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Empirically Assessing Medical Device Innovation

George Horvath*

ABSTRACT

Innovations in medical device technology hold the potential to improve health outcomes across the populace. Nearly half of all medical devices that enter the U.S. market each year are regulated by the Food and Drug Administration (FDA) under the 510(k) pathway. If FDA regulation of 510(k) devices stifles innovation, health outcomes will suffer over time because beneficial devices would not reach patients; on the other hand, if regulation facilitates innovation, health outcomes could improve. Most discussions of innovation under the 510(k) pathway have been either excessively reductionist (such as claims that the pathway stifles innovation) or wholly pessimistic (notably, the Institute of Medicine's conclusion that empirical study of the pathway would not be worth the time, effort, and money involved). Unfortunately, we lack an empirically grounded understanding of how innovation occurs in devices regulated by FDA under the 510(k) pathway, and how FDA regulation worsens or improves health outcomes through its effects on innovation.

This Article applies the "regulatory ancestry" methodology to study innovation in one 510(k) technology space: devices that are used to remove blood clots from the arteries of patients experiencing acute strokes. The study demonstrates that innovation in 510(k) devices occurs in more complex, nuanced ways than existing criticisms have captured. On the surface, competition between device manufacturers appears to be robust, but on closer inspection that competition may be far more limited. Incremental innovation, in which existing devices are modified in relatively limited ways, occurs frequently, but much of this activity involves the combination of existing technologies, as opposed to the incorporation of new technologies. And FDA may be able to strongly channel the direction of innovation through

routine administrative decisions, without the need for rulemaking or other formal procedures.

These and other useful insights and testable hypotheses concerning the effect of FDA regulation on 510(k) device innovation can be gained by using the methodologies adopted in the pilot study presented here. Considering the profound potential for device regulation under the 510(k) pathway to stifle or facilitate innovation, and thus to impact health outcomes, this Article offers a roadmap for a much-needed large scale study that would help to develop a robust, empirically grounded understanding of innovation under 510(k) regulation.

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INTRODUCTION

Not long ago, most medical devices sold in the United States could be characterized by their simple designs and limited purposes.¹ As recently as the mid-20th century, few devices performed critical functions and almost none sustained life on a minute-by-minute basis: Many devices in wide use today, such as the kidney dialysis machine, artificial hip and knee joints, and permanent pacemakers, did not exist prior to mid-1940s.²

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1. I set aside devices that were fairly characterized as nothing more than useless and quite possibly harmful quackery. *See, e.g.,* Jorie Braunold, *How Pseudoscience Generated US Material and Device Regulations*, 23 *AMA J. ETHICS* 721 (2021).

2. *See* Hamid Rabb, Kyungho Lee & Chirag R. Parikh, *Beyond Kidney Dialysis and Transplantation: What's on the Horizon?*, 132 *J. CLINICAL INVESTIGATIONS* 1, 1 (2022) (describing the first successful human hemodialysis machine used in 1943); William H. Harris & Clement B. Sledge, *Total Hip and Total Knee Replacement*, 323 *NEW ENG. J. MED* 725, 725 (1990) (citing the first modern artificial hip joint implanted in 1962); David A. Sonstegard, Larry S. Matthews & Herbert Kaufer, *The Surgical Replacement of the Human Knee Joint*, 238 *SCI. AM.* 44, 45 (1978) (noting that artificial knee joints were first developed in the 1950s); Hiroko Beck et al., *50th Anniversary of the First Successful Permanent Pacemaker Implantation in the United States: Historical Review and Future Directions*, 106 *AM. J. CARDIOLOGY* 810, 810 (2010) (describing the first pacemaker implanted in 1960).

Since then, innovation has altered the face of medical technology to the point where reliance on these devices and many others is taken for granted. Now at the cutting edge (for the moment), 3D printers create prosthetic hands and arms for thousands of amputees,³ mRNA vaccines offer protection against emerging pathogens,⁴ and artificial intelligence and machine learning systems are bruted as the next transformational technologies.⁵

“Innovation,” though, is not a singular process.⁶ Some innovation results in medical devices that so expand the boundaries of what is thought possible that they can be described as transformative. A useful example is provided by implantable cardioverter-defibrillators. Prior to 1980, cardiac patients at risk of sudden death due to arrhythmias had few options beyond a handful of drugs that were either ineffective or dangerous.⁷ The introduction of the first implantable defibrillator that year transformed the possibilities for these patients, providing continuous protection from sudden death without the need for drugs.⁸ Other innovation results in device technologies and uses that are divergent (in the sense of differing to a significant degree from existing technologies) but not transformative. Since 1980, many companies have entered the implantable defibrillator “technology space,”⁹ introducing dozens of defibrillators to the market.¹⁰ Still other innovation consists of smaller, incremental, changes made to existing

3. *About Us*, ENABLING THE FUTURE, <https://enablingthefuture.org/about/> (last visited Mar. 20, 2024).

4. See Hannah Burke, *Top 10 New Medical Technologies 2022*, PROCLINICAL (Apr. 14, 2022), <https://www.proclinical.com/blogs/2022-4/top-10-new-medical-technologies-2022>.

5. See, e.g., U.S. FOOD & DRUG ADMIN., CTR. FOR DEVICES & RADIOLOGIC HEALTH, ARTIFICIAL INTELLIGENCE/MACHINE LEARNING (AI/ML)-BASED SOFTWARE AS A MEDICAL DEVICE (SAMD) ACTION PLAN 1 (2021); W. Nicholson Price II, *Black-Box Medicine*, 28 HARV. J.L. & TECH. 419, 420 (2015).

6. See *infra* Part II.A.

7. Debra S. Echt et al., *Mortality and Morbidity in Patients Receiving Encainide, Flecainide, or Placebo: The Cardiac Arrhythmia Suppression Trial*, 324 NEW ENG. J. MED. 781, 783 (1991) (showing that commonly used drugs increased the risk of sudden death).

8. John P. DiMarco, *Implantable Cardioverter-Defibrillators*, 349 NEW ENG. J. MED. 1836, 1841 (2003).

9. I use the term “technology space” to refer to devices that are indicated for the same use(s) and that have similar modes of operation and design features.

10. DiMarco, *supra* note 8, at 1838.

devices. Over time, defibrillator manufacturers have modified their devices again and again in small steps, a process that can be described as incremental, iterative innovation.¹¹ The accumulation of many such small changes can result in significant changes in device technologies.¹²

A large body of scholarship has examined the impact of Food and Drug Administration (FDA) regulation on pharmaceutical innovation.¹³ However, there are important differences between drugs and devices that limit the relevance of this body of work to device innovation. For pharmaceuticals, changing the active molecule of an existing drug creates a new drug, which must undergo a new FDA evaluation.¹⁴ This limits the extent to which drug makers can engage in incremental, iterative innovation. By contrast, there are many ways to design medical devices for the same purpose, and modifications—as long as they are not substantial—do not necessarily require a new FDA evaluation.¹⁵ Further, drug and device development take place under very different economic models.¹⁶ Another large body of scholarship has focused on the relationship between patent law and medical device innovation.¹⁷ But the barriers to innovation that FDA

11. CENTER FOR DEVICES AND RADIOLOGIC HEALTH, U.S. FOOD & DRUG ADMIN., CDRH INNOVATION INITIATIVE 3 (2011) [hereinafter CDRH INNOVATION INITIATIVE]. To my knowledge, the term “incremental, iterative innovation” is one of my own making.

12. George Horvath, *Trading Safety for Innovation and Access: An Empirical Evaluation of the FDA’s Premarket Approval Process*, 2017 BYU L. REV. 991, 1014 (2017).

13. W. Nicholson Price II, *Making Do in Making Drugs: Innovation Policy and Pharmaceutical Manufacturing*, 55 B.C. L. REV. 491, 494 n.18 (2014) (collecting prior discussions about innovation policy on drug discovery and development).

14. 21 C.F.R. § 310.3(h) (noting that changes to active or inactive ingredients create a new drug).

15. 21 C.F.R. § 807.81(a)(3) (establishing that significant or major changes to already-marketed devices trigger the need for a new 510(k) submission).

16. Josh Makower, Aabed Meer & Lyn Denend, *FDA Impact on U.S. Medical Technology Innovation: A Survey of Over 200 Medical Technology Companies*, MEDTECH EUR., Nov. 2010, at 1, 38 (noting that “investment returns in the device industry are relatively small compared, for example, to those in the biotech and pharmaceutical industries.”).

17. See generally Erika Lietzan, Kristin M.L. Acri & Evan Weidner, *The Case of Missing Device Patents, Or: Why Device Patents Matter*, 33 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 409 (2023); Brenda M. Simon, *Patents, Information, and Innovation*, 85 BROOK. L. REV. 727 (2020); Adam Lewin, *Note: Medical Device Innovation in America: Tensions Between Food and Drug Law and Patent Law*, 26 HARV. J.L. & TECH. 403 (2013).

regulation creates are distinct from those created by patent law. Thus, the existing bodies of scholarly work tell us little about the relationship of regulation and innovation in the medical device world.

Some critical attention has focused on how innovation occurs in the largest set of devices that the Food and Drug Administration evaluates before they reach the U.S. market. These devices, which are deemed to pose an intermediate level of risk, are regulated under the so-called 510(k) pathway. Industry participants have consistently painted the pathway as overly burdensome, delaying and even preventing some devices from entering the U.S. market.¹⁸ Many critics have proposed reforms, which at the extreme, advocate for the replacement or even the elimination of 510(k) pathway.¹⁹ But the empirical basis for these criticisms and reform proposals is quite limited. A 2011 report by Institute of Medicine²⁰ concluded that empirical assessment of innovation in the complex world of 510(k) devices would not be worth the time, effort, and money involved.²¹

Unfortunately, we lack a comprehensive account of how innovation takes place in the tens of thousands of devices that are regulated under the 510(k) pathway. We also lack an understanding of how innovation in these devices differs from innovation in high-risk devices regulated under the more rigorous Premarket Approval (PMA) pathway, to which the 510(k) pathway is frequently compared. The goal of this Article is to begin to build such an account by using an empirical analysis of innovation in cohorts of medical devices in similar technology spaces: 510(k) and PMA devices that are intended for

18. See *infra* Part II.B.

19. Bonnie Scott, *Oversight Overhaul: Eliminating the Premarket Review of Medical Devices and Implementing a Provider-Centered Postmarket Surveillance Strategy*, 66 FOOD & DRUG L.J. 377, 398 (2011); NOEL D. CAMPBELL, POLICY ANALYSIS: REPLACE FDA REGULATION OF MEDICAL DEVICES WITH THIRD-PARTY CERTIFICATION 1 (Cato Inst. 1997).

20. The Institute of Medicine (IoM) was renamed The National Academy of Medicine. Because the 2011 Report was issued under the IoM name, I refer to the Academy as the Institute or IoM throughout. *About the National Academy of Medicine*, NAT'L ACAD. MED., <https://nam.edu/about-the-nam> (last visited Mar. 20, 2024).

21. INSTITUTE OF MEDICINE, MEDICAL DEVICES AND THE PUBLIC'S HEALTH: THE FDA 510(K) CLEARANCE PROCESS AT 35 YEARS 25 (2011) [hereinafter INSTITUTE OF MEDICINE 2011].

use in the cerebral arteries of patients experiencing acute strokes.²²

Since the Institute of Medicine's 2011 report, three significant developments suggest that such an endeavor has become feasible. First, publications in the medical literature have demonstrated the utility of the regulatory ancestry methodology, in which information that is publicly available from FDA's websites is used to reconstruct the web of device relationships, making it possible to trace how 510(k) device technology has evolved.²³ Second, the information that is available through FDA's websites has grown more robust and easily accessible. And third, computer coding languages that can automate the acquisition of this data, large language model artificial intelligence systems that can assist in data extraction, and techniques for network visualization and analysis have become better developed and more broadly accessible. Considering that some critics of the 510(k) pathway have called for its replacement or elimination—which would disrupt vast amounts of medical device innovation—it is past time to challenge the Institute of Medicine's pessimistic conclusion about the feasibility and value of empirical study of innovation in 510(k) devices.

This Article begins in Part I by providing the statutory and regulatory details of medical device regulation, focusing on how regulation addresses innovation. Part II develops a working definition of the term “innovation” that will be used in the empirical study to be presented. Part II then reviews the existing analyses and criticisms of the ways in which the 510(k) pathway affects innovation and argues that existing criticisms and reform proposals rest on a needlessly thin layer of empirical data. Part III introduces the regulatory ancestry methodology to readers of legal scholarship. Part IV presents a small pilot study that applies this methodology to one medical technology space, which consists of devices that are intended for the use in removing blood clots from the cerebral vessels in patients experiencing acute strokes. Part V draws a number of conclusions from the study and argues, contrary to the Institute of Medicine, that

22. This Article is a companion to a previously published pilot empirical study of 510(k) device safety. George Horvath, *Empirically Assessing 510(k) Device Safety*, 63 JURIMETRICS J. 113 (2023).

23. See *infra* Part III.

empirical evaluation of innovation under the 510(k) pathway is both feasible and valuable.

I. MEDICAL DEVICE REGULATION FROM AN INNOVATION PERSPECTIVE

Congress created the modern federal regulatory regime for medical devices with the passage of the Medical Device Amendments of 1976 (MDA or Act).²⁴ The Act tasked FDA with balancing an unwieldy set of policy objectives. Congress required the Agency to ensure that devices were safe and effective.²⁵ But Congress also sought to minimize any stifling effect on innovation that the new regulatory regime would have. Statements by many of the Act's sponsors reflect a deep concern with ensuring that the benefits of medical device innovation were sustained. Senator Javits, who introduced the bill along with Senator Kennedy, begin his remarks by listing many recent device innovations:

Electronic miniaturization, plastics, new methods of sterilization, and other advances in technology have worked a revolution in biomedical engineering. They have given us artificial heart pacemakers; kidney dialysis units; defibrillators; modern anesthetic equipment; cardiac, renal, and other catheters; surgical implants; artificial veins, arteries, and heart valves; intensive-care monitoring units; and a myriad of diagnostic and therapeutic instruments.²⁶

Javits noted that “[t]hese devices have saved many lives and contributed to better health care.”²⁷ In its final report, the House Committee on Interstate and Foreign Commerce described the MDA as being “intended to assure that the public is protected from unsafe and ineffective medical devices, that health

24. Medical Device Amendments of 1976, Pub. L. No. 94-295, 90 Stat. 539 (codified as amended in 21 U.S.C. § 360c and following sections).

25. *Id.* at 540 (specifying the levels of regulatory control required to ensure the safety and effectiveness of devices depending on their level of risk). *See also id.* at 539 (stating that the Act's purpose was “to provide for the safety and effectiveness of medical devices intended for human use”); S. REP. NO. 94-33, at 6 (1975) (justifying the need for federal regulation on several widely-publicized public health fiascos arising from the Dalkon Shield IUD, artificial heart valves, and permanent pacemakers); 121 CONG. REC. S1859 (daily ed. Jan. 30, 1975) (statement of Sen. Ted Kennedy) (stating that Congress's purpose was to give FDA “the necessary authority to require that medical devices be proven safe and effective before they reach the American consumer.”).

26. 121 CONG. REC. 10692 (daily ed. Apr. 17, 1975) (statement of Sen. Jacob Javits).

27. *Id.*

professionals have more confidence in the devices they use or prescribe, *and that innovations in medical device technology are not stifled by unnecessary restrictions.*²⁸ Representative Carter, a cosponsor of the House bill, also spoke of “the development of many lifesaving and life-sustaining devices” over the preceding two decades and of the “need to continue to encourage scientific investigation and to assure product innovation.”²⁹ As the Government Accountability Office (GAO) noted in a 1988 report, “Congress was concerned with . . . not unduly restricting development of innovative devices or improvements to existing devices.”³⁰

Beyond this, Congress has over the past few decades also espoused an even more ambitious policy goal: that FDA regulation should actually facilitate innovation.³¹ Writing in the prescription drug context, Professor Rebecca Eisenberg observed that “in the past twenty years Congress has repeatedly fine-tuned FDA’s mandate . . . in ways that might be better understood in terms of innovation policy.”³² This observation applies with equal force to medical device regulation.³³ Congress amended FDA’s Mission Statement, which now commits the Agency to “advancing the public health by helping to speed innovations that make medical products more effective, safer,

28. H.R. REP. NO. 94-853, at 12 (1976) (emphasis added).

29. 122 CONG. REC. 5851, 5852 (daily ed. Mar. 9, 1976) (statement of Rep. Tim Carter).

30. U.S. GOV’T ACCOUNTABILITY OFF., GAO-88-14, MEDICAL DEVICES: FDA’S 510(K) OPERATIONS COULD BE IMPROVED 11 (1988). *See also* Ralph F. Hall & Eva Stensvad, *A Failure to Comply: An Initial Assessment of Gaps in IOM’s Medical Device Study Committee*, 12 MINN. J.L. SCI. & TECH. 731, 733 (2011) (describing FDA’s responsibilities); Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1800 (1996) (describing FDA’s responsibilities before and after the Medical Device Amendments).

31. S. REP. NO. 94-33, at 2 (1975) (“[S]ophisticated, critically important medical devices . . . hold the promise of improving the health and longevity of the American people. The Committee wants to encourage their research and development.”).

32. Rebecca S. Eisenberg, *The Role of the FDA in Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345, 348 (2007).

33. *See* Food & Drug Admin. Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, 2369 (codified at 21 U.S.C. § 393(b)(1)) (adding to FDA’s mission statement a focus on prompt and efficient review and action to ensure “the marketing of regulated products in a timely manner”).

and more affordable.”³⁴ In recent years FDA has also emphasized the importance of facilitating device innovation as a regulatory objective, as it did in a set of proposals in a 2011 white paper, stating that

[t]he Food and Drug Administration’s (FDA) Center for Devices and Radiological Health (CDRH or the Center) is responsible for advancing public health and facilitating innovation to help bring novel technologies to market and make the medical devices that are already on the market safer and more effective.³⁵

Indeed, the architecture of the regulatory system established by the MDA clearly reflects the importance Congress attributed to innovation policy goals. The Act created a three-tiered classification scheme based on an *ex ante* assessment of device risk, and of three levels of regulatory requirements, or pathways to the U.S. market, that are now largely congruent with the risk tiers. Under this scheme, the impact of regulation on both safety and innovation escalates as the risk classification increases, with low risk (Class I) devices receiving no premarket scrutiny,³⁶ intermediate risk (Class II) devices receiving limited scrutiny,³⁷ and high risk (Class III) devices facing a relatively rigorous premarket evaluation.³⁸

None of this is meant to argue that Congress has prioritized innovation over safety and innovation. It is meant, however, to respond to those who would dismiss innovation as a policy goal of the original MDA and of device regulation more recently, demonstrating the importance of that goal.

Although interest often focuses on how to regulate transformative innovations, most medical device innovation follows a more prosaic course. In FDA’s words, most innovation is iterative in nature.³⁹ Manufacturers constantly introduce devices that are “modified version[s] of an already marketed model, or a novel application of existing tools or scientific

34. *What We Do: FDA Mission*, U.S. FOOD & DRUG ADMIN. (Nov. 21, 2023), <https://www.fda.gov/about-fda/what-we-do>.

35. CDRH INNOVATION INITIATIVE, *supra* note 11, at 3.

36. 21 C.F.R. § 890.3150, 21 C.F.R. § 880.5075 (including crutches and elastic bandages).

37. 21 C.F.R. § 892.1710, 21 C.F.R. § 874.3305 (including mammographic x-ray systems and many types of hearing aids).

38. 21 C.F.R. § 870.3925, 21 C.F.R. § 882.5820 (including replacement heart valves and implanted cerebellar stimulators).

39. CDRH INNOVATION INITIATIVE, *supra* note 11, at 4–5.

approaches.”⁴⁰ FDA regulation must attend to this entire spectrum of innovation. But to date little attention has focused on how to regulate this incremental innovation.

Presentations of the statutory and regulatory framework for device regulation have almost exclusively focused on how that framework seeks to ensure safety. That is, most presentations explain the assignment of a regulatory pathway based solely on a device’s risk classification. This Part presents the device regulatory framework from the perspective of how it addresses innovation and how the assignment of a regulatory pathway is determined both by the risk classification and by the kind of innovation that characterizes the development of that device.

Parts I.A through I.D discuss the statutory and regulatory provisions relevant to high-risk devices that are divergent or transformative, high-risk devices that are iteratively modified versions of existing devices, intermediate-risk devices that are iterative versions of existing devices, and divergent or transformative intermediate-risk devices, respectively.

A. REGULATING DIVERGENT AND TRANSFORMATIVE INNOVATION IN HIGH-RISK DEVICES: THE PMA PATHWAY

Medical devices are defined as high-risk, or Class III, if their safety cannot be assured through the general controls that apply to all medical devices and any special controls that apply to their generic device type.⁴¹ These Class III devices are required to successfully navigate the relatively rigorous Premarket Approval (PMA) process in order to reach the U.S. market. But devices submitted for PMA approval are also characterized by their innovation: PMA devices are typically the result of either

40. *Id.* at 4.

41. 21 U.S.C. § 360c(a)(1)(B). A generic device type is “a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.” 21 C.F.R. § 860.3. Devices are assigned to one of sixteen broad classifications based on their medical specialty. 21 C.F.R. §§ 862–892. For example, devices intended for use in the cardiac and vascular systems are assigned to the Cardiovascular Panel. 21 C.F.R. § 870. Within each classification, devices are assigned to specific regulatory categories. For example, diagnostic catheters assigned to the Cardiovascular Panel are governed by the regulations for the generic device type. 21 C.F.R. § 870.1250. Within each generic device type, devices may be administratively segregated into distinct product codes.

transformative innovation, such as the first implantable cardiac defibrillator, which FDA approved in 1985,⁴² or divergent innovation, in that they are neither transformative nor merely modified versions of other devices, such as the many subsequently approved implantable defibrillators.⁴³

To gain PMA approval, the manufacturer is required to submit evidence that provides a reasonable assurance that the device is safe and effective.⁴⁴ The required evidence includes “full reports of all information . . . concerning investigations which have been made to show whether or not such device is safe and effective.”⁴⁵ FDA’s decision whether to approve a PMA application is typically to be made “on the basis of well-controlled investigations, including 1 or more clinical investigations.”⁴⁶ The extensive information in an original PMA application, often running to several thousand pages, is reviewed by an independent panel of experts in the practice area into which the device is classified.⁴⁷ Once a device is approved, the manufacturer is required to adhere to the design, manufacturing, and labeling specifications contained in its PMA application.⁴⁸ Through these requirements, Congress created a

42. See Premarket Approval (PMA), U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P830060> (last updated Mar. 18, 2024) (listing the earliest PMA approval for the Ventak cardioverter defibrillator system as October 4, 1985, under the product code LWS).

43. Since FDA approved the Ventak, it has granted fifteen more original PMA approvals for new defibrillators bearing the same product code (LWS).

44. 21 U.S.C. § 360e(c)(1)(A).

45. *Id.* Manufacturers must also submit “a full statement of the components, ingredients, and properties and of the principle or principles of operation;” “a full description of the methods used in, and the facilities and controls used for, the manufacture” of the devices; “samples of such device and of components thereof;” “the labeling proposed to be used;” and “such other information relevant to the subject matter of the application.” 21 U.S.C. § 360e(c)(1).

46. § 360c(a)(3)(A). The provision that follows provides some latitude for the optional use of “valid scientific evidence” other than studies conducted in accordance with § 360c(a)(3)(A). See § 360c(a)(3)(B).

47. 21 U.S.C. § 360e(c)(3), 21 U.S.C. § 360c(b)(2).

48. § 360e(d)(5)(A)(i) (“[A] supplemental application shall be required for any change to a device subject to an approved application under this subsection that affects safety or effectiveness”); 21 C.F.R. § 814.80 (2017) (“A device may not be manufactured, packaged, stored, labeled, distributed, or advertised in a manner that is inconsistent with any conditions to approval specified in the PMA approval order for the device.”).

stringent process for the evaluation of the safety of high-risk devices.

These stringent requirements add to the development timelines and costs for Class III devices, and thus have an innovation-stifling effect. In one widely-quoted survey of a non-randomly selected cohort of device manufacturers, the mean reported interval between the initial contact with FDA and a final PMA approval was fifty-four months.⁴⁹ The costs of developing Class III devices were estimated at \$94 million,⁵⁰ much of which arose from these regulatory requirements. Admittedly, these estimates reflect a commitment of time, effort, and capital that are an order of magnitude smaller than the burdens imposed by the New Drug Application (NDA) process required for new pharmaceuticals. But the market for Class III devices is typically much smaller than for many drugs, and the life cycle of devices, which is on the order of two to three years or less, is far shorter than that of drugs.⁵¹ Thus, there is reason to believe that the PMA pathway stifles at least some innovation of transformative and divergent devices categorized as high risk.

B. REGULATING ITERATIVE INNOVATION IN HIGH-RISK DEVICES: PMA SUPPLEMENTS

Manufacturers of Class III devices that have received premarket approval by FDA will frequently wish to modify these devices, to address safety and effectiveness limitations that have been found once the devices are in widespread use, to incorporate new technological developments, and for a host of other reasons. Requiring manufacturers to submit a new PMA application, complete with clinical studies and thousands of pages of documentation for every modification of a PMA-approved device would impede incremental, iterative innovation. In fact, such a requirement might well compromise safety if the regulatory burden disincentivized manufacturers

49. Makower et al., *supra* note 16, at 23.

50. *Id.* at 28.

51. Compare INSTITUTE OF MEDICINE, WORKSHOP REPORT: PUBLIC HEALTH EFFECTIVENESS OF THE FDA 510(K) CLEARANCE PROCESS 20 (Theresa Wizemann ed., 2010) (noting that the standard medical device life cycle is eighteen to twenty-four months), with Hans H. Bauer & Marc Fischer, *Product Life Cycle Patterns for Pharmaceuticals and Their Impact on R&D Profitability of Late Mover Products*, 9 INT'L BUS. REV. 703, 703 (2000) (noting that successful drugs may pay back the costs of their development over a period of fifteen to twenty years).

from making improvements to their existing PMA devices. To address these concerns, the FDA Modernization Act of 1997 created a number of abbreviated PMA Supplement processes through which manufacturers may gain approval for relatively minor design, labelling, and manufacturing process changes to their approved devices without a full PMA submission.⁵² These include Real-Time Supplements, Manufacturing Site Change Notices, and 30-Day Notices.⁵³ The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) added several additional categories of supplemental PMAs, two of which allow for more significant modifications.⁵⁴ Panel Track Supplements are indicated for modifications that result in “a significant change in design or performance of the device, or a new indication for use of the device, and for which substantial clinical data are necessary to provide a reasonable assurance of safety and effectiveness.”⁵⁵ Panel Track Supplements require the

52. Food and Drug Administration (FDA) Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296, 2338 (codified at 21 U.S.C. § 360e(d)(6)(A)(i)); 21 C.F.R. § 814.39(a)(6) (2002) (allowing manufacturers to make changes in device labeling, indications for use, and manufacturing site or processes, and “changes in the performance or design specifications, circuits, components, ingredients, principles of operation, or physical layout of the device,” among other reasons).

53. Real-Time Supplements are indicated for “minor change[s] to the design of the device, software, sterilization, or labeling.” U.S. FOOD & DRUG ADMIN, GUIDANCE FOR INDUSTRY AND FDA STAFF: MODIFICATIONS TO DEVICES SUBJECT TO PREMARKET APPROVAL (PMA) - THE PMA SUPPLEMENT DECISION-MAKING PROCESS 15–17 (2008) (mentioning changes to the circuitry controlling a ventricular assist device’s battery usage, the sterilization procedure used for cardiac ablation catheters, and the method of bonding a balloon to the catheter in a transurethral microwave ablation system) [hereinafter FDA 2008 GUIDANCE]. Typically, these applications are supported only by bench testing. *Id.* at 15–17. Manufacturing Site Change Notices are indicated for a change to the “facility or establishment to manufacture, process, or package the device.” *Id.* at 21. Changes-Being Effected Notices are used when a manufacturer first learns of information about device safety that was not previously submitted to FDA, and which prompts “labeling changes that add or strengthen a contraindication, warning, precaution, or information about an adverse reaction for which there is reasonable evidence of a causal association.” *Id.* at 17. Finally, 30-Day Notices permit “a PMA applicant to submit written notification to the agency of a modification to the manufacturing procedure or method of manufacture affecting the safety and effectiveness of the device rather than submitting such change as a PMA supplement.” *Id.* at 19.

54. Pub. L. No. 107-250, 116 Stat. 1588, 1589-90 (codified in several provisions of the Food, Drug, and Cosmetic Act); FDA 2008 GUIDANCE, *supra* note 53, at 2 n.2.

55. FDA 2008 GUIDANCE, *supra* note 53, at 7–11 (citing as examples a new surgical usage of a laser originally used to reshape the outer surface of the

submission of “substantial clinical data.”⁵⁶ 180-Day Supplements are indicated for modifications involving “a significant change in components, materials, design, specification, software, color additives, or labeling.”⁵⁷

Modifying an approved device through the PMA Supplement pathways is far less burdensome than obtaining an original PMA approval. Most of the required information disclosures have already been completed through the original PMA process. For modifications through the PMA Supplements, typically “only new preclinical testing is needed to demonstrate reasonable assurance of safety and effectiveness of the modified device.”⁵⁸ The only PMA Supplement pathway that routinely requires clinical trial evidence of safety and effectiveness is the infrequently used Panel Track Supplement pathway. Even when data is necessary to support a PMA Supplement, FDA is statutorily limited to requiring only data related to the specific changes being made.⁵⁹ Clinical data about the overall safety of the modified device is rarely required.⁶⁰ Thus, FDA regulation would be expected to impose a far lower burden on the incremental, iterative innovation of already-approved devices than on the transformative or divergent innovation that leads to new Class III devices.

cornea to correct poor vision, adding a surgical usage to cut the cornea and then reshape the cornea’s inner surface; and a request for approval for use an artificial heart valve originally approved for use in the aortic position, for use in the mitral position).

56. *Id.* at 7.

57. *Id.* at 11–14 (citing as examples changes in the way the material used in aortic stent was woven together, and changes in the power supply of a ventricular assist device from compressed air to electricity).

58. *Id.* at 11.

59. 21 C.F.R. § 814.39(c) (“[T]he information required in a supplement is limited to that needed to support the change.”).

60. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SUPPLEMENTS TO APPROVED APPLICATIONS FOR CLASS III MEDICAL DEVICES: USE OF PUBLISHED LITERATURE, USE OF PREVIOUSLY SUBMITTED MATERIALS, AND PRIORITY REVIEW 7 (1998) (“Nonclinical data may be sufficient to demonstrate that the design/product modification creates the intended additional capacity, function, or performance of the device. The new provision clarifies, however, that FDA may require, when necessary, additional clinical data to evaluate the modification of the device to provide a reasonable assurance of safety and effectiveness.”).

C. REGULATING ITERATIVE INNOVATION IN INTERMEDIATE-RISK DEVICES: THE 510(K) PATHWAY

When the MDA took effect on May 28, 1976, about 40,000 medical devices were already being sold on the U.S. market.⁶¹ For these pre-amendment devices, the Act created a mechanism through which FDA was to assign each to one of the three risk classes.⁶² FDA promulgated regulations that define and establish requirements for all devices within each generic type.⁶³ The Agency classified the majority of pre-amendment device types as Class I (low risk) or Class II (intermediate risk).⁶⁴ These devices were grandfathered onto the market, with their manufacturers subjected only to FDA's post-market authorities.⁶⁵

The MDA established that all devices that were not on the market as of May 28, 1976 (known as post-amendment devices), were presumptively defined as Class III devices.⁶⁶ Thus, all of the post-amendment devices that would be developed would have been subjected to the regulatory burdens of the PMA process, while pre-amendment devices were subjected only to FDA's post-market requirements. This would have unfairly disadvantaged the manufacturers of low- and intermediate-risk (Class I and Class II) post-amendment devices and inhibited the introduction of innovative new technologies. Further, manufacturers who were marketing pre-amendment devices that FDA had classified as Class I or Class II would be required to submit new PMA applications if they substantially modified their devices. This would have had the effect of inhibiting the incremental innovation (and presumably the improvement) of existing low- and intermediate-risk devices.

The MDA contained a statutory provision—the 510(k) provision—that was intended to mitigate these adverse consequences. The pathway provides manufacturers with a

61. H. SUBCOMM. ON OVERSIGHT AND INVESTIGATIONS, COMM. ON ENERGY & COM., 98TH CONG., MEDICAL DEVICE REGULATION: THE FDA'S NEGLECTED CHILD 14 (Comm. Print 1983).

62. Medical Device Amendments of 1976, Pub. L. 94-295 § 513(b), 90 Stat. 539, 542 (codified as amended at 21 U.S.C. § 360c(b)).

63. *Id.*

64. Merrill, *supra* note 30, at n.182.

65. *Id.* at 1817.

66. Medical Device Amendments of 1976, Pub. L. 94-295 § 513(a), 90 Stat. 539, 540 (codified as amended at 21 U.S.C. § 360c(a)).

mechanism through which they can obtain a lower risk classification—and a less burdensome set of regulatory requirements—for their post-amendment devices. To do so, the manufacturer of a new post-amendment device (a subject device) is required to demonstrate that the subject device is “substantially equivalent” to an already-marketed predicate device.⁶⁷ If the manufacturer can demonstrate substantial equivalence, the subject device is assigned to the same risk class—and subjected to the same regulatory requirements—as its pre-amendment predicate.⁶⁸ Thus, subject devices for which a manufacturer can demonstrate substantial equivalence to a Class II predicate will be assigned the same Class II risk classification.⁶⁹ Although the original MDA permitted manufacturers to cite only pre-amendment devices as predicates, FDA quickly adopted a practice of clearing new devices if they were shown to be substantially equivalent to a pre- or a post-amendment predicate. The Safe Medical Device Act of 1990 (SMDA)⁷⁰ authorized this practice in 1990.⁷¹ This created the legal framework for a process of piggybacking, in which a device (call it D_0) can serve as the predicate for a new subject device (D_1), with D_1 later serving as the predicate for an even newer device, D_2 , which itself later serves as the predicate for D_3 , and so on.⁷²

A device that FDA agrees is substantially equivalent to an already-cleared Class II device must comply with general controls such as registering annually with FDA, ensuring that the device labeling comports with FDA regulations, and following published Good Manufacturing Practices.⁷³ Class II devices are additionally required to comply with any special controls (such as performance standards) that FDA may

67. Merrill, *supra* note 30, at 1817.

68. *Id.*

69. *Id.* at 1819. The 1997 FDA Modernization Act exempted most Class I and a small number of Class II devices from premarket notification requirement. FDA Modernization Act of 1997, Pub. L. 105-115 § 206, 111 Stat. 2296, 2339-2340 (codified as amended at 21 U.S.C. § 360e(d)).

70. Safe Medical Devices Act of 1990, Pub. L. 101-629, § 12(a), 104 Stat. 4511, 4523 (codified as amended at 21 U.S.C. § 360c(i)(1)(A)).

71. *Id.* (providing that any legally marketed device may serve as a predicate).

72. Rodney R. Munsey, *Trends and Events in FDA Regulation of Medical Devices over the Last Fifty Years*, 50 FOOD & DRUG L.J. 163, 169 (1995).

73. See 21 U.S.C. § 360c.

promulgate for each generic device type.⁷⁴ Manufacturers are required to inform FDA “at least ninety days before making such introduction or delivery” to the market.⁷⁵ Under current law, the device may not be marketed until FDA has made a substantial equivalence finding.⁷⁶

Establishing that a subject device is substantially equivalent to its predicate does not require that the devices be identical.⁷⁷ The SMDA established that “compared to a predicate device, that the device has the same intended use” and that the subject device:

- (i) has the same technological characteristics as the predicate device, or
- (ii)(I) has different technological characteristics and the information submitted . . . demonstrates that the device is as safe and effective as a legally marketed device, and
- (II) does not raise different questions of safety and effectiveness than the predicate device.⁷⁸

The statute defined “different technological characteristics” as “a significant change in the materials, design, energy source, or other features of the device.”⁷⁹ FDA regulations define a significant change as:

- (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device . . .
- (ii) A major change or modification in the intended use of the device.⁸⁰ The determination of whether a change is sufficiently significant to

74. 21 U.S.C. § 360c(a)(1)(B).

75. Medical Device Amendments of 1976, Pub. L. 94-295, § 510(k) 90 Stat. 539 (codified as amended at 21 U.S.C. § 360(k)). Originally, manufacturers could market their device if FDA did not object within ninety days; under current law, manufacturers must await an FDA determination of substantial equivalence before marketing the new device.

76. Until FDA makes a substantial equivalence determination, the subject device is by default a Class III device and can only be marketed after the Agency grants a PMA. 21 U.S.C. § 360c(c)(1)(C).

77. According to FDA, it is rare for a subject device to be identical to its predicate. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: THE 510(K) PROGRAM: EVALUATING SUBSTANTIAL EQUIVALENCE IN PREMARKET NOTIFICATIONS [510(K)] 6 (2014).

78. Safe Medical Devices Act of 1990, Pub. L. 101-629, § 12(a), 104 Stat. 4511, 4523 (codified as amended at 21 U.S.C. § 360c(i)(1)(A)).

79. 21 U.S.C. § 360c(i)(1)(B).

80. 21 C.F.R. § 807.81(a)(3) (2024).

require a new 510(k) submission is left to the manufacturers in the first instance, with FDA guidance and oversight.⁸¹

The 510(k) pathway was intended largely as a gap-filler, designed to prevent the manufacturers of pre-amendment devices from obtaining an unfair market advantage over the manufacturers of post-amendment devices and to enable pre-amendment device makers to modify their devices without confronting the burdens of a PMA application.⁸² But in the years following the effective date of the MDA, the 510(k) pathway provided the path to the U.S. market for Class I, II, and for many III devices. Later, the 1997 FDA Modernization Act⁸³ exempted most Class I and a small number of Class II devices from premarket notification requirement.⁸⁴ FDA eventually completed the process of ordering PMA submissions for all generic types of Class III devices in 2019.⁸⁵ Thus, demonstrating substantial equivalence under the 510(k) pathway now functions as the primary route to the U.S. market for the majority of Class II devices, which comprise the majority of devices bound for the market for which FDA conducts any premarket evaluation.⁸⁶

FDA's authority to require clinical data for 510(k) submissions is limited: the Agency may only require data to determine if an indication falls within the intended use the manufacturer claims or where the subject device has different technological characteristics from the predicate device.⁸⁷ The data must be necessary to establish that the subject device is as safe and effective as the predicate, and the Agency's request

81. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: DECIDING WHEN TO SUBMIT A 510(K) FOR A CHANGE TO AN EXISTING DEVICE 8–11 (2017).

82. Rachel E. Sachs, *Regulating Intermediate Technologies*, 37 YALE J. ON REGUL. 219, 245 (2020); Jonathan S. Kahan, *Premarket Approval Versus Premarket Notification: Different Routes to the Same Market*, 39 FOOD DRUG & COSM. L.J. 510, 514 (1984).

83. FDA Modernization Act of 1997, Pub. L. 105-115, 111 Stat. 2296 (codified in scattered provisions of 21 U.S.C.).

84. *Id.* at § 206, 111 Stat 2339-40.

85. See *515 Project Status*, US FOOD & DRUG ADMIN., <https://www.fda.gov/about-fda/cdrh-transparency/515-project-status> (last updated Dec. 20, 2019) (showing that all remaining pre-amendments devices have been classified).

86. Merrill, *supra* note 30, at 1819. Formal review of evidence of safety and effectiveness is neither required nor common in 510(k) submissions. Thus, devices entering the market through the 510(k) pathway are said to be “cleared,” as opposed to devices that are “approved” through the PMA pathway.

87. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 89.

must satisfy the requirements imposed by the Least Burdensome Principle.⁸⁸ Given these limitations, FDA and GAO reported that in the first decade of the 21st century only 10–15% of 510(k) submissions included clinical trial data.⁸⁹ For devices other than in vitro diagnostic tests, only 8% of 510(k) submissions contained clinical trial data.⁹⁰

These statutory and regulatory provisions create what is arguably a relatively non-burdensome framework for regulating the incremental innovation for intermediate-risk devices. The provisions are not intended to allow transformative devices and devices that are technologically remote from any already-marketed devices to reach the market through 510(k) clearance.⁹¹ The provisions permit an endless series of iterative changes to be made to Class II devices and only rarely impose requirements for clinical trial data. As a result, most (but not all) commentators have described the 510(k) pathway as more innovation friendly than the PMA pathway.⁹² While almost certainly correct, it is important to recognize that the 510(k) and PMA pathways regulate different kinds of innovation as well as devices in different risk categories: incremental, iterative innovation is regulated under the former, and transformative or divergent innovation under the latter. Little has been written about a more germane comparison, the relative burdens imposed on the incremental, iterative innovation of intermediate risk devices under the 510(k) pathway and of high-risk devices under the PMA supplement pathways.

D. REGULATING DIVERGENT AND TRANSFORMATIVE INNOVATION IN INTERMEDIATE-RISK DEVICES: THE DE NOVO PATHWAYS

Some divergent (and all transformative) devices differ from already-marketed devices to an extent that is sufficient to

88. *Id.* at 107–08.

89. U.S. GOV'T ACCOUNTABILITY OFF., MEDICARE DURABLE MEDICAL EQUIPMENT: CLASS III DEVICES DO NOT WARRANT A DISTINCT ANNUAL PAYMENT UPDATE 8 (2006).

90. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 108.

91. Such devices would not satisfy the substantial equivalence standard to any potential predicate device. Manufacturers of such devices could either navigate the PMA process for Class III devices or could seek a lower risk classification through the De Novo pathways. *See infra Part I.D.*

92. *See, e.g.,* Sachs, *supra* note 82, at 246; James M. Flaherty, *Defending Substantial Equivalence: An Argument for the Continuing Validity of the 510(k) Premarket Notification Process*, 63 FOOD & DRUG L.J. 901, 926 (2008).

preclude a finding of substantial equivalence. Under the original MDA, such devices would have been assigned to Class III status and their manufacturers would have been required to submit full PMA applications. Clearly, though, some new devices might present low or intermediate levels of risks. For such devices, compliance with general controls and, if relevant, special controls would be sufficient to provide a reasonable assurance of safety. In such cases, manufacturers of post-amendment devices may be able avoid the need for an extensive PMA submission by utilizing one of the De Novo processes. In 1997, the FDA Modernization Act created a mechanism through which a manufacturer who had submitted a 510(k) application and received a “not substantially equivalent” (NSE) determination by FDA could petition the Agency for reclassification to a lower risk class.⁹³ In 2012, the FDA Safety and Innovation Act added a mechanism through which a manufacturer who determines prior to making a 510(k) submission that no substantially equivalent predicate exists can petition the Agency to reclassify the device without waiting for an NSE determination.⁹⁴ De Novo devices, once assigned a Class I or II risk classification, are subjected to the same regulatory requirements and their predicates and can serve as the predicates for later 510(k) submissions.⁹⁵

FDA regulations for De Novo requests require manufacturers to submit detailed information about the device and its regulatory history, proposed special controls, and nonclinical and, in most cases, clinical trial data.⁹⁶ In contrast to 510(k) submissions, De Novo submissions are typically supported by one or more pivotal clinical studies.⁹⁷ The De Novo

93. FDA Modernization Act of 1997, Pub. L. 105-115, § 207, 111 Stat. 2296, 2340 (codified as amended at 21 U.S.C. § 360c(f)(2)(A)(i)); 21 C.F.R. § 860.200(b)(1) (2022).

94. Food and Drug Administration Safety and Innovation Act, Pub. L. 112-144, § 607, 126 Stat. 993, 1054-55 (codified as amended at 21 U.S.C. § 360c(f)(2)(A)(ii)); 21 C.F.R. § 860.200(b) (2022).

95. 21 U.S.C. § 360c(f)(2)(B)(i). See also Jeffrey K. Shapiro, *Substantial Equivalence Premarket Review: The Right Approach for Most Medical Devices*, 69 FOOD & DRUG L.J. 365, 376 (2014).

96. 21 C.F.R. § 860.220(a) (2022). See also Jacob S. Sherkow & Mateo Aboy, *The FDA De Novo Medical Device Pathway, Patents and Anticompetition*, 38 NATURE BIOTECHNOLOGY 1028, 1028 (2020).

97. James L. Johnston et al., *Clinical Evidence Supporting US Food and Drug Administration Clearance of Novel Therapeutic Devices via the De Novo Pathway Between 2011 and 2019*, 180 JAMA INTERNAL MED. 1701 (2020). The

pathways have been used infrequently since they were first established in the FDA Modernization Act of 1997.⁹⁸ According to FDA's De Novo database, the Agency has granted just 330 requests since 1998.⁹⁹ This may be due in part to the relatively burdensome requirements, which some claim approximate the burdens imposed by the PMA process.¹⁰⁰

* * *

In the foregoing sections, I have presented a somewhat idiosyncratic view of the medical device regulatory framework, in the service of showing that the 510(k) pathway has come to function primarily as the route to the U.S. market for some Class I and most Class II devices whose innovation can be characterized as incremental and iterative.¹⁰¹ As typically portrayed, the regulatory framework channels devices into specific regulatory pathways based solely on their risk classification. Most Class I and a small number of Class II devices are now exempt from all premarket regulatory pathways. A few "non-exempt" Class I and most Class II devices reach the market through the 510(k) pathway. Class III devices reach the market through the PMA pathway and its supplements.

But this typical portrayal is incomplete. It fails to explain the role of the De Novo pathways. The De Novo pathways are typically presented simply as another route to the market for those Class I and Class II devices for which manufacturers cannot cite to a substantially equivalent predicate device. But this overlooks the fact that De Novo devices may also be

authors reported, however, that 20% of devices cleared through the De Novo pathway did not have a pivotal clinical trial and that significant problems were present in one-third of the pivotal trials that were submitted. *Id.* at 1702.

98. Jonathan J. Darrow, Jerry Avorn & Aaron S. Kesselheim, *FDA Regulation and Approval of Medical Devices: 1976-2020*, 326 JAMA 420, 424 (2021) (reporting a median of twenty-six de novo clearances per year between 2013 and 2020).

99. See U.S. FOOD & DRUG ADMIN., DEVICE CLASSIFICATION UNDER SECTION 513(F)(2) (DE NOVO), <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm> (last updated Mar. 18, 2024).

100. See generally 510(k) Working Group: Preliminary Report and Recommendations, 70 Fed. Reg. 47,307 (Aug. 5, 2010).

101. I examine the relationship between innovation type and regulatory pathways, and its ramifications, in more detail in a separate work. See George Horvath, *Regulating Medical Device Innovation* (unpublished manuscript) (on file with the author).

characterized by the kinds of innovation involved in their development as well. The typical portrayal also fails to explain the difference between the rigorousness of the PMA pathway compared to the far less rigorous requirements imposed by the PMA Supplements, through which Class III devices reach the market.

By also considering the kind of innovation that results in the assignment of devices to different regulatory pathways, these and other confusing aspects of device regulation make more sense. The 510(k) and De Novo pathways offer routes to the market for Class I and II devices created through incremental, iterative innovation and through transformative innovation, respectively. The PMA and PMA Supplement pathways offer routes to the market for Class III devices created through transformative and divergent innovation, and through incremental iterative innovation, respectively.

Before proceeding, it is important to point out some of the ways in which my account of device regulation is incomplete. First, the 510(k) pathway does not function solely as a route to market for incrementally modified devices. Critics have pointed out that FDA has in many cases taken a very broad view of the scope of the substantial equivalence standard, clearing devices whose technologies differ a great deal from that of their predicates.¹⁰² Thus, at least in some cases, divergent or transformative innovations have reached the market through the 510(k) pathway. Further, incremental innovation of 510(k) devices can occur without new 510(k) clearances because manufacturers themselves primarily determine when a modification is significant enough to require a new clearance.

II. DEFINING AND ASSESSING INNOVATION IN 510(K) DEVICES

Although the 510(k) pathway has been the subject of extensive criticism, most of this writing has focused on the question of whether 510(k)-cleared devices are safe.¹⁰³ However,

102. See e.g., Jonas Zajac Hines et al., *Left to Their Own Devices: Breakdowns in United States Medical Device Premarket Review*, 7 PLOS MED., July 2010, at 1, 2–3.

103. See generally Horvath, *supra* note 22, at 127 (cataloguing safety-based criticisms of the 510(k) pathway). See also Jonathan R. Dubin et al., *Risk of Recall Among Medical Devices Undergoing US Food and Drug Administration 510(k) Clearance and Premarket Approval, 2008-2017*, 4 JAMA NETWORK

FDA must balance its responsibility for ensuring safety with its responsibility to “help to speed innovations that make medical products more effective [and] safer.”¹⁰⁴ This Part begins in Part II.A by justifying the working definition of “innovation” that will be used for the empirical study to be presented later. Part II.B then reviews the existing scholarly literature and other assessments of innovation under the 510(k) pathway.

A. DEFINING “INNOVATION”

The meaning of the term “innovation” is both critical for this project and subject to intense dispute.¹⁰⁵ A thorough review is beyond the scope of this article; this section will highlight a few major points en route to establishing the definition that will be used here. These points are that invention and innovation are distinct, albeit partially overlapping, concepts; that innovation can refer to the entire spectrum of activity from the scientific study of basic concepts to the successful integration of a new product into the marketplace; and that whether innovation requires improvement or merely change is open for debate.

Although innovation and invention are often assumed to be closely related, there is broad acceptance that the two are conceptually distinct.¹⁰⁶ Scholars have described invention as “the process of creating a new technology,”¹⁰⁷ “the embodiment of a new idea,”¹⁰⁸ and “the first confidence that something should

OPEN, May 2021, at 1, 4; Zachary E. Shapiro et al., *Nothing Generic About It: Promoting Therapeutic Access by Overcoming Regulatory and Legal Barriers to a Robust Generic Medical Device Market*, 98 N.C. L. REV. 595, 614 (2020); Frank Griffin, *Safety and Efficacy of Orthopaedic Surgical Devices Under the FDA’s Updated Premarket Notification Program*, 84 MO. L. REV. 779, 827 (2019); Diana M. Zuckerman, Paul Brown & Steven E. Nissen, *Medical Device Recalls and the FDA Approval Process*, 171 ARCH. INT. MED. 1006 (2011); Hines et al., *supra* note 102, at 2.

104. *What We Do: FDA Mission*, *supra* note 34.

105. Rachel E. Sachs, *Administering Health Innovation*, 39 CARDOZO L. REV. 1991, 1995 (2018) (“To be sure, ‘innovation’ is a slippery and much-debated concept . . .”). See also INSTITUTE OF MEDICINE 2011, *supra* note 21, at 164–167 (canvassing a wide variety of definitions).

106. W. Nicholson Price II, *The Cost of Novelty*, 120 COLUM. L. REV. 769, 771 n.1 (2020) (“Innovation policy scholars often distinguish invention—the process of creating a new technology—from innovation—the process of commercializing a new invention.”).

107. *Id.* at n.1.

108. Eva Stensvad & Ralph F. Hall, *Left to Their Own Devices: IOM’s Medical Device Committee’s Failure to Comply*, 13 MINN. J.L. SCI. & TECH. 75, 109 (2012).

work.”¹⁰⁹ These descriptions all turn on the concept of newness. Scholars have described innovation in broader terms, as a process “leading to technical change,”¹¹⁰ or “of commercializing a new invention,”¹¹¹ that “includes the entire cycle” of a product’s life,¹¹² and that results in “improving the quality of, efficiency of, or access to health care.”¹¹³ From these brief sound bites it is clear that innovation is less well defined than invention; indeed, the Institute of Medicine, after spending several pages reviewing the concept, concluded that “[t]here is no single accepted definition of innovation.”¹¹⁴ But it is clearly a much broader concept, one that encompasses a process that may begin even prior to invention and extend all the way to “commercializing a new invention.”¹¹⁵

Importantly, the innovation process is not necessarily linear. Invention is often considered to be the starting point for innovation, but even prior to innovation, new additions to the knowledge base may be necessary to guide inventors.¹¹⁶ Such new knowledge may come from basic science research or from actual experience with existing devices that illuminates unmet or poorly met clinical needs. Thus, marketed devices may serve as the basis for future incremental modifications and for divergent and transformative new devices, with innovative activity drawing on new research and incorporating newly gained or created knowledge. Device prototypes that emerge

109. SUSAN BARTLETT FOOTE, *MANAGING THE MEDICAL ARMS RACE: PUBLIC POLICY AND MEDICAL DEVICE INNOVATION* 16 (1992).

110. *Id.* at 15.

111. Price, *supra* note 106, at 771 n.1.

112. Hall & Stensvad, *supra* note 30, at 743.

113. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 167.

114. *Id.*

115. Price, *supra* note 106, at 771 n.1 (using “innovation” to refer to “the entire process, assuming a unified innovator whose inventive and commercialization efforts are driven by a desire to profit from the innovation.”). Some have taken the position that innovation comprises the steps that come after invention in the process of creating a new product or use of an existing product. *Id.* (noting that “[i]nnovation policy scholars often distinguish invention . . . from innovation”). Presumably, this view would also exclude from the definition of innovation any steps such as basic science research that precede invention.

116. Beethika Khan, Carol Robbins & Abigail Okrent, *The State of U.S. Science and Engineering 2020*, NAT’L SCI. FOUND., Jan. 2020 (“Scientific discovery and R&D increase the storehouse of knowledge, which then enables invention, innovation, and societal and economic benefits.”).

from the discovery phase may be tested by a small number of physicians as part of clinical trials. These early contacts sometimes identify design changes that are desirable, sending the product back to the product developers for further refining.¹¹⁷ Through such a recursive process, several newer versions of the device may be created before the device enters the diffusion phase.¹¹⁸ And of course, market adoption in the diffusion phase serves as a key indicator to developers and funders as to which new technologies are promising seeds for future innovation.

One difficult question is whether the definition of innovation necessarily connotes improvement. That is, for a product to qualify as an innovation, is it sufficient for that product to be new, or must it also be better than what has come before? Most health law commentators have held that medical device innovation by its very nature requires improvement.¹¹⁹ The Institute of Medicine, for example, stated that “[t]he committee believes that given the broad interpretation of the term it should define innovation not simply as a change but a favorable change in the context of public health,” and it “defined innovation as improving the quality of, efficiency of, or access to health care.”¹²⁰

However, aside from certain limited programs,¹²¹ FDA’s regulatory decisions to clear 510(k) devices and approve PMA

117. CDRH INNOVATION INITIATIVE, *supra* note 11, at fig.2.

118. *Id.*

119. *See e.g.*, Foote, *supra* note 109, at 15 (“Put most simply, innovation has been defined as certain technical knowledge about how to do things better than the existing state of the art.”); Hall & Stensvad, *supra* note 30, at 743 (“Innovation . . . includes the entire cycle starting from invention, research and development, financing, manufacturing, marketing, and societal improvement.”); Frank Griffin, *The Trouble with the Curve: Manufacturer and Surgeon Liability for ‘Learning Curves’ Associated with Unreliably-Screened Implantable Medical Devices*, 69 ARK. L. REV. 755, 784 (2016) (“Innovation is an important part of the advancement of medical science; however, newness is not the same as innovation. An advancement should move the field forward, not backwards or sideways.”). *But see* Robin C. Feldman et al., *Negative Innovation: When Patents Are Bad for Patients*, 39 NATURE BIOTECHNOLOGY 914, 914 (2021) (conceptualizing “negative innovation” in the pharmaceutical context as a process “which results in a harmful (but profitable) product”).

120. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 167.

121. Such programs currently include the Breakthrough Device Program. One criterion for this program is that a new device must “offer significant advantages over existing approved or cleared alternatives.” 21 U.S.C. § 360e-3(b). To date, only a very small number of devices have reached the market

devices do not take into account whether a new device is an improvement over existing devices.¹²² The standard for all devices that FDA is required by statute to apply is whether there is a reasonable assurance of safety and effectiveness.¹²³ The MDA limits the scope of the Agency's consideration to whether a new device is safe and effective for "the persons for whose use the device is represented or intended . . . , the conditions of use prescribed, recommended, or suggested . . . , and weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use."¹²⁴

Even if FDA were authorized to base its clearance and approval determinations on whether a new device was superior—safer, more effective—to existing devices, such a standard would be difficult, if not impossible, to implement. Assessment of the clinical benefits and costs of new devices may take six to eight or more years.¹²⁵ New devices that appear beneficial at first may later be shown to be, on balance, quite harmful.¹²⁶ Requiring that a device be beneficial in order to be

through this program. Breakthrough Devices Program, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program> (last modified Mar. 21, 2024) (noting that ninety-five devices had received marketing authorization under the program as of Dec. 31, 2023).

122. Price, *supra* note 106, at 827.

123. See 21 U.S.C. § 360c(a)(1)(A)(i) (establishing requirements of safety and effectiveness, but not improvement over existing devices).

124. 21 U.S.C. § 360c(a)(2).

125. INSTITUTE OF MEDICINE, *supra* note 51, at 20 (noting that the medical device life cycle is eighteen to twenty-four months, and that it may take four generations before the clinical benefits and costs of a new device can be determined).

126. Two examples illustrate the difficulties in requiring improvement as an element of the definition of innovation in the medical device context. One example of a Class III device that initially appeared to be an improvement over earlier devices is the Sprint Fidelis defibrillator lead. Within three years of its approval, the device was found to have a high failure rate and was withdrawn from the market. See Horvath, *supra* note 12, at 1014–15. An analogous example of a Class II device is the DePuy ASR hip prosthesis, whose metal-on-metal design was touted as an improvement that would offer younger patients decades of reliable function. Less than three years later, the device was withdrawn worldwide after multiple complications related to breakdowns of the metal components. See *A Delicate Balance: FDA and the Reform of the Medical Device Approval Process: Hearing Before the Sen. Special Comm. on Aging*, 112th Cong. 1 (2011) (statement of Katherine Korgaokar, patient). In each of these examples, whether the device was an innovation—an improvement over earlier devices—would differ depending on when the question was posed.

defined as an innovation would mean that a device could be defined as an innovation relative to its predecessors at one moment but not at another. Further, the uses to which a new device is put (and hence the benefits it provides relative to the risks it poses) are neither static nor limited to the intended uses stated by the manufacturer. Additionally, devices may be used off label by physicians, and they may provide benefits or cause harm that were not foreseen at the time of initial clearance or approval.¹²⁷

Furthermore, even a device that offers no clinical benefits over its predecessors and that causes a great deal of harm may contain new technological features that can serve as the basis for subsequent devices that do provide benefits at a low risk of harm. As Professor Rachel Sachs has framed this notion, the former device is an “intermediate technology” between an older device and a later, better device.¹²⁸ As a definitional matter, it makes little sense to exclude the intermediate device from the definition of innovation while including the latter device.

The approach used here is to sidestep these difficulties by adopting a working definition of innovation that focuses on the introduction of new technologies into the U.S. market. Innovation, as used here, comprises all of the stages of the cyclical process that result in the introduction of—or at least the legal ability to introduce—new devices to the market. It is possible to measure innovation at any point in that cycle.¹²⁹ However, for the purposes of an empirical study of the role that FDA regulation plays in innovation, the focus will be on the output of this phase of the innovation cycle. Thus, any medical device that receives 510(k) clearance, De Novo classification, an original PMA, or a PMA Supplement approval is defined as an innovation, without regard to whether the new device is an improvement over earlier devices.

127. See, e.g., George Horvath, *Emergent Regulatory Systems and Their Challenges: The Case of Combination Medical Products*, 94 WASH. L. REV. 1697, 1735, 1754 (2019) (discussing the harms caused by extensive off-label use of a spinal fixation system).

128. Sachs, *supra* note 82, at 223.

129. For example, many empirical studies of innovation have relied on the number of patents granted to or on the amount of research and development funding allocated to a given field. See, e.g., BRONWYN H. HALL & ADAM B. JAFFE, *MEASURING SCIENCE, TECHNOLOGY, AND INNOVATION: A REVIEW* 16–19 (2012). These metrics assess earlier phases of the innovation cycle than FDA regulatory phase.

Although this definition will fail to satisfy some readers, it is the only functionally useful definition for large-scale empirical study. At a minimum, the introduction of new devices is a necessary condition in order for innovation to be taking place. Technology spaces in which no new devices are being introduced cannot be described as being innovative.¹³⁰ Further, the amount of innovation in a medical device technology space is likely to be roughly correlated with the number of new devices being introduced to the market in that space. Admittedly, it is true that manufacturers may introduce modified versions of their devices for many reasons that do not include improving safety and effectiveness, including a desire to differentiate their devices from those of their competitors or, conversely, a desire to associate their device more closely with a successful device of their competitors. In such situations, though, the introduction of large numbers of new devices, even if devised for such purposes, would reflect robust competition, through which improvements would likely arise.

B. PRIOR ASSESSMENTS OF INNOVATION UNDER THE 510(K) PATHWAY

The most common and most general criticism of the 510(k) pathway from an innovation perspective is that the burdens it imposes stifle innovation. This criticism may be described as output focused, in that it looks at the ultimate effect of FDA regulation. Writing in 1996, Richard Merrill noted that according to industry representatives, “the 510(k) process remains a serious impediment to the introduction of new products and, just as important, the improvement of already marketed products.”¹³¹ Fifteen years later, the Institute of Medicine echoed that sentiment: “the medical-device industry and some patients have asserted that the process has become too burdensome and is delaying or stalling the entry of important new medical devices to the market.”¹³²

130. This does not mean that such technology spaces do not comprise highly effective, minimally risky devices; theoretically, such spaces might exist. As a practical matter, though, devices that are currently considered to meet these criteria might, as future technology is developed, seem less optimal. Thus, even in such spaces, the development and introduction of new devices—innovation as defined here—would be desirable over time.

131. Merrill, *supra* note 30, at 1831.

132. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 4.

In a widely cited survey of a sample of medical device companies by Makower, Meer, and Denend, critics within the industry urged that FDA regulation was imposing substantial delays in U.S. patients' access to new technology.¹³³ "On average, the products represented in the survey were available to patients in the U.S. a full two years after they were available to patients in Europe (range = 3 to 70 months later)."¹³⁴ Further, the respondents suggested that some devices may never be introduced onto the U.S. market; "some companies reported that they were now setting up operations overseas and developing strategies that do not rely on the U.S. market."¹³⁵

Many industry participants attributed these innovation-stifling effects to personnel issues, including the limited availability and competence of FDA personnel and their excessive risk aversion. In the Makower survey, respondents reported frequent FDA personnel changes during the review process and failures of key personnel to attend meetings.¹³⁶ Many complained that reviewers were less competent than equivalent personnel involved in European CE mark certification processes.¹³⁷ And an overwhelming majority believed that FDA had become overly risk-averse: "93 percent of participants in the study agreed or strongly agreed that FDA has become more risk-averse toward new products in the last decade."¹³⁸

Other criticisms have focused on the regulatory framework itself. These criticisms might be described as process focused. As early as the 1990s, arguments were made that the 510(k) pathway's burdens had come to approximate those of the PMA process, with some arguing that "[t]he 510(k) process . . . ballooned from a simple notification process into a

133. See generally Makower et al., *supra* note 16. The study reported the responses of 204 device companies out of a total of 4776 medical device manufacturers, representing just over 4% of the total. *Id.* at 18. Even using the authors' defined study population ("product-driven medical device manufacturers actively working on bringing innovative new medical technologies to market"), the survey respondents comprised to 20% of that population. *Id.*

134. *Id.* at 31.

135. *Id.*

136. *Id.* at 20.

137. *Id.* at 24.

138. *Id.* at 25.

system often tantamount to a full PMA.¹³⁹ Among the burdens cited by these critics is a requirement for clinical trial data in some 510(k) submissions.¹⁴⁰ The medical device industry continues to voice these complaints today,¹⁴¹ in spite of the fact that FDA requires such data for only 8% of 510(k) submissions concerning devices other than diagnostic tests.¹⁴²

Beyond these general criticisms of the 510(k) pathway's stifling effect on innovation, some have criticized the pathway for distorting the kind of innovation in which Class II device manufacturers engage, arguing that the substantial equivalence requirement incentivizes manufacturers to make only small changes to their devices. According to some, the pathway incentivizes manufacturers to make changes for the sake of differentiating their products from their competitors.¹⁴³ Others

139. CAMPBELL, *supra* note 19, at 15; Flaherty, *supra* note 92, at 914 (2008). *But see* INSTITUTE OF MEDICINE 2011, *supra* note 21, at 38 ("The gap in relative burdens on manufacturers between the 510(k) process and the PMA process created by the 1976 law has been maintained by administrative and legislative changes, which have encouraged preferential use of the 510(k) process.")

140. *See generally* Eleanor D. Kinney, *21st Century Cures Act and Medical Device Regulation: Departure from Principles or Catching the Wave*, 44 AM. J.L. & MED. 269, 286 (2018) ("Other critics might assert that the FDA is a slow, sclerotic bureaucracy with an unduly expensive approval process requiring the presentation of expensive scientific data.")

141. *See, e.g.*, Patricia Kontoudis, *The Impact of U.S. Regulation on Medical Device Innovation*, MCRA (Feb. 2018), <https://www.mcra.com/news-publications/news/impact-us-regulation-medical-device-innovation> ("The U.S. regulatory environment for medical devices generally inhibits the development of truly innovative products."); Kinney, *supra* note 140, at 285 ("The medical device industry maintains that procedures are too cumbersome and associated costs are unnecessarily excessive."); Flaherty, *supra* note 92, at 914 ("The 510(k) process, however, is not as quick and simple as many courts and commentators suggest [I]n many cases the standard of review has gone beyond mere substantial equivalence to what can be viewed as a pseudo safety and effectiveness review."); Stensvad & Hall, *supra* note 108, at 84 ("[O]ther groups argue that the 510(k) process is overly burdensome, unpredictable, and inconsistent such that it actually inhibits innovation.")

142. *See supra* text accompanying notes 89–90.

143. Shapiro et al., *supra* note 103, at 613–14 ("[T]he current section 510(k) process incentivizes innovators to make small, incremental improvements to differentiate themselves in the marketplace."). Other authors have argued that the incentive for creating slightly different products arises largely from the novelty requirement in patent law. Price, *supra* note 106, at 792 ("[I]nventing around requires that later innovators change an invention, not because they may improve it, or because they may increase the invention's social welfare value or market share, but rather because that change is necessary to avoid patent infringement. The second invention differs purely for the sake of difference."); Lewin, *supra* note 17, at 413 (discussing the use of the doctrine of

focus on the substantial equivalence standard, which puts a limit on the extent of the changes device makers can incorporate into modified versions of cleared devices.¹⁴⁴

Arguments that innovation occurs in sub-optimally small increments have been made in both the medical and legal literatures. In an article that proposed a model for assessing the risk-benefit trade-offs for innovative knee arthroplasty devices, a group of investigators from New Haven and Boston teaching hospitals criticized the substantial equivalence standard for preventing manufacturers from making more than minor modifications to their existing devices.¹⁴⁵ The authors assumed that device modifications through 510(k) clearances would yield improvements, albeit small in magnitude, but argued that this benefit was more than offset by increased costs.¹⁴⁶ Similar arguments have been made in the legal scholarship.¹⁴⁷ Professor Nicholson Price has positioned the incremental nature of innovation that the 510(k) pathway incentivizes within a patent-law created spectrum of divergence of new products from existing products.¹⁴⁸ This spectrum ranged from “deepening innovations,” which do not diverge at all, but rather increase the available knowledge about existing products, to “differentiating” innovations, which contain relatively minor modifications, to “exploring” innovations, which are “markedly different” from existing technologies.¹⁴⁹ Price described the 510(k) pathway’s substantial equivalence requirement as creating incentives for “innovation [that] is closer to differentiating innovation than

equivalents to police “the problem of trivial design-around meant for nothing more than evasion of patent claims”).

144. Shapiro et al., *supra* note 103, at 613; Price, *supra* note 106, at 815 (“Because the 510(k) preclearance process is so much cheaper, and requires that devices be substantially equivalent to existing devices, the overall FDA approval process creates substantial incentives for firms to diverge less from existing medical device technologies.”); Lewin, *supra* note 17, at 411 (“Overall, the vast majority of Class II and Class III submissions cleared through 510(k) do not deviate much from their predicates technologically . . .”).

145. Lisa G. Suter et al., *Medical Device Innovation — Is “Better” Good Enough?*, 365 NEW ENG. J. MED. 1464, 1465 (2011).

146. *Id.* at 1464 (“[T]he process may encourage the development of devices that provide only small improvements at higher cost than their predecessors.”).

147. Shapiro et al., *supra* note 103, at 613–14. *See also* Lewin, *supra* note 17, at 424 (“The ease of 510(k) as compared to PMA encourages the development of familiar products with familiar intended uses.”).

148. Price, *supra* note 106.

149. *Id.* at 775–76.

exploring innovation,” that is, for relatively minor divergences from the predicate technology.¹⁵⁰ Unlike the New Haven-Boston authors, Price argued that the 510(k) pathway’s incentives for differentiating innovation encouraged minor modifications for the sake of differentiation, with no requirement that the modifications actually improve the technology.¹⁵¹

Other critics have argued that the 510(k) pathway incentivizes manufacturers to bring new devices to the market that rely on older technology, with which FDA has greater familiarity.¹⁵² These observations have led to claims that the 510(k) pathway stands as an impediment to transformative innovation.¹⁵³ A diverse group of medical and legal scholars criticized the current regulatory regime for failing to facilitate the adoption of existing technologies across manufacturers within technology spaces. “[I]nstead of promoting widespread adoption of proven technology, the current section 510(k) process incentivizes innovators to make small, incremental improvements to differentiate themselves in the marketplace.”¹⁵⁴

A different line of criticism holds that the 510(k) pathway is too permissive—that it permits innovation to occur so rapidly that the regulatory system is unable to ensure the safety of evolving technologies. This concept, known as predicate creep, has been widely discussed by critics whose focus has been on safety.¹⁵⁵ Drawing many of these criticisms together, Professor Zachary Shapiro and colleagues have argued that “instead of promoting widespread adoption of proven technology, the current section 510(k) process incentivizes innovators to make small, incremental improvements to differentiate themselves in the marketplace. These product evolutions are subject to only weak standards, enabling ‘predicate creep.’”¹⁵⁶

A smaller number of commentators have taken a more favorable view of the role the 510(k) pathway plays in medical device innovation. James Flaherty, focusing on the speed of the process, has argued that “the 510(k) process . . . succeeds in

150. *Id.* at 822.

151. *Id.*

152. Lewin, *supra* note 17, at 425.

153. *Id.*

154. Shapiro et al., *supra* note 103, at 613–14.

155. See Hines et al., *supra* note 102, at 4.

156. Shapiro et al., *supra* note 103, 613–14.

achieving a useful balance between protecting public health through premarket review and promoting public health by providing access to medium-level risk devices.”¹⁵⁷ Professor Rachel Sachs, focusing on the concept of “intermediate technologies,” whose regulation should ideally permit modifications that will result in improvements, has argued that “the 510(k) pathway . . . presents one example of . . . lowered the regulatory barriers for companies to engage in incremental changes, and particularly incremental improvements.”¹⁵⁸

Another common, favorable assumption about the 510(k) pathway is that it is more innovation friendly than the PMA pathway because it provides a cheaper, easier, and faster route to the market. Respondents in the Makower study reported that the average cost of bringing a 510(k) device to the market was \$31 million, compared with \$94 million for a PMA device.¹⁵⁹ Industry participants also report that the 510(k) pathway is easier for device makers to navigate.¹⁶⁰ And most commentators have observed that FDA review times are shorter for 510(k) submissions.¹⁶¹

However, these observations, even assuming they are all true, do not demonstrate that the 510(k) pathway is more innovation-friendly than the PMA pathway. The often-cited lower cost of bringing 510(k) devices to the market is based on the results of a single survey of a limited sample of device manufacturers.¹⁶² And even if the cost of bringing 510(k) devices to the market is substantially lower than the cost of bringing

157. Flaherty, *supra* note 92, at 926–27.

158. Sachs, *supra* note 82, at 245.

159. Makower et al., *supra* note 16, at 7. These numbers, although based on survey results from a limited sample of device manufacturers, are widely cited as definitive.

160. *Id.* at 13.

161. See, e.g., Sachs, *supra* note 82, at 245 (“Compared to the PMA process, the 510(k) pathway is significantly cheaper and quicker for companies.”); Hall & Stensvad, *supra* note 30, at 734 (“Furthermore, because the 510(k) system requires a less detailed submission to the FDA than is required for PMA, 510(k) clearances are generally faster than PMA approvals.”); Eric P. Raciti & James D. Clements, *A Trap for the Wary: How Compliance with FDA Medical Device Regulations Can Jeopardize Patent Rights*, 46 IDEA 371, 374 (2006) (“The PMA pathway is far more comprehensive, detailed, time-consuming, and expensive than the 510(k) pathway.”).

162. Cf. Makower et al, *supra* note 16, at 6 (stating that responses were from 204 companies, representing 20% of all public and venture-backed medical device manufacturers in the U.S.).

PMA devices to the market, it is important to know how these costs relate to the anticipated revenues of those devices. Further, as noted above, some have argued that the burdens of navigating the 510(k) pathway have come to approximate those of the PMA pathway. Finally, even though 510(k) clearance is more rapid than PMA approval, this does not prove that the overall rate of innovation is more rapid. If manufacturers less frequently seek to modify their 510(k) devices or only modify those devices at much longer intervals compared with PMA devices, the apparent innovation friendliness of the 510(k) pathway may disappear. This highlights the fact that the appropriate comparisons between the rates of innovation that occur under FDA's medical device pathways need to be informed by the kind of innovation that comprises the majority of devices reaching the market through those pathways.¹⁶³ For incremental innovation, the relevant comparison is between the 510(k) pathway for Class II devices and the PMA Supplement pathways for Class III devices, while for divergent and transformative innovation the relevant comparison is between the De Novo pathways for Class II devices and the PMA pathway for Class III devices.

This discussion points to the near absence of empirical analysis of innovation in the universe of 510(k) devices. The existing discussions and criticisms of the 510(k) pathway have not attempted to characterize how innovation occurs under this pathway. The Institute of Medicine report noted that attempts to empirically critique the pathway have relied on assessments of “the ease of premarket review and relative speed to market compared with the European Union premarket process,” and on the number of particular types of devices on the market.¹⁶⁴ The committee did not consider these to be useful surrogates for innovation. And while the device industry and its allies have argued that increasing demands by FDA for clinical trial evidence are having an adverse effect on innovation,¹⁶⁵ no strong empirical evidence supports (or refutes) this claim.

In spite of this lack of empirical evidence, critics have put forward a wide range of reform proposals. Some have urged FDA “to exercise flexibility to relieve the burden of the regulatory

163. See *supra* Part I.A–D.

164. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 7, 12.

165. Kontoudis, *supra* note 141, at *6.

process whenever possible.”¹⁶⁶ This includes proposals for FDA to further limit how frequently it calls for clinical trial data for 510(k) submissions.¹⁶⁷ Others have proposed more fundamental changes to the medical device regulatory scheme. The 2011 Institute of Medicine report proposed eliminating the 510(k) pathway, concluding that “the FDA’s resources would be put to better use in obtaining information needed to develop a new regulatory framework for Class II medical devices and addressing problems with other components of the medical-device regulatory framework.”¹⁶⁸

Still other critics have proposed eliminating FDA premarket evaluation of medical devices entirely, and to rely instead on independent third parties to certify new devices,¹⁶⁹ or on a “sharp and efficient post-market surveillance system.”¹⁷⁰

In its assessment of the 510(k) pathway, the Institute of Medicine reported that FDA was unable to “reconstruct the ‘piggy-backing’ of devices without a manual review of perhaps thousands of files.”¹⁷¹ Ultimately, the report concluded that empirical study of the 510(k) pathway was not feasible, stating that “the cost of the exercise would be staggering; the benefit would be, it is hoped, small in terms of identifying devices that should not have gotten to the market by a 510(k) clearance.”¹⁷²

But since 2011, several changes call into question the Institute of Medicine’s pessimistic view of the feasibility and value of empirical study of the 510(k) pathway. The data that is available about devices cleared through the pathway in recent years has grown increasingly robust and easy to access. Techniques for automating the acquisition of the data needed have grown increasingly available. In addition, scholars in the medical literature have demonstrated the utility of a technique for reconstructing the web of subject-predicate relationships between 510(k) devices in qualitatively critiquing the safety function of the pathway. The next Part introduces this

166. *Id.* at *8.

167. *Id.* at *6.

168. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 8. *See also, e.g.*, Gregory D. Curfman & Rita F. Redberg, *Medical Devices—Balancing Regulation and Innovation*, 365 NEW ENG. J. MED. 975, 976–77 (2011).

169. CAMPBELL, *supra* note 19, at 1.

170. Scott, *supra* note 19, at 398.

171. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 81.

172. *Id.*

methodology to the legal literature and discusses how it might be adapted to assess innovation in devices regulated under the pathway.

III. REGULATORY ANCESTRY STUDY: A METHODOLOGY FOR ASSESSING INNOVATION

Since 2013, medical journals have published a number of ancestry studies (variously referred to as 510(k) ancestry, regulatory ancestry, and predicate ancestry studies) of devices cleared through the 510(k) premarket notification pathway.¹⁷³ In an earlier work, I used the ancestry study methodology to quantitatively study 510(k) device safety.¹⁷⁴ This methodology is applied here to the study of 510(k) device innovation.

Ancestry studies utilize data that are largely available from publicly accessible FDA databases to construct a network model of devices akin to a genealogical tree, linking each device to its predicates and to later devices that cite it as their own predicates.¹⁷⁵ In the first use of this methodology, Brent Ardaugh and colleagues traced the ancestry of one model of a hip prosthesis, the DePuy ASR XL Acetabular Cup System, through a total of ninety-five earlier 510(k) devices.¹⁷⁶ The authors assembled an ancestry map that related each device to its predicates. Their map showed that the DuPuy ASR device itself had been cleared on the basis of substantial equivalence to six immediate predicates.¹⁷⁷ This was possible under FDA's policy of clearing 510(k) submissions that cite multiple predicates, a

173. Brent M. Ardaugh, Stephen E. Graves & Rita F. Redberg, *The 510(k) Ancestry of a Metal-on-Metal Hip Implant*, 368 *NEW ENG. J. MED.* 97 (2013); Diana Zuckerman, Paul Brown & Aditi Das, *Lack of Publicly Available Scientific Evidence on the Safety and Effectiveness of Implanted Medical Devices*, 174 *JAMA INTERN. MED.* 1781 (2014); Carl J. Heneghan et al., *Trials of Transvaginal Mesh Devices for Pelvic Organ Prolapse: A Systematic Database Review of the US FDA Approval Process*, 7 *BRIT. MED. J. OPEN* 1 (2017); Nasim Zargar & Andrew Carr, *The Regulatory Ancestral Network of Surgical Meshes*, 13 *PLOS ONE*, June 2018, at 1; Jeremy Rosh, Chaim M. Bell & David R. Urbach, *The 510(k) Ancestry of Transvaginal Mesh: When the Subject Is Not a Predicate*, 156 *JAMA SURGERY* 701 (2021); Dhruv B. Pai, *Mapping the Genealogy of Medical Device Predicates in the United States*, 16 *PLOS ONE*, Oct. 2021, at 1; Alexander Y. Liebeskind et al., *A 510(k) Ancestry of Robotic Surgical Systems*, 98 *INT'L J. SURGERY* (2022).

174. Horvath, *supra* note 22, at 148.

175. Zargar & Carr, *supra* note 173, at 3.

176. Ardaugh et al., *supra* note 173, at 98–99.

177. *Id.* at 99.

practice used by manufacturers who create new devices by combining the technological features of several existing devices in ways that had never been done before. In these cases there is no single device to which a manufacturer can claim substantial equivalence; instead, the manufacturer cites multiple devices as predicates, each for those technological features that are incorporated into the new device.¹⁷⁸ In the ancestry map of the DePuy ASR device, each of that device's six predicates had from one to six predicates, and the ancestry extended back through six generations to devices cleared decades earlier.¹⁷⁹

Ardaugh and colleagues used their ancestry to argue that the 510(k) pathway was seriously flawed from a safety perspective.¹⁸⁰ Although not the authors' focus, their study also illustrated the potential utility of ancestry mapping for studying innovation. The authors provided a graphic illustration of the introduction of new innovations into this technology space.¹⁸¹ They highlighted the important role that combining existing technologies plays in the innovation process.¹⁸² Their study also offered a means of quantitating the proportion of innovation that occurs through combining existing technologies in novel ways.

A study by Nasim Zargar and Andrew Carr created an ancestry map of seventy-seven surgical meshes which FDA cleared over a three-year period.¹⁸³ Like Ardaugh and colleagues, Zargar and Carr used their regulatory ancestry to criticize the 510(k) pathway for compromising device safety.¹⁸⁴ But the authors also performed quantitative analyses of the

178. U.S. FOOD & DRUG ADMIN., *supra* note 77, at 11. Prior to 2014, FDA also granted 510(k) clearances based on "split predicates," in which a manufacturer cited different predicates for the intended use and technological features of a new subject device. *Id.* at 39. The Agency formally abandoned this practice in a guidance published in 2014. *Id.* at 11. However, the Agency continues to grant 510(k) clearances based on multiple predicates.

179. Ardaugh et al., *supra* note 173, at 99.

180. *Id.* at 98.

181. *Id.* at 99.

182. *Id.* at 98 (criticizing the fact that "[n]one of the predicates in the ancestry had the same combination of characteristics as the ASR XL acetabular component").

183. Zargar & Carr, *supra* note 173, at 4. Carl J. Heneghan and colleagues and Jeremy Rosh and coauthors constructed predicate ancestries of sets of meshes that are used for pelvic reconstruction surgeries. Heneghan et al., *supra* note 173, at 2–4; Rosh et al., *supra* note 173, at 702. Both groups focused on the safety risks created by predicate creep and not on innovation.

184. Zargar & Carr, *supra* note 173, at 10–11.

surgical mesh devices that provide insights into the ways in which innovation occurs in 510(k) spaces. For example, they determined that while “some devices have only been used as a predicate once,” others had “ultimately led to over 100 descendants.”¹⁸⁵ Although they did not elaborate on this finding, it suggests that ancestry study can be used to assess the relative innovation value of cleared devices through comparisons of how many times each device is cited as a predicate.

These and other studies demonstrate that ancestry study can be a useful tool for studying how innovation occurs under the 510(k) pathway. By creating a genealogic tree, ancestry studies can reveal information about the entry of manufacturers into a technology space and their innovative activity once in that space. This can provide information about how much innovation occurs in a space over time and how competitive the space has been. Spaces with few manufacturers are likely to have been less competitive and innovative than spaces with many manufacturers. And spaces with relatively few 510(k) clearances over time are likely to have been less innovative than spaces with many clearances. Ancestry studies might also be used to compare innovative activity at different times within the same spaces, facilitating an analysis of the effects of changes to the 510(k) statutory or regulatory framework on innovation.

Regulatory ancestry studies may also be useful for understanding the manner in which innovation occurs. For example, constructing and visualizing the subject-predicate relationships between devices can help to understand if device innovation is occurring predominantly internally—this is, through each manufacturer’s iterative modification of its own devices—or through transfers or borrowing (whether voluntary or otherwise) of technology from one manufacturer to another. Spaces characterized by internal evolution will present linear lines of descent in which subject-predicate relationships remain within the same manufacturer, whereas spaces characterized by frequent technology exchanges between manufacturers will exhibit a large proportion of subject-predicate relationships running between different manufacturers. Ancestry studies can also help in quantitating how much innovative activity occurs through combining existing technologies, which is reflected in 510(k) clearances that cite multiple predicates.

185. *Id.* at 6.

Ancestry study methodology may also facilitate comparisons of the amount and rate of innovation that occurs under different regulatory pathways. As discussed above, although commentators have sought to draw comparisons between the 510(k) pathway and the PMA pathway, such comparisons are inapt because they regulate very different kinds of innovation.¹⁸⁶ The appropriate comparator for the rate of innovation under the 510(k) pathway, which comprises incremental, iterative innovation, is the rate of innovation under the PMA Supplement pathways. At first blush, direct comparison of the intervals at which manufacturers modify devices through new 510(k) clearances and PMA supplements may appear to be inappropriate because the more intense regulatory scrutiny to which PMA devices are subjected might oblige manufacturers of these devices to obtain supplements for even minor modifications of these devices. However, the standard for when either of the MDUFMA supplements (Panel Track and 180 Day PMA supplements) is required is that a modification represents a significant change.¹⁸⁷ This is the same standard for when a new 510(k) clearance is required for an existing 510(k) device. Thus, examining how frequently manufacturers make use of Panel Track or 180 Day PMA Supplements should facilitate empirical testing of the proposition that the 510(k) pathway is more innovation-facilitating than the PMA Supplement pathways.

Regulatory ancestry study can also be used to assess the value of cleared devices to future innovation. A cleared device that is never cited as a predicate in subsequent 510(k) submissions likely contained technological features that were not valued by the market. Such a device would not be considered innovative. By contrast, a device that is cited as a predicate in the 510(k) submissions of many other devices or that is in the lineage of many later devices likely contained some useful features that serve as the basis for future innovations. Thus, ancestry study should make it possible to compare the relative innovation value of devices within a technology space.

The next Part applies the regulatory ancestry methodology to one specific space of medical device technology in order to begin to study how innovation occurs under the 510(k) pathway.

186. See *supra* text accompanying notes 162–63.

187. See *supra* text accompanying notes 54–57.

IV. AN EMPIRICAL STUDY OF INNOVATION UNDER THE 510(K) PATHWAY

This Part presents an empirical study of how innovation has occurred within a single, 510(k)-regulated technology space.¹⁸⁸ The purposes of this pilot study were three-fold. The first was to assess the feasibility of empirical study of safety and innovation in the 510(k) device context.¹⁸⁹ As noted earlier, the Institute of Medicine concluded in 2011 that such a study was not feasible.¹⁹⁰ However, given improvements in FDA's publicly available device databases, in computer-automated data acquisition and analysis techniques, and through the use of new methodologies, testing the Institute's pessimistic conclusion seems warranted. Second, the study was designed to assess whether (and what kinds of) useful information could be gained from the use of the methodologies adopted here. Third, the study was intended to begin to develop a nuanced understanding of safety and innovation in 510(k) devices and to formulate hypotheses that could be tested in a larger empirical study.

The technology space in this study comprises catheters that are intended for use in removing blood clots (thrombi) from the arteries in the brains (the cerebral vasculature or neurovasculature) of patients experiencing acute strokes. FDA assigns one or both of the product codes NRY and POL to these devices.¹⁹¹ NRY devices are "intended to restore blood flow by removing thrombus/clots in patients experiencing ischemic stroke."¹⁹² POL devices are "neurovascular mechanical

188. Throughout the discussion of the study, the set of all existing and all possible devices with this intended use is referred to as a technology space or simply as a space. Manufacturers who first obtain 510(k) clearance for a device bearing one of these indications are said to enter the space. Once a manufacturer has obtained a 510(k) for such a device, the manufacturer is said to be in the space. Predicate devices with different or more general intended uses that are regulated under other product codes are said to be outside the space.

189. A pilot empirical study of 510(k) device safety in the same technology space is presented in a prior publication. See Horvath, *supra* note 22, at 113.

190. INSTITUTE OF MEDICINE 2011, *supra* note 21, at 7–8.

191. FDA describes product codes as "a method of internally classifying and tracking medical devices" which are "assigned by CDRH to support their regulation." These three-letter codes are assigned by FDA staff. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: MEDICAL DEVICE CLASSIFICATION PRODUCT CODES *4 (2013) (using PDF page number) [hereinafter FDA PRODUCT CODE GUIDANCE].

192. *Product Classification entry for "NRY"*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?id>

thrombectomy device(s) for acute ischemic stroke treatment.”¹⁹³ The study treats these devices as a single technology space (the NRY/POL space) based on their overlapping intended uses, regulatory requirements, and the fact that all devices assigned the POL product code are also assigned the NRY product code.

The NRY/POL technology space has features that make it ideal for a pilot study. The space is limited in size, making data acquisition and analysis manageable. On the other hand, the space is large enough that empirical study can aid in beginning the development of a nuanced understanding of how innovation occurs in 510(k) devices as well as an assessment of the feasibility of more comprehensive studies. The space is relatively young, minimizing many of the difficulties associated with obtaining information about older devices.¹⁹⁴ Thus, a study of the devices in this space is useful to assess the utility of regulatory ancestry study and to obtain some initial insights into how innovation occurs in devices regulated under the 510(k) pathway.

A. BACKGROUND

Interest in using devices to physically extract thrombi from the cerebral vasculature was driven by limitations in what was, in the late 1990s and early 2000s, the state-of-the-art treatment for acute stroke. FDA had approved the first thrombolytic (or clot-busting) drug, recombinant tissue plasminogen activator (rt-PA), for treatment of acute ischemic stroke in 1996.¹⁹⁵ For

=3779 (last visited Mar. 24, 2024). An ischemic stroke is caused by blockage of an artery that supplies blood to the brain, typically a blood clot that either formed in the brain artery or traveled from an artery between the heart and the brain.

193. *Product Classification entry for “POL”*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?id=3940> (last visited Mar. 24, 2024). Neurovascular refers to the arteries that supply blood to the brain. Thrombectomy refers to the removal of blood clots within an artery.

194. Detailed information on 510(k) cleared devices is available online from FDA’s databases back to 2007–2008. For devices cleared prior to 2007, information, such as the cited predicates, is limited and may require FOIA requests to obtain.

195. Harold P. Adams et al., *Guidelines for the Early Management of Patients with Ischemic Stroke*, 34 *STROKE* 1056, 1065 (2003). See also *Entry for BLA103172*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/daff/index.cfm?event=overview.process&ApplNo=103172> (last visited Mar. 24, 2024).

patients presenting within 90 to 180 minutes of the onset of symptoms of an ischemic stroke, the American Stroke Association's 2003 guidelines recommended the intravenous (and in limited circumstances, intra-arterial) administration of rt-PA or related thrombolytic agents.¹⁹⁶

Unfortunately, thrombolytic treatment for acute ischemic stroke was far from ideal. The risk of potentially fatal hemorrhagic stroke (bleeding inside the brain) was markedly increased in patients who received rt-PA.¹⁹⁷ Further, in clinical practice, very few patients were candidates for thrombolytic therapy.¹⁹⁸ Moreover, thrombolytic therapy failed to prevent lasting neurologic damage in half to two-thirds of patients.¹⁹⁹ These shortcomings led physicians to seek innovative new approaches.

One such approach was mechanical. A variety of percutaneous devices featuring wire loops²⁰⁰ and wire grasping arms²⁰¹ had already been cleared by FDA for use in retrieving foreign bodies resulting from medical misadventures (such as guidewires and vascular catheters that had fractured and stents that failed to deploy in a stable position).²⁰² These devices had been designed for very different uses than removing blood clots in cerebral arteries, which had important ramifications for their safety and effectiveness when used to treat stroke patients. The existing devices had been designed for use in the peripheral

196. Adams et al., *supra* note 195, at 1065.

197. *Id.* at 1065 (citing study data in which “symptomatic brain hemorrhage . . . occurred in 6.4% of patients treated with rtPA and 0.6% of patients given placebo”).

198. Stephan A. Munich, Kunal Vakharia & Elad L. Levy, *Overview of Mechanical Thrombectomy Techniques*, 85 NEUROSURGERY S60, S66 (2019) (“[C]onstraints of intravenous tPA administration resulted in its use in only 2.4% of stroke patients in 1 study assessing its utilization.”).

199. Adams et al., *supra* note 195, at 1065 (citing study data showing that “[f]avorable outcomes were achieved in 31% to 50% of patients treated with rtPA”).

200. H. Christian Schumacher et al., *Endovascular Mechanical Thrombectomy of an Occluded Superior Division Branch of the Left MCA for Acute Cardioembolic Stroke*, 26 CARDIOVASCULAR INTERVENTIONAL RADIOLOGY 305, fig.3 (2003).

201. Hans Henkes et al., *A New Device for Endovascular Coil Retrieval from Intracranial Vessels: Alligator Retrieval Device*, 27 AM. J. NEURORADIOLOGY 327, fig.1 (2006).

202. Timothy L. Tittle, Ronald C. Prati & Steven T. McCormack, *The ‘Gooseneck’ Concept in Microvascular Retrieval*, 16 AM. J. NEURORADIOLOGY 1469 (1995).

vasculature (the arteries and veins outside of the heart),²⁰³ most of which feature straighter and thicker vessels than are found in the brain. The use of the existing retrieval devices in the cerebral arteries, which have thinner walls and more winding courses, might increase the risk of arterial rupture.²⁰⁴ The walls of the cerebral arteries have higher muscle tone than the peripheral arteries, which functions to limit the pulsatile pressure waves from the heart from reaching the delicate brain tissue; this muscle tone could be disrupted by the trauma inflicted by retrieval devices designed for the peripheral vasculature, exposing the brain to long-term damage.²⁰⁵ The wire loops²⁰⁶ and grasping arms²⁰⁷ used in the existing devices were intended to snare solid objects like stents and guidewires. Although it was possible for these objects to fragment and embolize (travel further downstream), the chances of this occurring were relatively low and the potential adverse outcomes, while serious, could often be mitigated surgically. But thrombi are fresh blood clots, which are not solid in the way that guidewires and catheter fragments are. Their consistency is more like jello, giving them a higher tendency to fragment into smaller pieces which can embolize.²⁰⁸ The delicacy and critical function of the downstream tissue—the brain itself—compounds the risks associated with embolization.

Unfortunately, the regulations governing the existing devices that been cleared for peripheral vascular use in the 1990s and early 2000s were not focused on ensuring their safe and effective use in the cerebral blood vessels.²⁰⁹ However, driven by clinical need, physicians began to use these devices off-label to remove thrombi in patients experiencing acute ischemic

203. See *Product Classification entry for “DQY”*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm?id=778> (last visited Mar. 24, 2024) (showing that predicate device for the first entrant into the NRY/POL space was a catheter for coronary and peripheral use).

204. Ethan A. Prince & Sun Ho Ahn, *Basic Vascular Neuroanatomy of the Brain and Spine: What the General Interventional Radiologist Needs to Know*, 30 SEMINARS INTERVENTIONAL RADIOLOGY 234–35 (2013).

205. MARILYN J. CIPOLLA, *THE CEREBRAL CIRCULATION* ch.2 (2010).

206. Schumacher et al., *supra* note 200, at fig.3.

207. Henkes et al., *supra* note 201, at fig.1.

208. Johannes Kaesmacher et al., *Risk of Thrombus Fragmentation during Endovascular Stroke Treatment*, 38 AM. J. NEURORADIOLOGY 991, 991 (2017).

209. See 21 C.F.R. §§ 870.1250, 870.5150.

strokes who had either failed or were ineligible for rt-PA treatment.²¹⁰ In response to this growing interest in mechanical thrombectomy, innovators began the process of developing devices specifically for this use.²¹¹ As the earliest of these new devices came to the attention of FDA, personnel in the CDRH administratively created the new NRY product code.

B. METHODS

The study population consisted of all 510(k)-cleared devices in the NRY/POL technology space (n = 85) as of mid-2022.²¹² The primary data source was FDA's 510(k) Premarket Notification Database.²¹³ FDA assigns each cleared device a unique 510(k) number; FDA's website entry for each unique 510(k) number includes the device name and manufacturer, the dates on which the 510(k) application was submitted and approved, any clinical trials that were part of the submission, and any FDA recalls that have been announced. I manually extracted this information for each device. The website also includes a hyperlink to the manufacturer's 510(k) summary for each device.²¹⁴ I downloaded these 510(k) summaries, which were available for 82 of the devices.²¹⁵ From each summary I manually extracted the reason for the 510(k) submission (demonstrating substantial equivalence to support a design, material, or process change; expanded indication), the 510(k) numbers of all predicate and

210. Schumacher et al., *supra* note 200, at 305–06; Munich et al., *supra* note 198, at 564.

211. See, e.g., *Merci Retriever: Concentric Medical, Inc.: Saving Stroke Victims*, UCLA TECH. DEV. GRP., <https://tdg.ucla.edu/merci-retriever> (last visited Mar. 24, 2024) (describing the Merci Retrieval System, which withdraws blood clots from the brain).

212. Further discussion of the creation of the database can be found in the previously published companion study of 510(k) device safety. Horvath, *supra* note 22, at 150.

One device that was reclassified as a Class II device through the De Novo pathway and was assigned an NRY product code is included in this population.

213. *501(k) Premarket Notification*, U.S. FOOD & DRUG. ADMIN., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm> (last updated Mar. 18, 2024).

214. A 510(k) summary must be submitted with a 510(k) submission, with certain exceptions. The summary must contain “sufficient detail to provide an understanding of the basis for a determination of substantial equivalence.” 21 C.F.R. § 807.92(a) (2024).

215. The 510(k) summaries for two devices were not available through FDA's 510(k) searchable database.

reference devices,²¹⁶ whether and what type of clinical trial data was submitted, the manufacturer and clearance date of the cited predicates and reference devices, the changes made from the predicate device(s), and certain information about the device technology. The initial data collection was performed on June 7, 2021, and the database was periodically updated, most recently on June 6, 2022. For devices for which a 510(k) summary was not available on FDA's website (n = 2), I obtained the summaries through Freedom of Information Act requests.

The data were entered into a spreadsheet (Microsoft Excel, version 2207). Using network analysis software (UCINET and NetDraw), I visually represented this technology space as a network in which each node represents a device and each connection between nodes represents a subject-predicate relationship. Statistical comparisons were made using Microsoft Excel, Social Sciences Statistics, and Minitab. Continuous variables were compared using unpaired t-tests assuming two-tailed outcomes and unequal variance. Dichotomous variables were compared using Chi-squared tests. A p value of less than .05 was considered to be statistically significant.

C. FINDINGS

1. Evolution of the NRY/POL Technology Space

The first device to enter the newly defined NRY/POL technology space was the Merci Retriever, made by Concentric Medical, which was cleared on August 11, 2004.²¹⁷ The Merci Retriever was a modified version of Concentric's peripheral vascular retrieval device (the Modified Concentric Retriever) and consisted of a catheter with a wire shaped into a helix at its tip.²¹⁸ The device was designed to be advanced through the cerebral vasculature beyond the stroke-causing thrombus and then withdrawn, grasping and removing the thrombus and thus

216. FDA defines a reference device as one that a 510(k) submission can cite for the purpose of "support[ing] scientific methodology or standard." Reference devices can only be cited after the manufacturer has established substantial equivalence to a legally marketed device. U.S. FOOD & DRUG ADMIN., *supra* note 77, at 13–16.

217. *510(k) Premarket Notification page for K033736*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?ID=K033736> (last visited Mar. 24, 2024) (showing FDA entry for Merci Retriever).

218. *Merci Retriever*, *supra* note 211.

averting the stroke. Concentric cited its Modified Concentric Retriever as the predicate to the Merci. Although similar to the Modified Concentric Retriever, the Merci Retriever featured a somewhat distinct tip design, and its intended use was different; while the Modified Concentric Retriever was intended to retrieve foreign bodies (generally as a result of medical misadventures) from “the neuro, peripheral, and coronary vascular systems,”²¹⁹ the Merci Retriever was “intended to restore blood flow in the neurovasculature by removing thrombus in patients experiencing ischemic stroke.”²²⁰

As of June 2022, eleven additional companies had entered this technology space.²²¹ In total, these companies had obtained 510(k) clearances for 84 devices. In addition, one device entered the space through De Novo reclassification as a Class II NRY device. Roughly half of the devices utilize mechanical means to remove thrombi. These devices feature catheter tips in a variety of shapes that were designed to snare the thrombus. In 2007, Penumbra obtained 510(k) clearance for the first NRY/POL device to use suction (aspiration) to remove clots.²²² Now, roughly half of the devices in this technology space use aspiration techniques. Thus, over a span of less than eighteen years, a biomedical technology space went from nonexistent to one in which twelve market participants had obtained clearances to market an array of 85 devices that feature widely varying technological features, all designed for the specific purpose of removing thrombi from the cerebral vessels.

Table 1

Company	Date of Entry (First 510k Clearance)	Number of Devices in the
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219. *510(k) Summary for K030476*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/cdrh_docs/pdf3/K030476.pdf (last visited Mar. 24, 2024) (showing FDA summary for Modified Concentric Retriever).

220. *510(k) Summary for K033737*, U.S. FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/cdrh_docs/pdf3/K033736.pdf (last visited Mar. 24, 2024) (showing FDA summary for Merci Retriever).

221. *See infra* Table 1.

222. *510(k) Summary for K072718*, U.S. FOOD & DRUG ADMIN., www.accessdata.fda.gov/cdrh_docs/pdf7/K072718.pdf (last visited Mar. 24, 2024) (stating that the catheter was designed to be used with Penumbra Aspiration Pump).

		NRY/POL Space
Concentric Medical, Inc.	8/11/2004	18*
Penumbra, Inc.	12/28/2007	22
Micro Therapeutics DBA EV3 Neurovascular	3/2/2012	18
Stryker	3/18/2018	9
InNeuroCo.	4/19/2018	3
Neuravi Ltd.	5/9/2018	4
MicroVention Inc.	6/11/2018	2
Medtronic Neurovascular	8/24/2018	1
Imperative Care, Inc.	4/17/2019	4
Codman & Shurtleff Inc.	7/20/2020	1
Rapid Medical, Inc.	3/23/2021	1
Wallaby Medical	11/16/2021	1

* Concentric Medical Inc. also obtained De Novo reclassification for one device.

Table 1 illustrates the time course of manufacturer entry into the NRY/POL space. Concentric was the sole company in the technology space for more than three years before Penumbra entered in late 2007. Three manufacturers (Penumbra, Concentric, and Micro Therapeutics) were the only participants until 2018. These three manufacturers dominated the space, having obtained 510(k) clearance for 22, 18, and 18 devices, respectively. These companies also acquired, were acquired by, or signed distribution deals with several of the other companies that have entered in the space.²²³ Thus, the three dominant companies respectively account for 22, 32, and 19 of the cleared devices in this space, amounting to 86% of the devices in the space. Figure 1 presents a graphic display of these devices and their manufacturers as a network, with each device displayed as a node (a square or circle) connected to each of its predicates and to all devices citing it as their predicate by a line.

223. See *supra* Table 1.

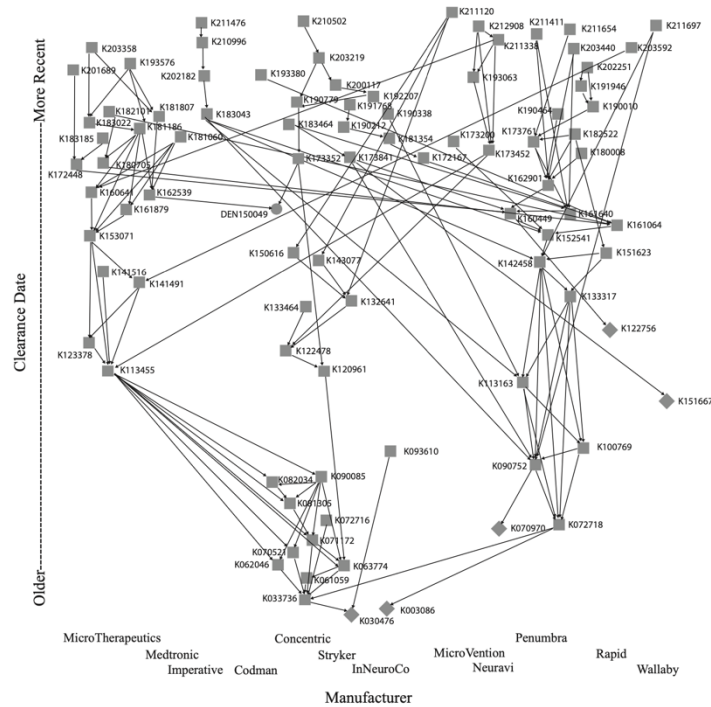


Figure 1. Network Visualization of Devices in the NRY/POL Space

All devices in the NRY/POL space, and predicates from outside that space, are displayed as nodes. Squares represent 510(k) cleared devices, with the 510(k) number labelled. Circle represents the De Novo device. Diamonds represent predicate devices that were not NRY/POL devices. Lines connect each device to its predicate(s), with the arrow pointing to the predicate(s). Older devices are displayed toward the bottom of the figure.

Companies first entering the NRY/POL space tended to cite older devices as predicates in comparison to companies that were already in the space. The predicates in clearances obtained by first-time market entrants²²⁴ had a mean age of 1714 ± 975 days, with no predicate less than 534 days old. This is significantly

224. The age of predicate cited by the first device to enter the space was not included, as there were no competitors in the space at that time.

longer than mean age of predicates for the devices of companies already in the space of 814 ± 675 days, $p < .001$. This finding suggests that new entrants into the space marketed devices that were based on older technologies.

FDA review for the first entry into the NRY/POL space, the Merci Retriever by Concentric, was longer than the review time for all but one of the other first-time entrants. The mean review time for first-time entrants who followed Concentric was 163 ± 66 days, while the review time for the Merci Retriever was 257 days.

Overall, first-time entrants also experienced longer review times at FDA. The interval between the 510(k) submission and FDA clearance for all first-time entrants was 170 ± 69 days, compared with an interval of 117 ± 92 days for manufacturers already in the space, $p = .03$. Review times for first time entrants were not significantly affected by whether clinical trial data was included in the 510(k) submission.²²⁵ Overall, FDA review times were significantly shorter for 510(k) clearances that neither included clinical trial data nor were the manufacturer's first entry into the space, at a mean of 112 ± 91 days, compared to a mean of 169 ± 80 days for all other submissions, $p = .011$.

2. Innovation Within the NRY/POL Technology Space

Of the devices in this space, 71.8% (61 of 85) served as predicates in later 510(k) clearances. That is, most devices in this space could be seen as providing the technological basis for later generations of devices. Devices that served as predicates were cited by subsequent devices a mean of 2.2 ± 1.4 times, ranging from 1 to 7 times. Notably, though, this leaves a sizeable minority of devices—28%—that had not, by the close of the study, been cited as a predicate. These devices might be considered to have been evolutionary dead-ends, devoid of value to future innovation.

Overall, cleared devices tended to be relatively young when they were modified (as reflected by the clearance of a new device citing the earlier device as a predicate). The mean age of the predicates at the time the subject device was cleared was 968 ± 806 days, ranging from 46 to 4439 days. Thus, manufacturers in

225. Review times for first time entrants and without clinical trial data were 162 and 174 days, respectively, $p = .79$.

the NRY/POL space innovated by modifying existing devices that were a mean of 2.7 years old.

Innovation in the NRY/POL space occurred predominantly internally to each manufacturer, not through technology transfers or borrowing from competitors.²²⁶ The majority of cleared 510(k) submissions (63, or 75%) cited only the same manufacturer's device or devices as predicates. Of the 21 cleared submissions that did cite a different manufacturer's device, three were submissions in which the predicate and subject devices manufacturers were in a relationship—in which one owned or had a distribution agreement with the other. Ten of the submissions were the manufacturer's first entry into the technology space, for which the manufacturer likely had no choice but to cite devices made by others. Taking these points into account, only 9.5% (n = 8) of the 510(k) clearances were obtained by manufacturers who were already in the technology space and who were citing technology belonging to a competitor, making this practice quite uncommon. Most innovation consisted of manufacturers modifying their own, already-cleared devices.

Further, the borrowing that did occur was of older technologies. When manufacturers cited a different manufacturer's device as a predicate, the predicates were older (1413 ± 850 days) than when manufacturers cited their own devices (753 ± 603 days, $p < .001$). This difference was even more pronounced when manufacturers' relationships were taken into account, 1518 ± 754 versus 770 ± 646 days, $p < .001$.²²⁷

Finally, the study provides evidence for how frequently manufacturers innovated by combining the features of more than one already-marketed device, as opposed to incorporating new technologies. Of the 510(k) clearances in the study, 40% cited more than one predicate, and 56% cited either more than one predicate or at least one predicate and at least one reference device. In this technology space, then, combining existing technologies was an important way in which manufacturers innovated. Considering that manufacturers rarely cited other

226. I use the term borrowing to refer to any adoption of one manufacturer's technological features by another manufacturer, whether through licensing or other agreements, or outside of such a relationship.

227. That is, if the subject and predicate device manufacturers had a relationship (one owned the other, had a distribution agreement), they were considered the same actor.

manufacturers' devices, this combination-based innovation most often involved manufacturers combining technological features of their own already-marketed devices in new ways.

3. Comparing Innovation Under the 510(k) and PMA Supplement Pathways

It has frequently been asserted that the 510(k) pathway is more innovation-friendly than the PMA pathway.²²⁸ This comparison is largely inapt. Because of the substantial equivalence standard that applies to 510(k) clearance decisions, most 510(k) devices are the result of relatively limited modifications of already-cleared Class II devices; that is, the 510(k) pathway functions as a regulator of incremental innovation in intermediate risk devices. By contrast, new devices submitted for an original PMA approval tend to diverge more substantially from earlier devices. Some devices submitted for new PMA approval are transformational. Their technologies or uses are novel, and their impact on clinical outcomes, are revolutionary. Other devices submitted for new PMA approval diverge substantially from the submitting manufacturer's already-approved devices; otherwise, the manufacturer could have opted to use one of the far less burdensome PMA Supplement pathways. Thus, the PMA pathway functions as a regulator of high-risk device innovation that tends much more toward the transformational or divergent. For intermediate risk devices, the De Novo pathways regulate a similar range of transformational and divergent innovation; thus, the more appropriate comparator for innovation under the PMA pathway is the De Novo pathway.

The PMA Supplement pathways, as noted above, regulate high-risk devices whose technology or uses are characterized as relatively limited modifications of already-approved devices. Thus, the PMA Supplement pathways serve a regulatory function for Class III devices analogous to the 510(k) pathway for Class II devices. Both regulate incremental innovation. As a result, comparisons of innovation that occurs under the 510(k) and PMA Supplement pathways are more appropriate. Unfortunately, there has been little empirical analysis comparing innovation under these two frameworks.

228. See discussion *supra* Part II.B.

The ideal way to assess the impact of FDA regulation on the incremental innovation of Class II and Class III devices would be to compare all innovations that have occurred under the 510(k) pathway and the PMA Supplement pathways. This is obviously impossible in a small-scale pilot project. Therefore, I used a different approach, which involved creating a limited comparison cohort of PMA Supplement devices that are as closely related to NRY/POL devices as possible. Although perfect analogs do not exist, the goal was to compare NRY/POL devices to a set of Class III devices that are intended for use in the cerebral arteries and that raise the same general risks as the NRY/POL devices.

To create the comparison group, I downloaded the complete set of FDA product codes in use on August 18, 2022 (n = 6761) from FDA website.²²⁹ I identified a subset of product codes, those for Class III Cardiovascular (CV) and Neurology (NE) devices (n = 135). These codes were examined to identify those that are assigned to devices that are (or are deployed by) catheters and that are intended for use in cerebral vessels. Seven product codes were identified; however, three of these codes (HBZ, NUF, LME) had not been assigned to any devices that had been granted premarket approval. As a result, four products codes were used to create the comparison group; they are summarized in Table 2.

Table 2: Class III Comparator Product Codes

Product Code	Description
NIM	Carotid Stent
OPR	Intravascular Flow Disruption Device
OUT	Intracranial Aneurysm Flow Diverter
QCA	Intracranial Coil-Assist Stent

I downloaded data about all PMA approvals (initial and supplements) for the devices bearing these four product codes

²²⁹. *Download Product Code Classification Files*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/medical-devices/classify-your-medical-device/download-product-code-classification-files> (last visited Mar. 24, 2024).

from FDA's PMA website.²³⁰ The same study period (August 11, 2004, to June 6, 2022) was used for the analysis.

All these devices utilized catheter-based technologies, were used in the cerebral vasculature, and thus raised similar safety issues related to vascular rupture, vascular trauma, downstream embolization, and so on. Thus, treating all four of the Class III devices product codes as a single technology space seemed reasonable to assess the feasibility of comparing innovation between devices regulated under the 510(k) and PMA Supplement pathways, and for beginning to develop hypotheses about how innovation differed that could be tested in a large-scale study.

Replicating parts of the analysis described above, I examined the proportion of PMA devices that served as the basis for future incremental innovation by examining how many original PMA approved devices were modified by at least one PMA Supplement.²³¹ All 15 of the original PMA approved devices in the database (100%) had been modified at least once. This was significantly higher than the 71.8% of 510(k) devices that were modified at least once (as reflected by being cited as a predicate) ($p = .019$).²³²

As discussed above, manufacturers of PMA devices may need to seek approval for modifications to their devices through the Real-Time Supplement, Manufacturing Site Change Notice,

230. *Premarket Approval (PMA)*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm> (last updated Mar. 11, 2024).

231. The data here do indicate that the barriers to entry into a technology space are higher for devices submitted for an original PMA approval. Unlike the analysis described in the body of the article above, to compare the entry of devices into the four technology spaces regulated using the NIM, OPR, OUT, and QCA product codes, I treated each code as sufficiently distinct from the others such that it is not appropriate to refer to them as comprising a single technology space like the NRY/POL space. Thus, comparing the total number of competitors that entered the four spaces is inapposite. Treating each code as a distinct technology space, the mean number of market participants was much smaller than the NRY/POL space at 3.0 (range 1–6). This is consistent with high barriers to entry for new participants into PMA technology spaces that others have suggested, particularly in comparison to barriers to entry for 510(k) spaces. See, e.g., Ariel Dora Stern, *Innovation Under Regulatory Uncertainty: Evidence from Medical Technology*, 145 J. PUB. ECON. 181, 193 (2017).

232. Because there were no PMA devices that were not modified, the value of that cell in a Chi Square test would be zero, making the test impossible. Fisher's Exact T-Test was used instead.

and 30-Day Notice PMA Supplement pathways.²³³ The standard for submitting one of these PMA supplements—when a manufacturer makes minor changes to their devices—is not the same as the standard for a new 510(k) submission, making comparisons of innovation under these pathways inappropriate. However, the standard for when a manufacturer of a PMA device must seek approval under the Panel Track and 180 Day PMA Supplement pathways is the same as the standard for when the manufacturer of a 510(k) device must seek a new 510(k) clearance for a modified version of that device. A new Panel Track or 180 Supplement approval or 510(k) clearance is required when a manufacturer makes a “significant change” to an existing device.²³⁴ When considering only 180-day or Panel Track supplement approvals, 13 of the PMA devices (86.7%) underwent at least one such modification. This difference was not significantly different from the 71.8% of 510(k) devices that underwent modification, $X^2(1, N = 85) = 1.5, p = .225$.

I also compared the rate of innovation of devices regulated under each pathway, using the time to first modification as a proxy. The time to first modification of a 510(k) device was defined as the interval from the date of the 510(k) clearance of that device to the date of the first subsequent 510(k) clearance that cited that device as a predicate. The time to first modification of a PMA device was defined as the interval from the date of the initial PMA approval to the date of the first supplemental PMA approved for that device. The mean interval from initial approval to the first modification for the PMA devices was 239 ± 278 days. This was significantly shorter than the mean interval to first modification of 510(k) devices (456 ± 400 days, $p = .02$). When considering only 180-day or Panel Track supplement approvals, the mean interval to the first modification was 312 ± 277 days. Compared with the interval to first modification of 510(k) devices, the mean interval for the PMA devices remains shorter, although the difference is no longer statistically significant ($p = .13$). This analysis provides support for a counterintuitive hypothesis: that the incremental innovation of 510(k) devices may not occur more frequently than the incremental innovation of PMA devices.

233. See *supra* notes 52–53 and accompanying text.

234. See *supra* notes 54–57 and accompanying text.

V. CONSTRUCTING AN EMPIRICAL ACCOUNT OF AND
GENERATING EMPIRICALLY TESTABLE HYPOTHESES
REGARDING 510(K) DEVICE INNOVATION

Many discussions of FDA regulation of medical devices under the 510(k) pathway can be reduced to the claim that such regulation stifles innovation. Under this view, potentially life-saving devices are never developed and even when they are, patients in the United States face substantial delays in gaining access to beneficial new technologies.²³⁵ A somewhat opposing viewpoint is that the 510(k) is more innovation-friendly than the PMA pathway. Under this view, manufacturers are incentivized to innovate incrementally, as opposed to developing transformative or divergent new devices. Other discussions are pessimistic about what we can know. They urge that empirical study of innovation under the 510(k) pathway is not feasible. A far more nuanced picture of innovation under the pathway emerges from the discussion of device regulation in Part I and the empirical findings presented in Part IV. The study also provides reason to challenge the Institute of Medicine's 2011 conclusion that empirical study of the 510(k) pathway would not be worth the time, effort, and money involved.

A. COMPETITION, INNOVATION, AND THE GROWTH OF THE
NRY/POL SPACE

The study provides a mixed picture of the vibrancy of medical device innovation under the 510(k) pathway. A large number of manufacturers entered into the NRY/POL technology space in a short period of time. Over less than two decades, a technology space that was, in 2004, nonexistent (except for off-label use of devices not specifically designed for use in the cerebral vasculature) grew into a space in which twelve companies marketed 85 different devices featuring a wide diversity of technological features. This rapid growth offered clinicians and their patients a range of options for averting the permanent and severe neurologic consequences of ischemic stroke, a common and devastating medical condition. The entry of such a large number of competitors prevented the original market entrant from maintaining a monopoly position and might have driven rapid and beneficial innovation, while lowering device-related costs.

235. See *supra* notes 131–35 and accompanying text.

All of this would suggest that innovation under the 510(k) pathway was robust and would seem to refute claims that FDA regulation under the pathway was stifling beneficial innovation. It would seem to support claims that barriers to entry for companies into a 510(k) technology space are relatively low, especially in comparison to the barriers to entry for devices marketed through the PMA pathway.²³⁶

However, innovation within this space of 510(k) devices was more limited than this superficial description would suggest. Although twelve companies have entered the NRY/POL space, the ultimate impact of this on competition and innovation is unclear.²³⁷ For many years, a very small number of companies were the only participants in the space. Entry by manufacturers into the space was delayed by longer review times, more frequent clinical trial requirements, and the practice of citing (and thus drawing on the technology of) older devices as predicates. To the extent that the entry of multiple competitors increased innovation, the level of competition was quickly reduced by the acquisition of newer, smaller firms by larger firms and by contractual relationships formed between would-be competitors.

Although twelve different companies had entered the NRY/POL technology space by the end of the study, the original entrant, Concentric, was the sole company in the technology space for more than three years before the Penumbra entered in late 2007. Until 2018, just three manufacturers (Penumbra, Concentric, and Micro Therapeutics) were the only participants in the space. Thus, over the first fourteen years of the existence of the NRY/POL space, competition was quite limited.

Further, new entrants faced barriers to entry that may have further diminished the levels of competition and innovation

236. See Stern, *supra* note 231, at 183.

237. In addition to the discussion that follows, the economics literature casts doubt on the widely-held belief in a monotonic, positive correlation between competition and innovation—that more competition equals more innovation. See, e.g., Zoltan J. Acs & David B. Audretsch, *Testing the Schumpeterian Hypothesis*, 14 E. ECON. J. 129, 130 (1988) (describing Schumpeter's later claims that less competition and even monopolism resulted in more innovation); Philippe Aghion et al., *Competition and Innovation: An Inverted-U Relationship*, 120 Q. J. ECON. 701, 701 (2005) (finding an inverted U-shaped relationship between competition and innovation. I claim no expertise in this field. I simply point out that analysis of the number of market participants is not sufficient, on its own, to determine how much innovation is occurring in a given technology space.

within the space. First-time entrants were more frequently required to provide clinical trial data. Clinical trial data was significantly more frequent in the 510(k) submissions of new entrants (33% of first-time clearances (4 of 12) compared with 9.7% (7 of 72) of subsequent clearances). Performing clinical trials is costly in terms of effort and expense, and it can delay market entry by several years at a time when young and undercapitalized companies are burning through their available funds. Additionally, although the methodologies used here do not permit an analysis of how many would-be market entrants simply never chose to develop an NRY/POL device, this possibility must not be discounted.

First-time entrants also experienced longer review times at FDA. The interval between the 510(k) submission and FDA clearance for first-time entrants was 170 ± 69 days, compared with an interval of 117 ± 92 days for manufacturers already in the space, $p = .03$. Although a difference of just under two months may seem relatively small, survey participants from the device industry reported average monthly expenditures during the process of seeking 510(k) clearance of over \$500,000.²³⁸ This burn rate would drain nearly one million dollars from company reserves, which is not a trivial amount for new companies who may not have marketed any devices up to that point.

Professor Ariel Stern has suggested the existence of a first-mover disadvantage in PMA devices that are the first to enter a new technology space (as defined by a new product code); that is, the first company to submit a new kind of device for FDA approval faces longer and more intensive regulatory scrutiny.²³⁹ In the PMA context, the reason for a first-mover disadvantage did not appear to be related to FDA's relative unfamiliarity with new technologies. Rather, the disadvantage arose from "uncertainty about the content and format of information required for regulatory approval."²⁴⁰ In the NRY/POL space, the first market entrant, Concentric, experienced a longer review time compared to the eleven companies that later entered the space. Concentric's first NRY/POL device, the Merci Retriever, had an FDA review time of 257 days. The mean review time for all other first-time entrants was 162 ± 66 days. Thus, the study

238. Makower et al., *supra* note 16, at fig.9.

239. Stern, *supra* note 231, at 183.

240. *See id.*

presented here is consistent with a first-mover disadvantage in 510(k) technology spaces as well. The reason for this may be similar to that in the PMA context. In the 510(k) context, Concentric was citing as its predicate for the Merci Retriever a device FDA had already cleared as a general cardiology catheter, Concentric's Modified Retriever. Given the substantial equivalence standard, the technological features of the Merci should not have deviated too far from those of the Modified Retriever. Thus, it seems reasonable to postulate that the longer review time—the first-mover disadvantage—was due to FDA's unfamiliarity with the use of a technology with which CDRH personnel were already familiar in a clinical setting with which those personnel were unfamiliar.

The study also showed that overall, first-time entrants experienced longer FDA review times than companies already in the technology space. Again, these new entrants were citing devices that the Agency had already cleared as predicates. For the entrants after Concentric, FDA personnel had experience with both the technologies and the clinical setting in which those technologies were to be used. Further, the later entrants should not have faced uncertainties over the content and format of the information required in a 510(k) submission. This suggests that the longer review times and more frequent requirements for clinical trial data for first-time entrants was related to FDA's unfamiliarity with the manufacturers' skill and expertise specific to the technology space, as opposed to the technology or the required information.

New market entrants tended to introduce devices modeled on older technologies. Their first devices in the NRY/POL space cited predicates that were on average twice as old as devices cited by manufacturers already in the space. The practice of citing older devices may have arisen in part from the perception that citing another manufacturer's device as a predicate exposes a new entrant to liability for patent infringement.²⁴¹ Although the 510(k) pathway allows manufacturers to rely on other companies' technology to support a substantial equivalence finding, the pathway does not relieve new market entrants of the

241. Suneel Arora et al., *The Interplay Between FDA and Patent Law: Infusing Organizational Knowledge for Medical Device Companies*, 39 WM. MITCHELL L. REV. 1176, 1187 (2013).

risk of liability for patent infringement.²⁴² Thus, new market entrants, who must often cite the technology of other companies as predicates, may be limited to citing older devices that are no longer patent-protected.²⁴³

Competition in the NRY/POL space was also limited by the formation of private relationships between would-be competitors. Three companies acquired, were acquired by, or signed distribution deals with several of the other companies that entered the space.²⁴⁴ Thus, the three dominant companies respectively account for 86% of the devices in the space. This finding is consistent with a commonly accepted account of innovation in the medical device industry, in which new technologies are developed by smaller startup companies, which, if promising, are later acquired by larger, existing companies.²⁴⁵

The results discussed here present a decidedly mixed picture of competition in the NRY/POL space of 510(k) devices. Although competition and innovation do not necessarily exhibit a monotonic relationship—that is, less competition may not equal less innovation—the early evolution of the NRY/POL space suggests that more competition can have favorable effects on innovation. It was Penumbra, a new entrant at the time, which introduced the aspiration technology that now comprises half of all devices that have been cleared. Ultimately, the question to be answered is whether device innovation is resulting in the high-level innovation policy goal of improving public health.²⁴⁶ Data such as that gathered here can provide

242. Although courts have generally refused to admit 510(k) submissions as evidence of infringement, some patent law attorneys caution that “information in the FDA submission may be used to develop a patent infringement case.” *Id.* at 1187.

243. This issue would better be explored using methodologies not adopted here, such as qualitative empirical study using data from interviews with company officials. I have abstained from this approach because it is difficult to use in large-scale study.

244. See *supra* Table 1.

245. Aaron V. Kaplan et al., *Medical Device Development: From Prototype to Regulatory Approval*, 109 CIRCULATION 3068, 3068 (2004) (“Although large medical device companies typically develop successive iterations of existing devices, most new device categories are typically developed by venture-backed start-up companies.”).

246. See *What We Do: FDA Mission*, *supra* note 34 (including in the Agency’s Mission Statement the “responsib[ility] for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable”).

useful insights into how the levels of competition and innovation in different technology spaces correlate with improved health outcomes.

B. CHARACTERIZING INNOVATION IN 510(K) DEVICES

The study also provides important insights into the patterns of innovation in the 510(k) devices of the NRY/POL technology space. Based on the findings, incremental innovation in the 510(k) space studied here was frequent, iterative (in that early models were modified again and again and again), mostly internal to each manufacturer (in that manufacturers rarely cited—and thus likely rarely drew on—the technologies of their competitors), and roughly equally divided between devices that introduced new (or at least modified) technologies and devices that combined existing technologies from two or more earlier devices.

One way to characterize innovation within a technology space is to examine the proportion of devices that are valuable for future innovation. Most of the devices in this space (71.8%) served as predicates in later 510(k) clearances, with these devices being cited by an average of 2.2 later devices. Thus, a large majority of devices appear to have contained technological features that were of value to future innovation. However, this leaves a sizeable minority—28%—of devices that were never cited as predicates. These devices might be considered to have been innovation failures—evolutionary dead-ends, devoid of future innovation value.²⁴⁷ This raises the question of the ideal level of dead-end innovation. Provided that devices satisfy the reasonable assurance of safety and effectiveness standard, some level of innovation failure likely reflects an ideal level of experimentation that can provide useful directions for future innovation. Larger studies might facilitate comparisons of the proportion of innovation failures to improvements (or declines) in health outcomes in different technology spaces over time, which could help to determine an ideal amount of dead-end innovation.

Another way to characterize innovation is by examining how rapidly it occurs. Based on the ages of the predicates cited in the

247. This conclusion, though, should be considered provisional, as the more recently cleared devices that had not been cited as predicates might be cited in the future.

510(k) submissions, the manufacturers in the NRY/POL space innovated by modifying existing devices that were a mean of 2.7 years old, ranging from 1.5 months to 12 years. Although these absolute numbers may have limited value in that there is no comparator, manufacturers might be expected to consider the predicate device to have reached the end of its life cycle, giving the devices in this space a mean market life of under three years. Large studies of 510(k) devices would facilitate comparisons between technology spaces or within the same space over time and thus would be useful for comparing the rates of innovation between related technology spaces or in response to changes in the statutes and regulations that structure FDA regulation. And larger studies, when combined with safety data²⁴⁸ and with health outcome data, might help to establish a threshold level for when innovation is occurring too rapidly—where the rate of iterative innovation outstrips the ability of the regulatory system and practical experience to detect when innovation is increasing patient risks without an adequate increase in improved outcomes.

Innovation may also be characterized by whether it occurs predominantly internally, with manufacturers modifying their own devices, or through technology transfers between manufacturers. In the NRY/POL space, innovation occurred almost entirely internally, with manufacturers modifying their own devices (as reflected by the large percentage of 510(k) clearance in which manufacturers cited only their own devices as predicates). In fact, cross-manufacturer technology borrowing appeared to be a rarity in the cohort of devices studied here, with relatively few 510(k) clearances citing other manufacturers' devices as predicates. Where cross-manufacturer technology transfers did occur, the technology tended to be considerably older. A great deal of the internal innovation in the NRY/POL space resulted from manufacturers combining technological features of their earlier devices in new ways. This suggests that much of the innovation in these devices does not consist of the incorporation of newly developed technologies but rather consists of the recycling of existing stores of technology, knowledge, and expertise. The amount of deepening innovation

248. See generally Horvath, *supra* note 22 (presenting a pilot empirical study of 510(k) device safety).

relative to differentiating innovation that takes place in the 510(k) may be greater than some have assumed.²⁴⁹

One other compelling finding of the study was that innovation may not occur more rapidly under the 510(k) pathway than under the PMA Supplement pathways. Although the 510(k) and PMA Supplement devices included in the study were not perfect analogues, the commonalities in their sites of use and technological features provide for apt comparisons. The study showed that 510(k) devices are not more frequently used as the basis for subsequent innovation (i.e., they are not cited more commonly as predicates than are original PMA devices modified through supplements) and are not modified more quickly than PMA devices. This might be due to specific features of the technology spaces that were studied—it is possible that the innovation of devices intended for use in the cerebral vessels is somehow different from the innovation of other devices. Therefore, this finding should be treated as hypothesis generating. Yet, it does suggest that important factors that limit the rate of innovation reside outside of the constraints imposed by the 510(k) pathway itself.

C. FDA'S ADMINISTRATIVE CHANNELING OF INNOVATION

The potential innovation-channeling function of FDA regulation under the 510(k) pathway is one of the most intriguing findings of this study. FDA designated the new NRY product code in 2004 for use by manufacturers seeking to market 510(k) devices specifically intended to remove clots from the cerebral vessels in patients experiencing an acute stroke. The Agency noted that “[t]he prior clearances in this category have been limited to simply identifying catheter placed in the peripheral, coronary, and cerebral vessels. It is felt that this is a unique claim and should not be combined with previously cleared catheters under a general [product code].”²⁵⁰ According to Agency guidelines, product codes are “a method of internally classifying and tracking medical devices.”²⁵¹ They are created and assigned by CDRH personnel,²⁵² and do not involve rulemaking.

249. Cf. Price, *supra* note 106.

250. *Product Classification entry for “NRY”, supra* note 192.

251. FDA PRODUCT CODE GUIDANCE, *supra* note 191, at *4.

252. *Id.*

The creation of the NRY product code had several important real or potential impacts on device innovation. The new code allowed FDA to exercise closer oversight over catheters intended for the removal of blood clots in the cerebral vasculature. Unlike older cardiovascular catheters like the Modified Concentric, which were regulated under the regulations for the entire generic device type of intravascular catheters,²⁵³ FDA deemed NRY and POL devices not eligible for third-party review.²⁵⁴ This ensured that premarket evaluation would be conducted solely by FDA. The Agency also deemed NRY and POL devices to be ineligible for summary malfunction reports,²⁵⁵ ensuring that FDA receives full information about device-related harms. The clerical assignment of a product code allowed the Agency to exercise closer regulatory oversight over these devices.

The new product code also gave FDA the ability to impose specific requirements to ensure the safety of neurovascular catheters. Although the Agency has not done so to date, it has the authority to adopt performance standards, consensus standards, and other requirements specifically tailored to the risks posed by NRY and POL devices. Thus, by channeling new devices through the NRY and POL product codes, FDA provided itself with the ability to tailor regulation to the specific risks posed by these devices.

Finally, by creating the NRY and later the POL product codes, FDA may have channeled the direction of innovation, ensuring that new devices would build on the specific features of earlier NRY/POL devices instead of the features of general cardiology catheters. The database assembled for this study clearly demonstrates this innovation-channeling possibility. After FDA cleared the Merci Retriever, the devices that gained 510(k) clearance almost exclusively cited other NRY/POL devices as predicates. Out of a total of 83 later clearances, only three cited a device outside the NRY/POL space as a predicate, and of these, two also cited at least one NRY/POL device. Thus, the NRY/POL technology space that FDA created evolved through the iterative modification of earlier NRY/POL devices.

253. 21 C.F.R. § 870.1250.

254. *Product Classification entry for "NRY", supra note 192 (showing NRY devices ineligible for third-party review).*

255. *Id.*

Prior to the creation of the NRY product code, general purpose catheters used to retrieve foreign bodies from the peripheral vasculature were being used off-label as physician's sought mechanical ways to interrupt ischemic strokes. These general-purpose catheters had evolved through iterative 510(k) clearances, but their technological features were more appropriate for use the peripheral arterial system and for removing rigid objects.

Once the first NRY device was cleared, though, the evolution of devices used for removing thrombus from the cerebral vessels took on a new direction. FDA guidance documents establish an expectation that a new subject device will cite a predicate that bears the same product code.²⁵⁶ This expectation—and the resulting reality—of subsequent device innovation building almost exclusively on NRY (and later POL) devices led to novel technological features that are better adapted for use in the cerebral vessels and for use in extracting friable thrombi.²⁵⁷ Although these features could have evolved even without a new product code, FDA clearly provided an incentive for and likely accelerated their development.

One illustration of this channeling effect is seen in the development of thrombectomy catheters that utilize suction or aspiration—instead of grasping the easily fragmented blood clots, these catheters use suction to remove the clot from the artery into the catheter itself. Another illustration is the evolution of the tips of catheters utilizing mechanical retrieval processes.

This channeling effect was accomplished largely through soft power. FDA did not need to promulgate regulations establishing performance standards or recognizing consensus standards; nor did the Agency need to issue guidance specifically addressed to devices in this technology space. Instead, FDA channeled the innovation of these devices through the administrative expedient—essentially a housekeeping chore—of creating a new product code. Thereafter, the development of the NRY/POL technology space took place from the bottom up, through manufacturers iteratively modifying devices to better

256. FDA PRODUCT CODE GUIDANCE, *supra* note 191, at *5.

257. See, e.g., William Boisseau et al., *Direct Aspiration Stroke Thrombectomy: A Comprehensive Review*, 12 J. NEUROINTERVENTIONAL SURGERY 1099 (2020) (discussing the development and application of aspiration catheters for thrombectomy in acute strokes).

tailor them for their specific intended use, in response to administrative decisions at a sub-regulatory level within CDRH. FDA, it turns out, can exert a strong influence on the direction of innovation using means that fall under the radar. There is little reason to think the Agency cannot do the same in other technology spaces.

Some may question the legitimacy of FDA regulation through product code creation and maintenance. On the other hand, the creation of the NRY product code enabled the Agency to ensure the safety of a new set of devices. The devices from which the NRY/POL devices descended were already being used off-label for this purpose. Such off-label uses of medical devices, which are legally permitted and are essential to the delivery of medical care, are not regulated by FDA. By creating a new product code, the Agency ensured that devices used to remove clots from the cerebral vessels in stroke patients fell within a technology space over which FDA had regulatory authority. Had the Agency not created the technology space it would have possessed only a limited ability to ensure the safety of the products used in this procedure.

CONCLUSION

In 2011, the Institute of Medicine concluded that empirical study of the 510(k) pathway would not provide enough useful information to justify the time, effort, and money that would be involved. The study presented here suggests that this conclusion, even if sound at the time, is no longer supportable. If the methods used here can be sufficiently scaled up,²⁵⁸ empirical study of innovation (and safety) under the 510(k) pathway would not only be feasible but would be valuable to formulating proposals to reform the pathway.

258. This question is part of a planned, larger feasibility study.