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Patent Eligibility and Cancer Therapy

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As an empirical legal scholar,[1] I am pleased to report that Sasha Hoyt has done what very few law students—and even many law professors[2]—could achieve. She successfully conducted a novel empirical study to assess the real-world impact of a U.S. Supreme Court decision, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*,[3] on venture capital

* Professor of Law and Director, Frances Lewis Law Center, Washington and Lee University School of Law. I thank Lauren Robertson and Elizabeth Hudson for inviting me to participate in the *Washington and Lee Law Review* Student Notes Colloquium, and I particularly thank Alexandra (Sasha) Hoyt for asking me to serve as the Faculty Advisor for her Note. This Comment is dedicated to my family, and all those who are fighting or have fought cancer.

1. *See generally* Christopher B. Seaman, *Noncompetes and Other Post-Employment Restraints on Competition: Empirical Evidence from Trade Secret Litigation*, 72 HASTINGS L.J. 1183 (2021); David S. Levine & Christopher B. Seaman, *The DTSA at One: An Empirical Study of the First Year of Litigation Under the Defend Trade Secrets Act*, 53 WAKE FOREST L. REV. 105 (2018); Ryan T. Holte & Christopher B. Seaman, *Patent Injunctions on Appeal: An Empirical Study of the Federal Circuit's Application of* eBay, 92 WASH. L. REV. 145 (2017); Christopher B. Seaman, *Permanent Injunctions in Patent Litigation After* eBay*: An Empirical Study*, 101 IOWA L. REV. 1949 (2016); Christopher B. Seaman, *Ongoing Royalties in Patent Cases After* eBay*: An Empirical Assessment and Proposed Framework*, 23 TEX. INTELL. PROP. L.J. 203 (2015); Christopher B. Seaman, *Willful Patent Infringement and Enhanced Damages After* In re Seagate*: An Empirical Study*, 97 IOWA L. REV. 417 (2012).

2. *See* Kathryn Zeiler, *The Future of Empirical Legal Scholarship: Where Might We Go From Here?*, 66 J. LEGAL EDUC. 78, 81, 87–90 (2016) (criticizing the quality of empirical research published in student-edited law reviews and blaming in part law professors' lack of training to conduct such studies).

3. 566 U.S. 66 (2012).

(VC) investment in startups and other companies that develop medical diagnostic technology.[4]

As Ms. Hoyt notes, patent protection is particularly important for startup companies, as it can help protect their innovations from unauthorized use, attract funding and other investments, and foster collaboration with third parties.[5] In the *Mayo* case, the Supreme Court made it extremely difficult for medical diagnostic companies to obtain patent protection for their technology, no matter how novel or useful it is.[6] Using a sophisticated difference-in-difference methodology to evaluate the impact of the Supreme Court's decision in *Mayo* on VC funding for medical diagnostic startups, Ms. Hoyt finds that medical diagnostics firms received almost $10 billion less in VC funding that they would have compared to other industries that were unaffected by the decision.[7] And importantly, this result is statistically significant using an ordinary least squares (OLS)

4. *See generally* A. Sasha Hoyt, Note, *The Impact of Uncertainty Regarding Patent Eligible Subject Matter for Investment in U.S. Medical Diagnostic Technologies*, 79 WASH. & LEE L. REV. 393 (2022) (finding that the U.S. Supreme Court's decision in *Mayo* and subsequent Federal Circuit decisions regarding patent ineligibility of medical diagnostics has resulted in $9.2 billion less investment in medical diagnostic technologies than otherwise would have occurred).

5. *See id.* at 397.

6. *See* Illumina, Inc. v. Ariosa Diagnostics, Inc., 967 F.3d 1319, 1325 (Fed. Cir. 2020) ("Under *Mayo*, we have consistently held diagnostic claims unpatentable as directed to ineligible subject matter."); Athena Diagnostics Inc. v. Mayo Collaborative Servs., LLC, 927 F.3d 1333, 1352 (Fed. Cir. 2019) (Moore, J., dissenting from denial of rehearing en banc) ("Since *Mayo*, we have held every single diagnostic claim in every case before us ineligible."); *see also* Shahrokh Falati, *Patent Eligibility of Disease Diagnosis*, 21 N.C. J.L. & TECH., March 2020, at 63, 67 ("[T]he Supreme Court's recent *Mayo* decision resulted in a dramatic increase in patent offices [sic] rejecting applications related to personalized medicine and medical diagnostics fields."); Shridhar Jayanthi, Note, *A Potential Eligibility Safe Harbor for Diagnostic Patents Creates More Confusion in the* Alice/Mayo *Test*, 34 HARV. J.L. & TECH. DIGEST 1, 1 (2021) ("[S]ince *Mayo*, diagnostic claims have frequently been found to be patent-ineligible under Section 101."); 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, 517–18 (2016) (explaining that "the Federal Circuit has adopted a broad and exacting interpretation of *Mayo*" which "has foreclosed patent eligibility for some important diagnostic innovations").

7. Hoyt, *supra* note 4, at 442.

regression analysis.[8] In short, Ms. Hoyt's Note is a valuable contribution to the literature on patent eligibility and its impact on innovation, and policymakers should take note of her study.[9]

In the remainder of this Comment, I build upon Ms. Hoyt's contributions by discussing the importance of patent protection as an incentive to help develop better diagnostics and treatments for a particular category of illness: cancer. Once considered a monolithic disease classified primarily by cancer cells' site of origin (e.g., breast cancer, prostate cancer), modern genetic research has discovered that cancer is enormously complex,[10] and it is often the result of the multiple mutations that accumulate over time.[11] Moreover, tumors undergo an evolutionary process in the human body and can develop into genetically distinct subclones that are resistant to therapy.[12] As a result, "what we call 'cancer' is, in actuality, a multitude of hundreds of separate diseases with no single etiological source."[13]

Medical diagnostics are critically important to fighting cancer in at least four ways. First, medical diagnostics involve the discovery and use of biomarkers that indicate the presence

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8. *Id.*

9. *Cf.* Comment of A. Sasha Hoyt, In the Matter of Request for Comments on the Current State of Patent Eligibility Jurisprudence in the United States, Docket No. PTO-P-2021-0032, U.S. Patent & Trademark Office (Oct. 12, 2021), https://perma.cc/6ELT-BQXS (informing the U.S. Patent and Trademark Office of the negative correlation between patent eligibility and VC funding for medical diagnostics found in Ms. Hoyt's Note).

10. *See* SIDDHARTHA MUKHERJEE, THE EMPEROR OF ALL MALADIES: A BIOGRAPHY OF CANCER 183 (2010) ("[C]ancer, a shape-shifting disease of colossal diversity, [was] recast as a single, monolithic entity.").

11. *See* Iñigo Martincorena & Peter J. Campbell, *Somatic Mutations in Cancer and Normal Cells*, 349 SCIENCE 1483, 1483 (2015) ("[T]he progressive accumulation of mutations throughout life can lead to cancer . . . ."); Iñigo Martincorena et al., *Universal Patterns of Selection in Cancer and Somatic Tissues*, 171 CELL 1029, 1034 (2017) (noting that there are over 250 known cancer genes).

12. Roberto Vendramin et al., *Cancer Evolution: Darwin and Beyond*, EMBO J., Aug. 30, 2021, at 18; Mel Greaves & Carlo C. Maley, *Clonal Evolution in Cancer*, NATURE, Jan. 18, 2012, at 5. Cancer researcher Peter Nowell, who was a co-discoverer of the Philadelphia chromosome (a gene translocation present in certain kinds of leukemia), is credited with developing the theory of Darwinian-like evolution in cancer cells. *See* Peter C. Nowell, *The Clonal Evolution of Tumor Cell Populations*, 4260 SCIENCE 23, 23–24 (1976).

13. Jacob S. Sherkow, *Cancer's IP*, 96 N.C. L. REV. 297, 305–06 (2018).

of cancer.[14] To effectively treat a patient, physicians must first determine what medical condition or disease the patient has. A biomarker is "a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease."[15] In other words, a biomarker requires the discovery of a naturally-occurring relationship between a biological process in the human body and the presence and level of a corresponding substance produced by or related to that process.

In oncology, medical diagnostics have led to the development of tests that can detect the presence and levels of biomarkers for specific types of cancer.[16] For instance, prostate-specific antigen (PSA) is a well-known biomarker for prostate cancer, one of the most common types of cancer affecting men.[17] While PSA naturally occurs at low levels in all adult males, an elevated level—particularly one that increases significantly over time, in both absolute and relative terms—is correlated with prostate cancer.[18] Since the FDA's approval of a PSA screening test in 1994,[19] thousands of prostate cancer cases have been discovered, although current evidence is mixed about whether the benefit of lives saved due to routine PSA screening is outweighed by complications caused by cancer treatment, the

14. Kyle Strimbu & Jorge A. Tavel, *What Are Biomarkers?*, CURRENT OP. HIV & AIDS, Nov. 2010, at 2.

15. *Biomarker*, NAT'L CANCER INST., https://perma.cc/MFG3-EQDQ.

16. *See generally* N. Lynn Henry & Daniel F. Hayes, *Cancer Biomarkers*, 6 J. MOL. ONCOLOGY 140 (2012).

17. *See generally* William J. Catalona, *History of the Discovery and Clinical Translation of Prostate-Specific Antigen*, 1 ASIAN J. UROLOGY 12 (2015); Danil V. Makarov & H. Ballentine Carter, *The Discovery of Prostate Specific Antigen as a Biomarker for the Early Detection of Adenocarcinoma of the Prostate*, 176 J. UROLOGY 2385 (2006).

18. *See Prostate-Specific Antigen (PSA) Test*, NAT'L CANCER INST., https://perma.cc/L96J-G8SR (last updated Feb. 24, 2021) ("In general, however, the higher a man's PSA level, the more likely it is that he has prostate cancer. Moreover, a continuous rise in a man's PSA level over time may also be a sign of prostate cancer.").

19. *See PSA Test Is Approved for Use in Conjunction with Digital Rectal Examination as Aid in Prostate Cancer Detection*, 272 JAMA 1160, 1160 (1994).

slow growth of many prostate cancers, and side effects caused by biopsies from false positive tests.[20]

Biomarkers also can be used by physicians "to distinguish between different possibilities . . . in [a] differential diagnosis."[21] For instance, if a patient is found to have a lung nodule during a scan, a "histologic evaluation of the biopsy specimen can determine whether the tissue is cancer, infection, inflammation, or another benign process. If cancer is detected, further evaluation with specific immunohistochemical markers can be used to try to identify the tissue of origin."[22]

One particularly important new development is a "liquid biopsy," which consists of a "test done on a sample of blood to look for . . . pieces of DNA from tumor cells that are in the blood."[23] Although scientists recognized the existence of cell-free DNA (cfNDA) circulating in the bloodstream as early as 1948, it was not used to diagnose cancer until 2013, when cfNDA testing inadvertently discovered carcinoma in a pregnant woman who had undergone non-invasive prenatal testing for potential

20. *Compare* Paul F. Pinsky et al., *Extended Mortality Results for Prostate Cancer Screening in the PLCO Trial with Median Follow-Up of 15 Years*, 123 CANCER 592 (2016) (finding no reduction in prostate cancer mortality due to periodic PSA testing), *and* Richard M. Martin et al., *Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality*, 319 JAMA 883 (2018) (finding that a single PSA screening intervention detected more prostate cancer cases but had no significant impact on prostate cancer mortality rates after a median follow-up of ten years), *with* Fritz H. Schröder et al., *Prostate-Cancer Mortality at 11 Years of Follow-Up*, 366 NEW ENG. J. MED. 981 (2012) (finding a 21 percent reduction in risk from death of prostate cancer due to PSA cancer screening), *and* Fritz H. Schröder et al., *Screening and Prostate Cancer Mortality: Results of the European Randomised Study for Screening of Prostate Cancer (ERSPC) at 13 Years of Follow-Up*, 384 LANCET 2027 (2014) (finding that one prostate cancer death was averted per 781 men screened at thirteen years following PSA testing). The current prostate cancer screening guidelines by the U.S. Preventive Services Task Force do not recommend PSA testing for men seventy years and older and suggest that the decision to undergo PSA testing for men between fifty-five and sixty-nine years should be an individual one after discussing the potential risks and benefits with their physician. *See Final Recommendation Statement: Prostate Cancer: Screening*, U.S. PREVENTATIVE SERVS. TASK FORCE (May 8, 2018), https://perma.cc/X2XV-2A88.

21. Henry & Hayes, *supra* note 16, at 141.

22. *Id.*

23. *Liquid Biopsy*, NAT'L CANCER INST., https://perma.cc/HD4X-TBMC.

genetic anomalies for her fetus.[24] Liquid biopsies hold "great promise for detection, prognosis, and prediction of response to cancer treatment."[25] For instance, genetic-screening company GRAIL received a coveted Breakthrough Device designation from the U.S. Food and Drug Administration (FDA) in 2019 for its multi-cancer liquid biopsy test.[26] GRAIL projects that its liquid biopsy test could prevent up to 100,000 cancer deaths annually if it was administered to all Americans fifty and older.[27]

Prior to *Mayo*, the discoverers of new biomarkers like PSA could obtain patent protection for both the biomarker molecule itself and new diagnostic tests incorporating that biomarker.[28] But because biomarker-based diagnostics rely upon a "natural phenomena" or a "law of nature"—namely, the correlation between the biomarker molecule and the existence and/or level of cancer—they are normally ineligible for patenting following *Mayo*.[29] For instance, the Federal Circuit, applying *Mayo*, has held that a cfDNA diagnostic test for genetic mutations in a fetus was patent ineligible,[30] thus casting serious doubt on whether any cfDNA-based cancer diagnostics could be patented. This lack of patent protection can discourage innovation and investment in identifying and validating new and more accurate

24. Irma G. Dominguez-Vigil et al., *The Dawn of the Liquid Biopsy in the Fight Against Cancer*, 9 ONCOTARGET 2912, 2912 (2018) (citing C. Michael Osborne et al., *Discordant Noninvasive Prenatal Testing Results in a Patient Subsequently Diagnosed with Metastatic Disease*, 33 PRENATAL DIAGN. 609 (2013)).

25. *Id.*

26. *See GRAIL Announces Significant Progress with Multi-Cancer Early Detection Test Including FDA Breakthrough Device Designation*, GRAIL (May 13, 2019), https://perma.cc/CXX3-3PYQ.

27. Allysia Finley, *Regulatory Hurdles Block a Cancer Miracle*, WALL ST. J. (Oct. 8, 2021, 1:35 PM), https://perma.cc/MJ33-VUP8.

28. *See, e.g.*, U.S. Patent No. 4,446,122; U.S. Patent No. 5,599,677; U.S. Patent No. U.S. 5,672,480.

29. Mayo Collaborative Servs. v. Prometheus Labs., Inc., 566 U.S. 66, 88–92 (2012).

30. Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015), *reh'g en banc denied*, 809 F.3d 1282 (Fed. Cir. 2015); *see also* CareDx, Inc. v. Natera, Inc., No. CV 19-0567-CFC-CJB, 2021 WL 4439600, at *14 (D. Del. Sept. 28, 2021) (holding that three U.S. patents for a method of determining organ transplant rejection using cfDNA are patent ineligible in the wake of *Mayo*).

biomarkers, which can be a costly and time-consuming process.[31] Without the security of patent rights, VC firms and other investors may decline to help fund the development and approval process for new biomarkers.[32]

Second, diagnostics are important in cancer treatment for risk assessment. The presence or absence of certain genetic markers can indicate the level of risk of contracting cancer, disease progression, and ultimate outcome. For instance, the BRCA1 and BRCA2 germline mutations on chromosomes 17 and 13 are correlated with a greatly increased risk of breast and ovarian cancer among women.[33] The discovery of BRCA1 and BRCA2 led to enhanced screening, medication, and in some cases surgery, to reduce the risk of cancer occurring in women who had these mutations. The patent eligibility of the BRCA1 and BRCA2 genes was the subject of litigation that went all the way to the Supreme Court, which in 2013 held that naturally occurring DNA sequences like BRCA1 and BRCA2 were not patent eligible, but that artificially created complementary DNA (cDNA) sequences created through human intervention could be patented.[34]

Third, diagnostics are valuable in oncology for the development of tailored therapies. For decades, standard cytotoxic treatments like chemotherapy and radiation were widely used to fight cancer.[35] These therapies kill cancer cells,

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31. *See generally* BOOZ ALLEN HAMILTON, COST DRIVERS IN THE DEVELOPMENT AND VALIDATION OF BIOMARKERS USED IN DRUG DEVELOPMENT 2–3 (2018), https://perma.cc/JJ6U-HVHD (PDF) (noting that the mean cost of developing a new predictive biomarker is over $15 million and can take up to three years).

32. *See* Bronwyn H. Hall, *Is There a Role for Patents in the Financing of New Innovative Firms?* 5 (Nat'l Bureau of Econ. Rsch., Working Paper No. 24370, 2018), https://perma.cc/PP4P-GBA2 (noting the "undoubted empirical fact that patenting and VC funding are correlated when one looks across [VC] firms"); *see also id.* at tbl.A-2 (listing studies).

33. *Hereditary Breast and Ovarian Cancer: BRCA1 and BRCA2*, CDC, https://perma.cc/K9HL-DLK2 (last updated Mar. 25, 2020).

34. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. 576 (2013); *see generally* JORGE CONTRERAS, THE GENOME DEFENSE: INSIDE THE EPIC LEGAL BATTLE TO DETERMINE WHO OWNS YOUR DNA (2021).

35. *See generally* MUKHERJEE, *supra* note 10; Vincent T. DeVita, Jr. & Steven A. Rosenberg, *Two Hundred Years of Cancer Research*, 366 NEW ENG. J. MED. 2207 (2012) (detailing the history of surgery, radiation therapy, and chemotherapy from the 19th century through the 1990s).

but they also destroy numerous healthy (nonmalignant) cells, causing numerous short- and long-term side effects, including fatigue, nausea, vomiting, weight loss, risk of infection, permanent nerve damage, organ dysfunction, and the development of secondary malignancies.[36] And in some cases, they are (or become) ineffective, inflicting suffering on patients without corresponding benefit.[37]

As previously mentioned, historically, cancers were classified based on where in the body they originated.[38] But thanks to advances in medical diagnostics, we know now that cancers arising in the same organ are often fundamentally different at a genetic level. This discovery has led to a shift toward tailored therapy—also called personalized medicine—that targets specific mutations that occur in a patient's cancer cells.[39] Diagnostic tests can now reveal whether genetically-targeted therapy would be beneficial as a complement or adjuvant to traditional treatments like radiation and chemotherapy,[40] or potentially replace them entirely.[41]

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36. *Chemotherapy Side Effects*, AM. CANCER SOC., https://perma.cc/LKK3-6QLU; *Radiation Therapy Side Effects*, AM. CANCER SOC., https://perma.cc/EX7K-PRPP).

37. *See, e.g.*, Holly G. Prigerson et al., *Chemotherapy Use, Performance Status, and Quality of Life at the End of Life*, 1 JAMA ONCOLOGY 778, 782–83 (2015) (discussing lack of impact of palliative chemotherapy for some patients with end-stage cancer on their quality of life); *see also* Alice Park, *When Chemotherapy Does More Harm than Good*, TIME (July 23, 2015, 11:00 AM), https://perma.cc/MZZ4-ZA3X.

38. *See supra* notes 10–13 and accompanying text.

39. *Personalized Medicine*, NAT'L CANCER INST., https://perma.cc/D8EN-6UTP ("A form of medicine that uses information about a person's own genes or proteins to prevent, diagnose, or treat disease. In cancer, personalized medicine uses specific information about a person's tumor to help make a diagnosis, plan treatment, find out how well treatment is working, or make a prognosis.").

40. *See, e.g.*, Howard West & Jill O. Jin, *Adjuvant Therapy*, 1 JAMA ONCOLOGY 698, 698 (2015) (explaining that "adjuvant therapy refers to any treatment that is given for cancer after the main treatment, with the goal of making the main treatment more likely to be successful").

41. *See, e.g.*, Gina Kolata, *Cancer Without Chemotherapy: A 'Totally Different World'*, N.Y. TIMES, D1 (Sept. 28, 2021) (describing how oncologists are prescribing targeted therapy as the initial treatment of certain types of breast and lung cancer); Alice Park, *No More Chemo: Doctors Say It's Not So Far-Fetched*, TIME (June 26, 2013), https://perma.cc/B7NP-DYTG (quoting Dr. Martin Tallman, Chief of Leukemia Service at Memorial Sloan-Kettering Cancer Center, as stating "I think we are definitely moving farther and farther

For instance, Herceptin (trastuzumab) is a monoclonal antibody that is a targeted therapy for certain types of cancer, including breast and stomach cancer, that are positive for an oncogene called HER2.[42] In combination with standard-of-care treatment, Herceptin reduced the chance of recurrence by half and risk of dying from breast cancer by a third.[43] The basis for Herceptin was the identification by researchers at Genentech and UCLA of a link between the HER2 oncogene and an aggressive form of breast cancer in the 1980s.[44] After demonstrating in clinical trials that Herceptin, which is an anti-HER2 antibody, plus chemotherapy produced durable responses in a significant number of HER2-positive patients,[45] the FDA approved Herceptin in 1998.[46] Genentech and its parent company, Roche, obtained numerous patents on both the monoclonal antibody and various methods of manufacturing it.[47] But the underlying discovery that made Herceptin possible—the "natural phenomena" of the HER2 oncogene and its relationship to aggressive breast cancer—likely would not be patentable after *Mayo*.[48]

In addition, diagnostics are important to help assess how the human body processes anti-cancer drugs. Pharmacogenetics is the field of study on how a patient's genetics affect her

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away from chemotherapy, and more toward molecularly targeted therapy" for certain forms of cancer).

42. *See generally* ROBERT BAZELL, HER-2: THE MAKING OF HERCEPTIN, A REVOLUTIONARY TREATMENT FOR BREAST CANCER (1998).

43. Kolata, *supra* note 41.

44. *See generally* Corinne L. Williams, *H. Michael Shepard, Dennis J. Slamon, and Axel Ullrich Honored with the 2019 Lasker-DeBakey Clinical Medical Research Award*, 129 J. CLINICAL INVESTIGATION 3963 (2019).

45. *See generally* Jose Baselga, *Phase I and II Clinical Trials of Trastuzumab*, 12 ANNALS ONCOLOGY S49 (2001).

46. *See* Charles L. Sawyers, *Herceptin: A First Assault on Oncogenes that Launched a Revolution*, 179 CELL 8, 10 (2019).

47. *See, e.g.*, U.S. Patent No. 5,821,337; U.S. Patent No. 6,054,297; U.S. Patent 6,407,213; U.S. Patent No. 6,627,196; U.S. Patent No. 7,371,379.

48. For instance, U.S. Patents No. 7,846,441 and No. 7,892,549, which claimed a method of treating patients with breast cancer that overexpresses HER2 by using a monoclonal antibody in combination with chemotherapy and/or other monoclonal antibodies, was recently invalidated by the Federal Circuit, although on obviousness grounds rather than lack of patent eligibility. Genentech, Inc v. Iancu, 809 F. App'x 781, 786–87 (Fed. Cir. 2020).

response to specific drugs.[49] For instance, a gene called TPMT encodes the thiopurine methyltransferase enzyme, which metabolizes common chemotherapy agents like 6-mercaptopurine (6MP) and thiopurine.[50] Patients with mutated versions of TPMT are at high risk for severe, even fatal, toxicity if given a normal dose of one of these drugs.[51] Researchers at St. Jude Children's Hospital discovered the relationship between the TPMT genetic polymorphism (mutation) and TMPT deficiency in the 1990s,[52] and subsequently obtained patent rights to both isolated DNA sequences containing the mutated TPMT gene and a diagnostic assay (Test) for determining whether a patient has the TPMT-deficient gene.[53] Today, however, these patent claims would almost certainly be ineligible—the naturally-occurring DNA sequences would be unpatentable in light of *Ass'n for Molecular Pathology v. Myriad Genetics Inc.*,[54] and the diagnostic test would be precluded by *Mayo*.

Another revolutionary development in oncology is the rise of immunotherapy. While the existence of antibodies as part of the adaptive immune system was discovered over a century ago, the first antibody-based cancer therapy, rituximab, was only approved by the FDA to treat B-cell lymphoma in 1997.[55] Today, "[a]ntibody-based therapy . . . is now one of the most successful

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49. *Pharmacogenetics*, NAT'L CANCER INST., https://perma.cc/NP8J-72C9; *see also* Liam Drew, *Pharmacogenetics: The Right Drug for You*, 537 NATURE S60 (2016).

50. Eugene Krynetski & William E. Evans, *Drug Methylation in Cancer Therapy: Lessons from the TPMT Polymorphism*, 22 ONCOGENE 7403, 7403 (2003).

51. *Id.* (citing William E. Evans et al., *Altered Mercaptopurine Metabolism, Toxic Effects, and Dosage Requirements in a Thiopurine Methyltransferase-Deficient Child with Acute Lymphocytic Leukemia*, 119 J. PEDIATRICS 985 (1991)).

52. Eugene Y. Krynetski & William E. Evans, *Pharmacogenetics of Cancer Therapy: Getting Personal*, 63 AM. J. HUM. GENETICS 11 (1998).

53. U.S. Patent No. 5,856,095 (issued Jan. 5, 1999). St. Jude's subsequently granted an exclusive license to the patent rights to a joint venture of PPD, Inc., and Axys Pharmaceuticals, Inc. *PPGx Secures Exclusive Worldwide License for TPMT Testing from St. Jude Children's Research Hospital*, PR NEWSWIRE (Apr. 7, 2000), perma.cc/4QWN-2KDM.

54. 569 U.S. 576 (2013).

55. DeVita & Rosenberg, *supra* note 35, at 2212.

and important strategies for treating [cancer] patients,"[56] and dozens of antibodies have been approved or are in various stages of clinical trials to target specific antigens that appear on cancer cells.[57] Other forms of cancer immunotherapy include antibodies that inhibit immune system checkpoints which would otherwise hinder the immune system's response in attacking cancer cells (checkpoint inhibitors); cancer "vaccines" that present antigens to T cells, leading to their activation against cancer cells bearing the same antigen; and genetically engineered human T cells (CAR-T), which act as "living drugs" that target specific proteins on the surface of cancer cells.[58] These remarkable therapies have extended survival, and even resulted in cures, in some patients when other treatment options have failed.[59]

Despite its growing importance, immunotherapy is not immune from potential patent eligibility issues. Although some forms of cancer immunotherapy, such as CAR-T cells and monoclonal antibodies, are "a product of genetic engineering [that] may support a conclusion that they are a 'manufacture' or 'composition of matter'" under § 101,[60] they are still based on underlying natural phenomena—namely, the existence of naturally-occurring antigens on the surface of cancer cells and receptors that can bind to these antigens.[61] For example, in *Bristol-Meyer Squibb Co. v. Merck & Co.*,[62] the defendants argued that U.S. Patent No. 9,073,994 (the '994 Patent), which

56. Andrew M. Scott et al., *Antibody Therapy of Cancer*, 12 NATURE REVS. 278, 278 (2012).

57. *Id.* at 281; *see also* David Zahavi & Louis Weiner, *Monoclonal Antibodies in Cancer Therapy*, 9 J. ANTIBODIES 34 tbl.1 (2020) (listing FDA-approved monoclonal antibodies for cancer).

58. *See generally* Emilie Alard et al., *Advances in Anti-Cancer Immunotherapy: CAR-T Cell, Checkpoint Inhibitors, Dendritic Cell Vaccines, and Oncolytic Viruses, and Emerging Cellular and Molecular Targets*, 12 CANCERS 286 (2020).

59. *See* Gina Kolata, *'Desperation Oncology': When Patients Are Dying, Some Cancer Doctors Turn to Immunotherapy*, N.Y. TIMES (Apr. 26, 2018), https://perma.cc/RVA9-NGER.

60. Ellen Shamasky, *The Cancer Immunotherapy Pilot Program and Chimeric Antigen Receptor T-Cell Treatments*, 2018 B.C. INTELL. PROP. & TECH. F. 1, 26 (citing Diamond v. Chakrabarty, 447 U.S. 303 (1980)).

61. *See* Juno Therapeutics, Inc. v. Kite Pharma, Inc., 10 F.4th 1330, 1333 (Fed. Cir. 2021) (further describing the relationship between receptors that are reprogrammed on CAR-T cells and antigens on the surface of cancer cells).

62. No. 15-572, 2016 WL 1698385 (D. Del. Mar. 29, 2016).

claimed a method of treating melanoma (a type of skin cancer) using an anti-PD-1 monoclonal antibody, was drawn to patent ineligible subject matter because "it merely claims the result of a natural phenomenon": the PD-1 pathway, which cancer cells suppress by "producing PD-1 ligands that shut down T cells and prevent T cells from attacking them."[63] The District Court ultimately denied the defendants' motion to dismiss, but in doing so, it found that the '994 Patent "touches upon a natural phenomenon by using T cells to activate the immune system"—specifically, that it "relies on the known scientific fact that blocking activation of the PD-1 pathway causes this effect in the body, which enables the patient's T cells to perform their normal biological activity of removing cancer cells."[64] As a result, the District Court concluded that "[t]his interaction is a natural phenomenon" under the first step of the *Mayo*/*Alice* test for patent ineligibility.[65]

Fourth, diagnostics are important in oncology to assess treatment response and provide long-term surveillance. Biomarkers can determine whether treatments for cancer are effective and serve as ongoing surveillance once remission has been achieved. For example, a biomarker called CEA (carcinoembryonic antigen) is used to monitor the progress of colorectal cancer,[66] based on a patented discovery in the 1960s by researchers at LaRoche.[67] Similarly, biomarkers like alpha fetoprotein (AFP) are regularly monitored in germ cell tumor

63. Defendants Merck & Co., Inc. & Merck Sharp & Dohme Corp.'s Brief Supporting Their Motion to Dismiss, Bristol-Myers Squibb Co. v. Merck & Co., No. 15-572 (D. Del. Aug. 28, 2015), 2015 WL 9811960.

64. *Bristol-Myers Squibb*, 2016 WL 1698385, at *1 n.2.

65. *Id.* The District Court denied the motion to dismiss under the second step of the *Mayo*/*Alice* test, holding that disputed factual allegations about whether the '994 Patent's claims "do significantly more than simply describe these natural relations" precluded granting the motion under Federal Rule of Civil Procedure 12(b)(b). *Id.* The case ultimately was dismissed with prejudice prior to a final judgment on the merits. Stipulation of Dismissal of Entire Actions with Prejudice, Bristol-Myers Squibb Co. v. Merck & Co., No. 15-572 (D. Del. Jan. 20, 2017), 2017 WL 7688123.

66. Gershon Y. Locker et al., *ASCO 2006 Update of Recommendations for the Use of Tumor Markers in Gastrointestinal Cancer*, 24 J. CLINICAL ONCOLOGY 5313 (2006).

67. U.S. Patents No. 3,663,684; No. 3,697,638; No. 3,956,258.

patients to detect early disease recurrence.[68] Again, however, the naturally-occurring correlation between these biomarkers and disease progression or relapse are probably unpatentable under the Court's current patent eligibility jurisprudence.

To be sure, patent protection for diagnostics and treatment for cancer comes at a significant cost to both patients, insurance companies, and the public. The BRCA1/BRCA2 test was $4,000 at the time of the Supreme Court's decision.[69] Now that patent protection is unavailable for naturally occurring DNA after *Myriad*, competitors have developed and offered their own BRCA tests for a fraction of the cost.[70] And even after patent protection has expired on Gleevec (imatinib), a drug that is used as a first-line treatment for Philadelphia-chromosome positive chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL), it is still incredibly expensive with a retail price of over $100,000 per year,[71] costing U.S. taxpayers over $1 billion annually.[72] Treatments like CAR-T cell immunotherapy are even more expensive.[73] More needs to be done to bring down the cost of these revolutionary new therapies, and discussion of potential reforms to the patent system that may help lower prices is ongoing.[74] But entirely eliminating patent protection

68. Timothy D. Gilligan et al., *American Society of Clinical Oncology Clinical Practice Guidelines on Uses of Serum Tumor Markers in Adult Males with Germ Cell Tumors*, 28 J. CLINICAL ONCOLOGY 3388 (2010).

69. David B. Argus, *The Outrageous Cost of a Gene Test*, N.Y. TIMES (May 20, 2013), https://perma.cc/95B5-HV9B.

70. Elizabeth Lopatto, *Genetic Testing for Breast Cancer Gets More Affordable*, VERGE (Apr. 21, 2015, 12:01 AM), https://perma.cc/YE5W-U2TC.

71. Roxanne Nelson, *Prices Drop at Last for Transformative Cancer Drug*, MEDSCAPE (Dec. 19, 2019), https://perma.cc/FAB4-HDA2.

72. *Prices for and Spending on Specialty Drugs in Medicare Part D and Medicaid: An In-Depth Analysis* 44 tbl.2 (Cong. Budget Off., Working Paper 2019-02, 2019), https://perma.cc/5MUN-DJ2S.

73. *See, e.g.*, Reith R. Sarker et al., *Cost-Effectiveness of Chimeric Antigen Receptor T-Cell Therapy in Pediatric Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia*, 111 J. NAT'L CANCER INST. 719, 720 (2019) (noting that a single dose of Kymriah (tisagenlecleucel) can cost up to $475,000).

74. *See* Executive Order 14036, Promoting Competition in the American Economy, 86 Fed. Reg. 36,987, 36,988 (July 9, 2021) ("[T]oo often, patent and other laws have been misused to inhibit or delay—for years and even decades—competition from generic drugs and biosimilars, denying Americans access to lower cost drugs."); *see also* Letter from Janet Woodcock, M.D., Acting Commissioner of Food and Drugs, to Andrew Hirshfeld, Performing the Functions and Duties of the Undersecretary of Commerce for Intellectual

for medical diagnostics, and thus decreasing incentives to help detect, treat, and cure life-threatening diseases like cancer, does not seem to be the optimal approach.

Property and Director of the U.S. Patent and Trademark Office (Sept. 10, 2021), https://perma.cc/KD7V-JEA6 (PDF) (raising concerns regarding the high cost of pharmaceuticals and biosimilars and raising potential reforms at the U.S. Patent and Trademark Office to address these issues).