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Opting Into Device Regulation in the Face of Uncertain Patentability

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OPTING INTO DEVICE REGULATION IN THE FACE OF UNCERTAIN PATENTABILITY

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INTRODUCTION

It is a great honor for me to deliver the Helen Wilson Nies Memorial Lecture in Intellectual Property Law at Marquette University Law School. I want to begin with a few words about Judge Nies. I had the good fortune of speaking with Judge Nies about her career years ago when she returned to her alma mater, the University of Michigan Law School, and gave a guest lecture to my patent law class.

Judge Nies was a distinguished alumna who graduated Order of the Coif in the Class of 1948, and we are very proud of her at Michigan. She had a distinguished career in trademark law before her appointment to the federal bench in 1980. When the Court of Appeals for the Federal Circuit was created in 1982, she became one of its first judges, and eventually served as chief judge. Although the Federal Circuit is often viewed as a specialized patent court, prior to her appointment Judge Nies had little background in patent law.² But of course, patent law is still law, and Judge Nies was an excellent lawyer, so she rolled up her sleeves and figured it out. I admire that fearlessness, especially at a relatively late career stage. Rarely can individuals see where their career will take them, and if we want to take advantage of new opportunities—or

1. Robert & Barbara Luciano Professor of Law, University of Michigan Law School. This research was supported by the William W. Cook endowment of the University of Michigan Law School. My understanding of this topic owes much to a collaborative project with Harold Varmus. See Rebecca Eisenberg & Harold Varmus, *Insurance for broad genomic tests in oncology*, 358 SCIENCE 1133 (2017).

2. Her husband, John Nies, was also a Michigan law grad and patent lawyer.

simply provide the advice clients require in an ever-changing world—from time to time we all need to roll up our sleeves and learn something new.

Among Judge Nies's lasting contributions to the Federal Circuit were her early opinions on legal process and procedural issues.³ These decisions were vital to the new court's mission to consolidate appellate jurisdiction over patent law and to standardize its interpretation.⁴ Judge Nies's opinions on burden of proof, standard of review, the role of juries, and the authority of prior opinions of other courts are still cited today, while many substantive decisions of her Federal Circuit brethren from the same era have been overturned by subsequent decisions of the Supreme Court.⁵ The enduring significance to the patent system of these process issues reminds us that patent law is not an island apart from the rest of the legal system. It works alongside other bodies of law, and operates through rules for administrative and judicial practice that are not unique to patent law.

The primary focus of my patent scholarship has been biomedical innovation. Patent law is often credited with motivating investments in biomedical innovation, particularly from the pharmaceutical industry, which relies heavily on patent protection and works hard to strengthen patent laws throughout the world. But patent law does not work alone. This is a lesson I keep learning. Other sources of legal regulation provide crucial assistance when patent law would otherwise fail to achieve its goals.

Today, I examine the intersection of patent law, FDA regulation, and Medicare coverage in a particularly promising field of biomedical innovation: genetic diagnostic testing. First, I will discuss current clinical uses of genetic testing and directions for further research, with a focus on cancer, the field in which genetic testing has had the greatest impact to date. Second, I will turn to patent law and address two recent Supreme Court decisions that called into question the patentability of many of the most important advances in genetic testing.⁶ Third, I will step outside patent law to take a broader view of the legal environment for new developments in genetic testing, with a focus on two federal regulatory agencies: the Food & Drug Administration (FDA), which regulates new drugs and medical devices under statutory standards for safety and effectiveness; and the Centers for Medicare and Medicaid Services (CMS),

3. See Stephen A. Soffen, *Hon. Helen W. Nies – A Conscientious Jurist Who Led the court in Defining the Role of Juries in Patent Cases*, 8 J. FED. CIR. HIST. SOC'Y 97, 97–99 (2014) (examining Judge Nies' opinions on the role of the jury, summary judgment, and standard of review).

4. See *id.*; Helen W. Nies, *The Federal Circuit: A Court for the Future*, 41 AM. U. L. REV. 571, 571 (1992).

5. See Soffen, *supra* note 3, at 100–01.

6. This is how I came to this topic as a patent scholar. I was worried that the absence of patent protection might undermine incentives for innovation in this important field.

which sets reimbursement policies for Medicare under statutory standards that limit coverage to technologies that are reasonable and necessary.

Last, with this background, I will explain a recent surprising development: developers of next generation sequencing (NGS) diagnostic tests for tumor DNA have begun seeking FDA approval or clearance for tests they are at liberty to provide, and in fact have already begun to provide, without asking FDA for permission. The answer lies in understanding the rules and practices that govern health insurance coverage and the important role of FDA in assessment of new technologies. This episode sheds an interesting light on the roles and interactions of different sources of legal regulation in supporting innovation outside the patent system.

I. CURRENT TRENDS IN GENETIC TESTING AND A SHIFT IN CANCER DIAGNOSES

Advances in genetics and molecular biology have transformed scientific understanding of the basis of many diseases, identifying new molecular targets for therapy and rearranging diagnostic categories. Nowhere are these developments more striking than in cancer. Traditional cancer diagnosis focuses on the tissue of origin of a tumor. Caregivers look to the tissue of origin to specify what type of a cancer a patient has, and then consider different treatment options depending on whether the patient has breast cancer, colon cancer, lung cancer, etc. But increasingly it appears that what really matters is not so much the tissue of origin, but the genetic mutation that is driving the tumor.

Studies to date have revealed hundreds of genes in which mutations associated with cancer arise.⁷ Some of these mutations are common and well understood, while others are rare, and their role in cancer remains unclear.⁸ Drug companies have developed a new generation of “targeted therapies” that are designed to work against tumors that have specific mutations.⁹ Sometimes these targeted therapeutic products are developed and submitted to FDA for approval along with a “companion diagnostic” test to detect the targeted mutation.¹⁰

7. A catalogue of these genes is maintained at Cancer Gene Census, Catalogue of Somatic Mutations in Cancer, http://cancer.sanger.ac.uk/census#cl_search [<https://perma.cc/974D-K537>].

8. *See id.*

9. Nickolas Papadopoulos, Kenneth W. Kinzler & Bert Vogelstein, *The role of companion diagnostics in the development and use of mutation-targeted cancer therapies*, 24 NATURE BIOTECHNOLOGY 985, 985 (2006).

10. U.S. Food & Drug Admin., *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff* 5–6 (2014),

FDA-approved indications for targeted therapeutics may specify tissue of origin as well as the genetic mutation targeted by the drug. An example is the drug Herceptin® (trastuzumab), one of the earliest FDA-approved targeted cancer therapies.¹¹ Initially, FDA approved the drug “for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.”¹² Later, FDA expanded the approved indications to include treatment of patients with tumors from other tissues that have the same genetic signature, specifically “the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma.”¹³ Although breast cancer and gastroesophageal cancer arise in different types of tissues, if the resulting tumors are overexpressing the HER2 protein, both groups of patients are candidates for treatment with the same targeted drug.¹⁴ In 2017, for the first time, FDA expanded the approved indications for another targeted cancer drug, Keytruda® (pembrolizumab), to include all tumors with the specified genetic profile, regardless of tissue of origin.¹⁵ In the future, the most meaningful information for diagnosis of cancer type and selection of treatment may no longer be tissue of origin, but rather results of genetic testing.¹⁶ However, much work remains to be done to understand the significance of different mutations in driving different cancers.

Meanwhile, the cost of more extensive DNA sequencing has fallen significantly with the advent of next generation sequencing (NGS) technology, which makes it feasible to derive more information from a single DNA sample quickly and at little incremental cost relative to narrower tests that only look for particular mutations.¹⁷ This technology alters the logical approach to

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf> [<https://perma.cc/Q8ZB-NPLB>].

11. Papadopoulos et al., *supra* note 9, at 989.

12. Letter from Jay P. Siegel to Robert L. Garnick (Sept. 25, 1998),

https://www.accessdata.fda.gov/drugsatfda_docs/applletter/1998/trasgen092598L.pdf [<https://perma.cc/TP3N-DUK9>].

13. See current label for Herceptin® (trastuzumab) at https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103792s5330lbl.pdf (revised Mar. 2016) [<https://perma.cc/BGF5-55YE>].

14. *Id.*

15. FDA News Release, FDA approves first cancer treatment for any solid tumor with a specific genetic feature (May 23, 2017), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm> [<https://perma.cc/R8ZW-9HNG>].

16. David M. Hyman, Barry S. Taylor, & Jose Baselga, *Implementing Genome-Driven Oncology*, 168 CELL 584, 584 (2017).

17. Erwin L. VanDijk et al., *Ten years of next-generation sequencing technology*, 30 TRENDS IN GENETICS 418, 418–19 (2014).

genetic testing for cancer patients. In 1998, when Herceptin was first approved for treatment of HER2/neu overexpressing breast cancer,¹⁸ it seemed sensible to test tumor DNA from breast cancer patients only for the particular aberration that would indicate a likely response to Herceptin. But today, with a larger set of targeted therapies available against different mutations and with the ability to sequence more DNA at lower cost, it is questionable whether such limited testing still makes sense. For a modest incremental cost, it is now possible to fully sequence, a DNA sample from a patient's tumor, the 350–400 genes known to be associated with cancer, making it possible to screen patients for multiple treatments at once. Even if no targeted therapies exist for the mutations that are found in a patient's tumor DNA, such testing could shed light on the patient's diagnostic odyssey.¹⁹ It could also contribute to understanding of cancer by illuminating the mutations that may be causing particular tumors.²⁰ Multiple laboratories now offer such tests, both in academic medical centers and in commercial firms.

II. PROCESS PATENTABILITY AND THE SUPREME COURT

The proliferation of new tests suggests a flourishing of innovation in the field of genetic testing, despite recent developments in patent law that have cast serious doubt on the patentability of many of the most important advances in DNA diagnostics. Doubts about patentability arise from two U.S. Supreme Court decisions.

First was the Court's 2012 decision in *Mayo Collaborative Services v. Prometheus Laboratories*.²¹ The patent at issue claimed a diagnostic algorithm that involved observing a biomarker and then drawing a diagnostic inference about the patient's need for treatment.²² More specifically, the patent claimed a method of optimizing treatment with thiopurine drugs by measuring levels of certain drug metabolites in a patient's blood and determining on that basis whether the drug dosage needs to be adjusted.²³ A patient's body produces metabolites as the body breaks down a drug after ingesting it. The patent recited both a lower level of drug metabolites that would indicate a need for a higher dosage of the drug (to be sure that it is therapeutically effective) and an upper level that would indicate a need to lower the dosage (to minimize toxic

18. See Siegel, *supra* note 12, at 1.

19. See Hyman et al., *supra* note 16, at 585.

20. *Id.* at 585–86.

21. *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 66–67 (2012) (noting that the patent at issue involved “the use of thiopurine drugs to treat autoimmune diseases.”).

22. Kevin E. Collins, *Prometheus Laboratories, Mental Steps, and Printed Matter*, 50 HOUSTON L. REV. 391, 398 (2012).

23. *Id.* at 399.

side effects).²⁴ The Supreme Court held that the patent claims were invalid because the metabolite levels that would indicate a need to adjust the dosage of the drug are unpatentable “natural laws,” and once those natural laws are excluded, the remaining steps in the claim were not sufficiently novel to count as a patentable invention.²⁵ Although it may have been possible to interpret this decision narrowly, a fair reading of the Court’s analysis seems to count all predictions regarding the effects of treatment in patients as “natural laws.”²⁶ Subsequent decisions have read the *Mayo* decision broadly, dealing a major blow to patenting strategies for innovative diagnostic tests.²⁷

The next year the Supreme Court dealt another major blow to patentability of DNA diagnostics with its decision in *Association for Molecular Pathology v. Myriad Genetics*.²⁸ The patent at issue in that case claimed DNA molecules with sequences corresponding to the BRCA1 and BRCA2 genes associated with susceptibility to developing breast cancer.²⁹ The Supreme Court held that the BRCA1 and BRCA2 genes, as they exist in patients’ cells, are unpatentable because they are natural products.³⁰ Again, although it might be possible to read the opinion more narrowly, a fair reading of the Court’s analysis seems to count all naturally occurring DNA biomarkers used in genetic testing as “natural products.”³¹

Considered together, these two decisions cast considerable doubt on the patentability of both the biomarkers and the associated diagnostic predictions involved in genetic diagnostic testing. Subsequent lower court decisions have offered little reason to expect that these decisions will be narrowly interpreted.³²

III. GENETIC TESTING AND FEDERAL REGULATION

What does doubtful patentability mean for incentives for investment in development of genetic diagnostic tests? If the conventional wisdom for the

24. *Id.* at 398.

25. *Id.* at 403. For a fuller analysis and critique of this opinion, see Rebecca S. Eisenberg, *Diagnostics Need Not Apply*, 21 BOSTON U.J. SCI. & TECH. L. 256, 264–70 (2015).

26. *See id.* at 266.

27. *See Ariosa Diagnostics v. Sequenom*, 788 F.3d 1371, 1377 (Fed. Cir. 2015), *cert. denied*, 136 S. Ct. 2511 (2016).

28. *Ass’n for Molecular Pathology v. Myriad Genetics*, 569 U.S. 576, 576 (2013) (holding “a naturally occurring DNA segment is . . . not patent eligible.”).

29. *Id.*

30. *Id.* at 580.

31. *Id.*

32. Anne Paxton, *AMP v. Myriad: driving or disrupting innovation?* (2017), <http://www.captodayonline.com/amp-v-myriad-driving-disrupting-innovation/> [<https://perma.cc/864Y-FM9H>].

biopharmaceutical industry applies to diagnostics,³³ one might worry that patent incentives are essential and that without reliable patent protection, investments in this promising field will dry up. On the other hand, the Supreme Court decisions that cast doubt on the patentability of diagnostic inventions were applauded by some innovators in this field, especially in university laboratories that were eager to offer NGS testing to examine a great many genes in a single test, without having to worry about multiple patent holders trying to stop them.³⁴ Perhaps innovation in genetic testing is different from the paradigm case of new drug development, the example long used to illustrate the need for patents to preserve incentives for new product development. Perhaps patents are less necessary, or even counterproductive, for incentives to develop new diagnostic tests.

One difference between diagnostics and therapeutics is the regulatory burden imposed on the two types of products. The costs and risks of FDA regulation loom large in standard accounts of why the pharmaceutical industry needs patents on new drugs.³⁵ Before a firm may lawfully sell or even ship a new drug in commerce, FDA must approve it under statutory standards for safety and efficacy based on data from clinical trials that meet stringent scientific standards.³⁶ These trials are both costly and risky, with many failures at every stage. Even after approval, many drugs get withdrawn from the market after new risks come to light. Or after further data shows that risks were more substantial than was initially apparent. Drug developers must cover the costs of failure with lucrative sales of successful products, and patents allow them to charge prices that are high enough to do that.

The FDA has statutory authority to regulate genetic tests for safety and efficacy as medical devices.³⁷ But it regulates medical devices less stringently than drugs.³⁸ Medical devices are a diverse category that ranges from simple

33. See Iain Cockburn & Genia Long, The importance of patents to innovation: updated crossindustry comparisons with biopharmaceuticals, 25 *EXPERT OPINION ON THERAPEUTIC PATENTS* 739, 739 (2015).

34. Anne Paxton, *AMP v. Myriad: driving or disrupting innovation?* (2017), <http://www.captodayonline.com/amp-v-myriad-driving-disrupting-innovation/> [<https://perma.cc/864Y-FM9H>].

35. Joseph A. DiMasi, Henry G. Grabowski, & Ronald W. Hanson, *Innovation in the Pharmaceutical Industry New Estimates of R&D Costs*, 47 *J. HEALTH ECON.* 20, 26 (2016) (noting that for approved drugs, the “fully capitalized total cost estimate is \$2558 million.”).

36. 21 U.S.C. § 355.

37. U.S. Food & Drug Admin., Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory-Developed Tests (LDTs), 7 (Oct. 3, 2014), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf> [<https://perma.cc/4LW9-PG2A>].

38. *Id.* at 8–9.

items like tongue depressors and bandages to complex implanted devices like cardiac pacemakers.³⁹ The statute directs FDA to take a stratified, risk-based approach to device regulation, sorting devices into three classes (I, II, and III) according to the kinds of controls that are necessary to ensure their safety and effectiveness.⁴⁰ Only the riskiest Class III devices require “premarket approval” from FDA before they may be sold, while intermediate risk Class II devices may be sold after a less onerous “premarket clearance” process (sometimes called “510(k) clearance” after the relevant statutory provision).⁴¹ Even for Class III devices that require premarket approval, the burden and cost are considerably less than for premarket approval of drugs. Whenever possible, FDA relies less heavily on premarket testing and more on post-approval monitoring and data collection to ensure safety and effectiveness for devices.⁴²

Sometimes the FDA regulates specific genetic tests as “companion diagnostics” for new drugs that target the specific mutations that these tests detect, approving the diagnostic and therapeutic products together.⁴³ Coordinated submission of data on both products can be advantageous for drug companies seeking approval for targeted therapies.⁴⁴ Using a validated diagnostic to screen patients for participation in clinical trials may allow a new drug to get approval after trials that are smaller and shorter in duration than FDA would otherwise require.⁴⁵ This is because the diagnostic allows the sponsor to design the trial to focus on patients who have the targeted mutation and are therefore likely to respond to the drug.⁴⁶ Put differently, trial results

39. U.S. Food & Drug Admin., *Classify Your Medical Device*, <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm> [https://perma.cc/48M3-N4WS].

40. 21 U.S.C. § 360c et seq.

41. U.S. Food & Drug Admin., *Overview of Device Regulation*, <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm> [https://perma.cc/Q9TN-FENQ].

42. U.S. Food & Drug Admin., *Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval: Guidance for Industry and Food and Drug Administration Staff*, 6 (2015), <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393994.pdf> [https://perma.cc/F4YZ-VTHM].

43. U.S. Food & Drug Admin., *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff*, 6 (2014), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf> [https://perma.cc/3LFA-N6RL].

44. Papadopoulos et al., *supra* note 9, at 993–94.

45. 45. U.S. Food & Drug Admin., *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food and Drug Administration Staff*, 8 (2014), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf> [https://perma.cc/B2JE-BAAB].

46. Papadopoulos et al., *supra* note 9 at 993.

are more likely to favor a given drug if a genetic test administered before the trial allows a drug company to exclude patients who are unlikely to respond to the targeted therapy because they do not have the targeted mutation. Drug companies are therefore motivated to do the necessary trials to validate the clinical significance of diagnostics that detect these targeted mutations, whether or not they can patent the validated tests themselves. Validating the tests will expedite approval to sell the new, and presumably patented, drugs that target the mutations that the tests detect.⁴⁷

The FDA has generally classified companion diagnostics for targeted therapies as Class III medical devices, requiring premarket approval.⁴⁸ But FDA Guidance Documents have indicated that FDA might in future cases allow companion diagnostic devices to use the less onerous “premarket notification” clearance process for Class II devices if FDA determines that such a process is sufficient to provide a reasonable assurance of safety and efficacy.⁴⁹ As FDA explained in 2014:

FDA will apply a risk-based approach to determine the regulatory pathway for IVD [in vitro diagnostic] companion diagnostic devices, as it does with all medical devices. This means that the regulatory pathway will depend on the level of risk to patients, based on the intended use of the IVD companion diagnostic device and the controls necessary to provide a reasonable assurance of safety and effectiveness. Thus, the level of risk together with available controls to mitigate risk will establish whether an IVD companion diagnostic device requires a premarket approval application (PMA) or a premarket notification submission (510(k)).⁵⁰

This is consistent with FDA’s flexible approach to device regulation. Although typically a new type of device that is not equivalent to any previously approved device will begin in Class III, requiring premarket approval,⁵¹ FDA may later reevaluate this classification and permit “de novo” reclassification if initial concerns about safety and effectiveness prove to be manageable with less burdensome regulatory controls.⁵²

47. *See Id.* at 993–94.

48. U.S. Food & Drug Admin., *In Vitro Companion Diagnostic Devices: Guidance for Industry and Food & Drug Administration Staff*, 10 n.10 (2014).

49. *Id.*

50. *Id.* at 10.

51. *Id.* at 10 n.10; 21 U.S. Code § 360c(f)(1).

52. U.S. Food & Drug Admin., *De Novo Classification Process (Evaluation of Automatic Class III Designation): Guidance for Industry and Food and Drug Administration Staff*, 5 (2017),

Another important limitation on FDA regulation of diagnostic tests has provided a huge break for genetic testing laboratories without regard to their medical device classification. As a matter of administrative discretion, FDA has so far chosen not to require approval or clearance of what it calls “laboratory developed tests.”⁵³ A laboratory developed test (LDT) is a diagnostic test that is designed, manufactured, and used all within the same laboratory, rather than sold or licensed for use in other facilities.⁵⁴ This is an old policy dating back to the 1970s that has allowed many laboratories to provide genetic testing services without the burden of FDA regulation.⁵⁵ A few years ago, FDA appeared to be on the verge of reconsidering this discretionary policy.⁵⁶ In a Draft Guidance issued in 2014, FDA proposed to use expert advisory committees to determine the level of risk posed by different kinds of LDTs and to enforce their existing authorities to regulate some kinds of LDTs more aggressively.⁵⁷ But in the final days of the Obama administration, FDA put these plans on hold.⁵⁸ For now at least, most laboratories that perform genetic testing services do not need approval or clearance for their tests from the FDA. In this environment, when an applicant has sought FDA approval for a genetic test, it has generally been for a specific companion diagnostic product developed in tandem with a targeted drug and used to identify which patients are likely to respond to that drug.

Meanwhile, more-comprehensive genetic tests that use NGS technology to examine hundreds of genes to detect mutations driving a patient’s cancer have become available without FDA approval or clearance. These tests have proliferated in both academic medical centers⁵⁹ and commercial laboratories.⁶⁰

<https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf> [<https://perma.cc/4D7S-A9PR>].

53. U.S. Food & Drug Admin., Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests, 6 (2014).

54. *Id.* at 5.

55. *Id.* at 6.

56. *Id.* at 12.

57. *Id.*

58. U.S. Food & Drug Admin., Discussion Paper on Laboratory Developed Tests (LDTs), 1 (Jan. 17, 2017), <https://www.fda.gov/downloads/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/laboratorydevelopedtests/ucm536965.pdf> [<https://perma.cc/6E7K-L557>].

59. *See, e.g.*, D.T. Cheng et al., *Memorial Sloan Kettering-Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT): A Hybridization Capture-Based Next-Generation Sequencing Clinical Assay for Solid Tumor Molecular Oncology*, 17 J. MOLECULAR DIAGNOSTICS 251, 251 (2015).

60. *See, e.g.*, Garrett M. Frampton et al., Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing, 31 NATURE BIOTECHNOLOGY 1023, 1024 (2013).

Perhaps the successful development of this new technology, in the face of considerable uncertainty about the availability of patents, suggests a need to refine the conventional wisdom about the role of patents in providing incentives for biomedical innovation.

IV. LEGAL REGULATION OUTSIDE THE PATENT SYSTEM

Before we discard the conventional wisdom, we should consider two explanations for why this particular technology might flourish in the absence of patents. Both of these explanations are consistent with the familiar story from the pharmaceutical industry that it needs patents to cover high costs of product development. First, perhaps innovators are willing to invest in LDTs only because of the FDA's exercise of administrative discretion, at least so far, to refrain from regulating these products. This explanation leaves open the possibility that patents may be necessary to motivate investment in more heavily regulated therapeutic products such as drugs. Second, perhaps pharmaceutical firms are willing to invest in genetic companion diagnostic products because it helps them to develop and get regulatory approval for lucrative new patent-protected drugs targeted against specific mutations. Indeed, as explained earlier, development and validation of companion diagnostics may accelerate FDA approval of these targeted drugs.

In both of these stories, innovators seek to avoid the costs of FDA regulation and are more inclined to invest in the face of lower regulatory costs and risks. In this sense, these stories are also consistent with broader narratives about costly regulation as a drag on innovation.⁶¹

Neither of these stories explains why laboratories that offer genetic testing of tumor DNA have begun to seek FDA approval of their products, even when it is not legally necessary because the products qualify as LDTs. Laboratories are free to offer these tests without the FDA's blessing, and in fact they are already lawfully offering them before they voluntarily submit applications to the FDA.⁶² Last year, the FDA approved two very similar NGS tests for LDTs that detect mutations in hundreds of genes in tumor DNA samples.⁶³ One

61. DiMasi et al., *supra* note 35, at 26 (noting that for approved drugs, the “fully capitalized total cost estimate is \$2558 million.”).

62. U.S. Food & Drug Admin., Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory-Developed Tests (LDTs), 6 (Oct. 3, 2014), (noting that the FDA does not always enforce LDT regulation), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf> [<https://perma.cc/Ry85-WR63>].

63. Letter from Reena Philip to Christine England (Nov. 15, 2017), https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170058.pdf [<https://perma.cc/Y3C6-LEFZ>] [hereinafter Philip Letter MSKCC]; Letter from Reena Philip to Christine Vietz (Nov. 30, 2017),

application was from Memorial Sloan-Kettering Cancer Center (MSKCC) for FDA clearance of its IMPACT test as a Class II device.⁶⁴ The other was an application from a private firm, Foundation Medicine, for premarket approval of its Foundation One test as a Class III device.⁶⁵ The choices of different regulatory pathways have had interesting consequences that I will consider soon.

But first, why would these laboratories take upon themselves the costs and risks of submitting their products to FDA regulation when FDA does not require it? The short answer is that health insurers were refusing to pay for testing. This itself is a bit of a puzzle, since the cost of testing is trivial compared to the overall costs of cancer care.⁶⁶ It is not obvious why insurers that readily pay in excess of \$100,000 a year for expensive new targeted drugs would decline to pay a few thousand bucks up-front for testing that might reveal in a single test whether the patient is a candidate for any of more than a dozen previously approved cancer therapies.⁶⁷ Some insurers are willing to cover less comprehensive genetic tests that focus only on clinically validated mutations that have been shown to predict treatment response, but not the more-informative tests that sequence more DNA and are likely to reveal mutations of unknown significance in hundreds of genes.⁶⁸ This position follows model coverage guidelines for NGS testing in oncology, as proposed in 2015 by the Green Park Collaborative-USA, a multi-stakeholder program hosted by the nonprofit Center for Medical Technology Policy.⁶⁹

Although the difference in cost between limited testing to detect particular validated mutations and more-comprehensive testing that will reveal many more mutations is small, some insurers see an important principle at stake: their role is to pay for clinically validated care, but not experimental care, and certainly not research.⁷⁰ There is some truth to the charge that coverage for broader genetic testing would have the effect of using insurance to pay for

https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019a.pdf [https://perma.cc/T6MZ-GV5W]
[hereinafter Philip Letter Foundation].

64. Philip Letter MSKCC, supra note 63.

65. Philip Letter Foundation, supra note 63.

66. Rebecca Eisenberg & Harold Varmus, *Insurance for Broad Genomic Tests in Oncology*, 358 SCIENCE 1133, 1134 (2017).

67. *Id.* at 1133–34.

68. Green Park Collaborative. Initial Medical Policy and Model Coverage Guidelines for Clinical Next Generation Sequencing in Oncology, 2 (Aug. 17, 2015), http://www.cmtpnnet.org/docs/resources/Full_Release_Version_August_13__2015.pdf [https://perma.cc/HU2Y-NVJ9].

69. *Id.*

70. Rebecca S. Eisenberg, Shifting institutional roles in biomedical innovation in a learning healthcare system, 14 J. INSTITUTIONAL ECONOMICS 1139, 1141 (2018).

research.⁷¹ Although there is immediate clinical value in genetic testing to identify candidates for targeted therapies, there is also considerable research value in detecting additional mutations in genes that are known to play a role in cancer.⁷² The biological significance of these mutations may not be clear yet, but they are suspects that may prove to be culprits in driving cancers. Tracking these mutations in registries of cancer patients, along with their health records, would provide valuable data for researchers seeking a better understanding of cancer, perhaps enabling future improvements in cancer treatment. NGS testing uncovers both clinically validated mutations that are targeted by FDA-approved drugs and other mutations of unknown significance. In other words, genetic testing has significant value as data collection for research, in addition to its immediate value in matching patients with currently available treatments.

Insurers have a tradition of not paying for research, at least as a formal matter.⁷³ But, in fact, insurers have always paid for innovative treatment choices that have not yet been validated through clinical trials.⁷⁴ Even when FDA requires premarket testing for drugs and medical devices, substantial questions about clinical validity and utility may remain at the point of initial approval—questions that can be answered only in the course of subsequent clinical care.⁷⁵ Many healthcare innovations do not require FDA approval at all. The FDA does not regulate the practice of medicine, and caregivers are free to adopt new innovations in the course of clinical care without first having to await studies that would satisfy the FDA's standards for proof of safety and efficacy.⁷⁶ Insurers might balk at paying for an expensive new procedure, such as autologous bone marrow transplantation for cancer patients, on the grounds that it is experimental, but much experimental medical care flies beneath the radar of insurance gatekeepers and gets covered based on the choices of caregivers.⁷⁷ Insurance coverage is especially important to facilitate innovation in areas that are not regulated by the FDA, because without FDA demanding data from clinical trials, it is less likely that innovators will collect data prior to

71. Eisenberg & Varmus, *supra* note 67, at 1133.

72. *Id.*

73. Eisenberg, *supra* note 71, at 1141, 1150.

74. Richard R. Nelson et al., *How Medical Know-How Progresses*, 40 RESEARCH POL'Y 1339, 1341 (2011); Eisenberg & Varmus, *supra* note 67, at 1134.

75. U.S. Food & Drug Admin., *Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval: Guidance for Industry and Food and Drug Administration Staff*, 9 (2015), <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393994.pdf> [<https://perma.cc/6MUS-UQWS>].

76. Eisenberg, *supra* note 71, at 1143.

77. *Id.* at 1153-54.

clinical use in the course of health care.⁷⁸ Moreover, clinical use is unlikely to proceed in the absence of insurance coverage, making insurance coverage important to spur innovation.

Therein lies the Catch-22 for unregulated NGS genetic testing: insurers will not pay for testing unless the results have validated clinical significance.⁷⁹ Drug companies will pay for premarket validation of the relatively small number of mutations that allow them to get targeted therapies approved by the FDA. But beyond these “druggable” mutations, drug companies have less interest in understanding the clinical significance of the much larger universe of variants in genes that play a role in cancer. Because many of these variants are relatively rare, it is not economically feasible to study them in premarket clinical trials on the scale that drug companies typically undertake in pursuit of FDA approval.⁸⁰ Studies in much larger populations of patients are necessary to correlate these variants with health outcomes in order to validate their clinical significance, a job better done in observational studies in the course of clinical care.⁸¹ But clinical care will not happen without insurance coverage. Validation requires use in clinical care, use in clinical care requires insurance coverage, and insurance coverage requires validation.⁸²

This dilemma highlights an important function of FDA regulation that goes far towards explaining why innovators might seek FDA approval for new technologies that they are free to market without that approval: the FDA performs a technology assessment function that public and private insurers rely on in deciding what they will pay for.⁸³ For public insurance such as Medicare, federal law authorizes payment for “reasonable and necessary” care.⁸⁴ Centers for Medicaid and Medicare Services (CMS) regulations interpret this language to exclude “experimental” care.⁸⁵ Private insurance policies often include similar language, and private insurers often follow the lead of Medicare in deciding what they will cover, although they need not do so as a matter of law.⁸⁶

“Reasonable and necessary” care under the laws governing Medicare coverage is not necessarily the same thing as “safe” and “effective” care under

78. Eisenberg & Varmus, *supra* note 67, at 1133.

79. *Id.*

80. *Id.* at 1134.

81. *Id.*

82. *Id.* at 1133.

83. Eisenberg, *supra* note 71, at 1154.

84. 42 U.S.C. § 1395y(a)(1)(A).

85. 42 C.F.R. § 411.15(o).

86. James D. Chambers et al., Private Payers Disagree with Medicare Over Medical Device Coverage About Half the Time, 34 HEALTH AFFAIRS 1376, 1382 (2015).

the laws administered by the FDA.⁸⁷ Nonetheless, for the most part, health insurers provide coverage of FDA-approved technologies, although they may require prior authorization when cheaper alternatives are available.⁸⁸ Sometimes federal or state law mandates require them to cover these products,⁸⁹ and sometimes they are simply avoiding the burden of conducting their own technology assessment by relying on the FDA's determinations.

This is a significant benefit of FDA approval that may explain why innovators such as Foundation Medicine and MSKCC decided voluntarily to submit their products to FDA regulation even though they are not required to do so. Perhaps they hoped that FDA approval would serve as a good enough proxy for clinical utility to persuade insurers to pay for testing. This is particularly clear in the case of Foundation Medicine, which took advantage of a coordinated parallel review process that involves overlapping review of some new technologies by FDA and CMS in order to facilitate earlier access to new technologies for Medicare beneficiaries.⁹⁰

As I noted earlier, Foundation Medicine and MSKCC pursued different regulatory pathways for similar tests at FDA. Foundation Medicine chose the more arduous pathway. They sought FDA approval of their test as a Class III medical device, calling it a “companion diagnostic” that was intended to be used “to identify patients who may benefit from treatment with” a list of targeted therapies previously approved by FDA “in accordance with the approved therapeutic product labeling,” as well as for “tumor mutation profiling . . . by qualified health care professionals in accordance with professional guidelines.”⁹¹ MSKCC asked FDA to classify their test as a Class II device,⁹² allowing use of the less arduous “premarket clearance” or “510(k)” process.⁹³ To approve this classification, FDA had to determine that the lesser regulatory controls applicable to Class II devices were sufficient to ensure that the device was safe and effective for its intended use.⁹⁴ MSKCC characterized

87. Eisenberg, *supra* note 71, at 1151.

88. 42 U.S.C. § 1396r-8(d)(1)(A).

89. *See* 42 U.S.C. § 1396r-8(d)(2) (requiring state Medicaid programs that choose to cover drug to cover all FDA-approved drugs, with limited exceptions); 42 U.S.C. § 1395x(t)(2)(B) (requiring health insurers to cover all FDA-approved cancer drugs); 42 U.S.C. § 1395w-104(b)(3) (allowing private insurers that provide prescription drug coverage under Medicare Part D to determine which drugs within a therapeutic class to include in preferred formularies).

90. Food and Drug Admin., Centers for Medicare and Medicaid Serv., and Health & Human Services, Program for Parallel Review of Medical Devices, Fed. Reg. 81, 73113, 73114 (Oct. 24, 2016).

91. Philip Letter Foundation, *supra* note 63.

92. Philip Letter MSKCC, *supra* note 63.

93. Federal Food, Drug & Cosmetic Act 510(k), codified as amended at 21 U.S.C. § 360(k).

94. 21 U.S.C. 360c(a).

its product as a “tumor profiling test” that is intended “for use by qualified health care professionals in accordance with professional guidelines,” but unlike Foundation Medicine they did not call it a “companion diagnostic,” instead indicating that it is “not conclusive or prescriptive for labeled use of any specific therapeutic product.”⁹⁵ FDA gave each applicant the approval or clearance it sought. But the difference between FDA’s approval for the Foundation One test as a “companion diagnostic” and clearance for the MSKCC test as a “tumor profiling test” seems to have made a big difference to CMS.⁹⁶

On the same day that FDA approved the Foundation One test as a companion diagnostic, CMS issued a proposed national coverage determination for “Next Generation Sequencing for Medicare Beneficiaries with Advanced Cancer,” opening up a window for the submission of public comments.⁹⁷ Under part A of that proposed decision, CMS would authorize Medicare coverage of NGS testing for Medicare beneficiaries with advanced cancer who have not previously had the same test if the test is “an FDA-approved companion *in vitro* diagnostic” and “used in a cancer with an FDA-approved companion diagnostic indication.”⁹⁸ That was sufficient to provide Medicare coverage for the Foundation One test, because it is an FDA-approved companion diagnostic. But the MSKCC test was a tumor-profiling test, not a companion diagnostic.⁹⁹ Moreover, as a Class II device, it was technically “cleared” through a “premarket notification” process rather than “FDA-approved.”¹⁰⁰ For products that are not companion diagnostics and that are merely “FDA-cleared” rather than “FDA-approved,” CMS proposed more limited coverage under Part B of its proposed decision.¹⁰¹ Under Part B, CMS proposed to authorize “coverage with evidence development,” or CED, only for patients enrolled in certain clinical trials or data registries.¹⁰²

95. Philip Letter MSKCC, *supra* note 63.

96. See Philip Letter MSKCC, *supra* note 63 (noting the device should be classified as Class II); See Philip Letter Foundation, *supra* note 63 (noting the test should be classified as Class III).

97. Philip Letter Foundation, *supra* note 64. See Center for Medicare & Medicaid Serv., Proposed Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (November 30, 2017), <https://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?NCAId=290&bc=AAAAAAAAAAQAAA%3D%3D> [https://perma.cc/3HVB-V9FY].

98. *Id.*; Center for Medicare & Medicaid Serv., Decision Memo for Next Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (March 16, 2018), <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290&bc=AAAAAAAAACAA&> [https://perma.cc/B5PZ-H2CU].

99. See Philip Letter MSKCC, *supra* note 63.

100. 21 U.S.C. § 360c et seq. (requiring only Class III devices go through pre market approval).

101. Center for Medicare & Medicaid Serv., Proposed Decision Memo (November 30, 2017).

102. *Id.*

CED is an interesting innovation that provides Medicare funding for some experimental technologies, but only for use in ongoing studies. The goal of CED is to collect data to permit later evaluation of the technology so that CMS can make a more informed decision about coverage.¹⁰³ CED is an interesting departure from the traditional refusal of insurers to pay for research that would permit insurers to conduct their own technology assessment on the effects of healthcare technologies in clinical use. So far, it has mostly been used for new medical procedures that do not require FDA approval, like autologous bone marrow transplants for cancer patients. Sometimes the result has been to generate data that prevented costly and toxic new technologies from becoming the standard of care.¹⁰⁴ For NGS genetic testing, CED could provide a solution to the Catch-22 problem that arises when insurance coverage is necessary to achieve data collection on a meaningful scale to determine the clinical significance of rare genetic variants. The data collected in patient registries if testing were provided under CED would be a valuable resource for cancer researchers, in addition to its value in assessing clinical outcomes for patients that get testing.

Nonetheless, from the perspective of the laboratories that provide testing, CED is clearly inferior to full coverage not limited to those patients willingly participating in clinical trials or registries. Many patients and caregivers that are interested in genetic testing of their tumors can be expected to prefer to use an FDA-approved test that Medicare will cover without further requirements rather than an otherwise similar test that will be covered only if they are willing to serve as research subjects and make their data available to researchers. The difference in treatment would thus make it advantageous for other testing laboratories to follow the more arduous regulatory path of Foundation Medicine, seeking premarket approval of their tests as Class III companion diagnostic products, rather than the less arduous regulatory path taken by MSKCC, which sought premarket clearance for their test as a Class II tumor

103. Centers for Medicare & Medicaid Serv., Guidance for the Public, Industry, and CMS Staff: Coverage with Evidence Development (Nov. 20, 2014), <https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=27> [<https://perma.cc/NM77-3ADL>].

104. See, e.g., CENTERS FOR MEDICARE & MEDICAID SERV., DECISION MEMO FOR LUNG VOLUME REDUCTION SURGERY (CAG 00115R), 3 (August 20, 2003), <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=96&ver=7&NcaName=Lung+Volume+Reduction+Surgery&SearchType=Advanced&CoverageSelection=Both&NCSelection=NCA%7CCAL%7CNCD%7CMEDCAC%7CTA%7CMCD&ArticleType=Ed%7CKey%7CSAD%7CFAQ&PolicyType=Final&s=—%7C5%7C6%7C66%7C67%7C9%7C38%7C63%7C41%7C64%7C65%7C44&KeyWord=Lung+Volume+Reduction+Surgery&KeyWordLookUp=Doc&KeyWordSearchType=And&kq=true&bc=IAAABAAIAAAA&> (explaining LVRS is appropriate for only certain patients) [<https://perma.cc/GLW3-LN73>].

profiling test. The proposed decision could thus be expected to lead innovators to opt for heightened FDA regulation, even though they are not legally required to incur this more costly burden.

After receiving hundreds of comments on its proposed decision, CMS modified its final national coverage determination to eliminate the provision for CED and to provide full coverage for both “FDA-cleared” and “FDA-approved” tests.¹⁰⁵ But the final decision retains the limitation on coverage to “companion diagnostics,” thus excluding nationwide coverage of the MSKCC test that FDA cleared as a “tumor profiling test,” although regional Medicare Administrative Contractors may provide coverage of other NGS tests within their territories if they so choose.¹⁰⁶ As modified, the decision no longer steers innovators towards a more costly regulatory pathway than FDA requires, so long as the FDA is willing to affirm the utility of the test as a companion diagnostic.¹⁰⁷

The decision memo reads like an exercise in technology assessment by CMS to determine whether NGS testing in cancer patients meets its standards for reasonably and necessary care.¹⁰⁸ It devotes many pages to reviewing the published literature on the clinical utility of NGS testing for cancer patients.¹⁰⁹ Yet little use is made of this bibliography to support the terms of the final national coverage determination.¹¹⁰ In the end, it appears that CMS’s coverage decision rests more on FDA’s technology assessment than on its own.¹¹¹

CONCLUSION

In addition to its role as a regulatory of new medical technologies, FDA plays an important role in technology assessment. FDA approval or clearance of a new technology makes doctors and patients more willing to use it and insurers more willing to pay for it, even when the FDA would otherwise do nothing to stop the technology from reaching the market. Although public and

105. Centers for Medicare and Medicaid Serv., Decision Memo for Net Generation Sequencing (NGS) for Medicare Beneficiaries with Advanced Cancer (CAG-00450N), 3 (March 16, 2018), <https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=290> [hereinafter Final CMS Decision Memo] [<https://perma.cc/KKM2-9YEE>].

106. *Id.*

107. The *Final CMS Decision Memo* notes that after it released its proposed decision, FDA “cleared” a companion diagnostic as a Class II device, indicating FDA’s willingness to use this pathway for companion diagnostics with appropriate evidence. *Id.* at 102.

108. *Id.* at 12–68 (reviewing various articles on clinical trials involving NGS for cancer treatment).

109. *Id.*

110. *Id.* at 3 (stating that coverage expands to those tests that have received FDA approval or clearance).

111. *Id.*

private insurers could and sometimes do perform their own technology assessment, it is often cheaper and easier to free ride on the work done by FDA. The willingness of CMS to provide Medicare coverage for FDA-approved or FDA-cleared NGS genetic tests suggests it is comfortable giving great deference to FDA's technology assessment. Although CMS considered using CED to get more data on the clinical utility of NGS testing for cancer patients, it ultimately decided not to bother. This may have been a missed opportunity to collect more data that could improve cancer care for the Medicare population.

This case study sheds an interesting light on the interacting regulatory regimes that set the stage for biomedical innovation. Patent law is often a crucial part of the regulatory environment that supports biomedical innovation, but not always. With or without patents, innovators cannot make money unless new technologies are adopted. In the healthcare context, this means persuading caregivers to prescribe new products, and persuading insurers to cover them. Sometimes federal and state laws mandate insurance coverage for certain kinds of care, such as FDA-approved cancer drugs, but sometimes it is up to public and private insurers to decide what counts as reasonable and necessary care. Yet even when they are free to make their own coverage determinations, insurers may prefer to rely on the assessments of trusted regulators. This may lead innovators to seek regulatory approval even when regulators do not require it.

You have to look beyond patent law to understand the rules that determine how innovators will pay for the development of new technologies, even within the patent law heartland of biomedical innovation. For now, at least, the end of patents on diagnostics does not seem to mean the end of innovation in this important field. And surprisingly, regulatory entry barriers may prove to be a part of the solution rather than a part of the problem.