note 2, at 51 ("To keep up with the technology, every corner of the health care spectrum must come together to advance science-driven, value-based

Fourth, underinvestment in medical diagnostics may lead to underinvestment in potential treatments, particularly for rare or genetically-based conditions. Medical diagnostics receive immense attention in the scientific community because physicians and researchers need to know how to diagnose a disease in order to create efficacious, *targeted* treatments.[333] In particular, knowledge of a disease's biological mechanism will aid researchers in the development of drugs or biologics that uniquely target the biomarkers associated with that disease.[334] For instance, the drugs imatinib and nilotinib were developed using rational drug design to specifically target the BCR-ABL genetic mutation present in patients with CML and Ph-positive ALL.[335] Fortunately for innovators

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solutions. Regulatory authorities must establish a clear set of guidelines for evaluating and approving personalized drugs and, significantly, the diagnostics that identify patients who can benefit from them.").

[333] *Cf* Gary Kurtzman, *A Business model for a New Generation of Diagnostics Companies*, 2 BIOTECHNOLOGY HEALTHCARE 51 (2005) ("[T]argeted therapies typically require an accompanying diagnostic test to identify candidates for the therapy . . . ."); *see id.* at 50 ("We now are able to begin to determine the best treatment approach for some cancers, based on the genetics of the tumor or the genetic makeup of the patient.").

[334] *See* Soma Mandal et al., *Rational Drug Design*, 625 EUR. J. PHARMACOLOGY 90, 91 (2009) (explaining that small molecule prodrugs bind to a biomolecule that "play[s a] critical role in disease progression" and either (a) "inhibit [its] function," (b) "inhibit[its] biomolecular interactions" with other biomolecules, or (c) "activat[e] biomolecules (for normal functions) that are functionally deregulated in some diseases such as cancer").

[335] *See id.* at 92 (discussing the drugs and their efficacy).

developing precision treatments, the Federal Circuit in *Athena* conceded the patent eligibility of treatment methods.[336] Small molecule drugs may also be eligible for patent protection under § 101 as chemical compositions.[337] However, patent protection for the treatment or drug alone may not be enough to incentivize the up-front R&D costs necessary to identify the biomarker of a disease. Thus, the concerns about decreased funding for R&D of medical diagnostic technologies are certainly credible.

Lastly, the findings of this Note suggest that VC firms employ a higher degree of caution when assessing whether to invest in a company aiming to develop diagnostic technologies. Thus, individuals may face greater barriers in forming start-up companies devoted to researching and developing novel disease diagnostic methods. Indeed, Judge Paul Michel noted this potential consequence of the restrictive § 101 doctrine in his testimony during the Patent Eligibility Hearings.[338] But funding for R&D is only step one.

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336 *See* Athena Diagnostics, Inc. v. Mayo Collaborative Servs., LLC, 915 F.3d 743, 753 (Fed. Cir. 2019), *cert. denied,* 140 S. Ct. 855 (2020) ("Claiming a natural cause of an ailment and well-known means of observing it is not eligible for patent because such a claim in effect only encompasses the natural law itself. But claiming a new treatment for an ailment, albeit using a natural law, is not claiming the natural law.").

337 *See* 35 U.S.C. § 101 (enumerating "composition[s] of matter" as a category of patent eligible subject matter).

338 *The State of Patent Eligibility in America: Part I: Hearing Before the S. Judiciary Comm., Subcomm. on Intellectual Property*, 116th Cong. (2019) (statement of Judge Paul Michel, Former C.J., United States Court of Appeals for the Federal Circuit), at 2 ("Uncertainty, unpredictability, inconsistent results and undue and harmful exclusions of

The hypothetical company will need funding not only to engage in research to find a biological correlation between a biomarker and a disease and to develop a reliable method of detecting said biomarker, but also to commercialize a diagnostic test, to seek patent protection, and to fund clinical trials to obtain FDA approval.[339]

IX. Conclusion

Personalized medicine has revolutionized healthcare by enabling physicians to provide patient-tailored treatments. Part of this success stems from the use of medical diagnostics tests to determine that a patient has a certain condition or disease, and to ensure that the patient qualifies for related treatments. Unfortunately, the confusing, inconsistent interpretations of § 101 and of the judicial exclusions to § 101 have created an environment where medical diagnostics have been deemed patent ineligible.

This Note has demonstrated that this uncertainty following *Bilski* and *Mayo* has led to a decrease in the rate of VC investment in disease diagnosis technologies as compared to the overall rate of VC investment. This result adds to a body of research confirming

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new technologies abound. Consequently, patents are considered unreliable by the very people—business executives and innovation investors like venture capital firms—who make the necessary, but risky, investments. The results point to decreased formation of start-ups . . . .").

339 *See* Hannah Mamuszka, *Moving Diagnostics to the Forefront of Precision Medicine*, 4 J. PRECISION MED. 26, 30 (2017) ("A properly powered clinical trial to validate a test for launch as a Lab Developed Test (LDT) can easily run over $10 million, while adding the required regulatory and manufacturing costs required to bring an In Vitro Diagnostic (IVD) to the market can surpass $25 million.").

concerns of professors, judges, and industry players alike—that the current state of § 101 disincentivizes investment in medical diagnostics. Although VC investment is not the sole method of funding research, to burgeoning start-up companies creating medical diagnostic technologies it is the *sine qua non* of ensuring growth and a path towards commercialization of their products. To keep a competitive edge in the global pharmaceutical and medical diagnostics industries, § 101 should receive Congress' immediate attention.