

REGULATING PERSONALIZED MEDICINE

Sarah Y. Kwon[†]

In this time of exceptional scientific and technological breakthroughs, health care is in a historic transition towards personalized medicine.¹ Personalized medicine, or precision medicine, is an emerging health care model for disease treatment and prevention strategies that takes into account each person's genetic variations, environment, and lifestyle.² Advances in genetic testing allow diagnosis of diseases,³ identify risk of genetic transmission of diseases,⁴ assess future risk of disease,⁵ and help target treatments.⁶ Today, a single laboratory can sequence an entire human genome in about twenty-four hours for just a few thousand dollars—making routine genomic profiling a near-reality.⁷ Drawing on this momentum, President Obama announced his Precision Medicine Initiative during the 2015 State of the Union address,⁸ energizing both public and private efforts to usher in personalized medicine.

The success of personalized medicine hinges on diagnostic tests involving key innovations such as genomic sequencing technologies.⁹ Such innovative diagnostic tests, however, also pose both potentially greater risks

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[†] J.D. Candidate, 2017, University of California, Berkeley, School of Law.

1. See PERSONALIZED MEDICINE COAL., *THE CASE FOR PERSONALIZED MEDICINE* 3–5 (4th ed. 2014).

2. Nat'l Insts. of Health, *Precision Medicine*, GENETICS HOME REFERENCE (Jan. 11, 2016), <http://ghr.nlm.nih.gov/handbook/precisionmedicine?show=all> [<https://perma.cc/8T9B-UHXA>].

3. See, e.g., *Testing for CF*, CYSTIC FIBROSIS FOUND., <https://www.cff.org/What-is-CF/Testing> [<https://perma.cc/N5RP-KU4S>].

4. See, e.g., *Learning About Tay-Sachs Disease*, NAT'L HUM. GENOME RES. INST. (Mar. 17, 2011), <https://www.genome.gov/10001220> [<https://perma.cc/3RXC-NQDW>].

5. PERSONALIZED MEDICINE COAL., *supra* note 1, at 8.

6. Margaret A. Hamburg & Francis S. Collins, *The Path to Personalized Medicine*, 363 *NEW ENG. J. MED.* 301, 301 (2010).

7. Francis S. Collins & Margaret A. Hamburg, *First FDA Authorization for Next-Generation Sequencer*, 369 *N. ENGL. J. MED.* 2369, 2369 (2013).

8. *The Precision Medicine Initiative*, WHITE HOUSE, <https://www.whitehouse.gov/precision-medicine> [<https://perma.cc/D338-4TWP>].

9. See Hamburg & Collins, *supra* note 6, at 302.

to patients and new regulatory challenges.¹⁰ Rapid advances in genomic sequencing technologies not only strain the U.S. Food and Drug Administration's (FDA) present regulatory framework, but also cast doubt on the agency's regulatory role in this new clinical landscape.

Recognizing the promise and challenge of personalized medicine, FDA is currently finding its regulatory foothold during this transition in the practice of medicine.¹¹ After decades of non-enforcement, the agency recently announced its plan to actively regulate diagnostic tests developed and used by laboratories ("laboratory-developed tests" or LDTs).¹² FDA's efforts to keep pace with these technological advances have been met with heated opposition from various stakeholders who challenge FDA's authority to regulate LDTs.¹³ The success of FDA's efforts will thus depend on its ability to adeptly modernize its regulatory framework to ensure that clinicians and patients can safely rely on increasingly complex and prevalent diagnostic tests without barring access to innovation.¹⁴

Part I of this Note provides a brief overview of the science and technology behind DNA sequencing technologies and diagnostic tests and compares the traditional health care model with the emerging field of personalized medicine. Part II introduces current federal regulatory oversight of diagnostic tests. Part III discusses the challenges in adapting regulatory oversight to today's diagnostics landscape. Specifically, FDA must first address regulatory gaps before it can begin to regulate diagnostic tests vital to the success of personalized medicine. Part IV analyzes the legal viability of FDA's attempts to fill in the regulatory gaps regarding diagnostics. In particular, Part IV considers FDA's statutory authority over LDTs, the practice of medicine limitation, potential pre-emption by the Clinical Laboratory Improvement Amendments (CLIA), and undesirable consequences of FDA oversight of LDTs.

10. See generally Eric S. Lander, *Cutting the Gordian Helix—Regulating Genomic Testing in the Era of Precision Medicine*, 372 N. ENGL. J. MED. 1185 (2015).

11. See *Continuing America's Leadership: Realizing the Promise of Precision Medicine for Patients: Hearing Before the Comm. on Health, Ed., Labor & Pensions*, 114th Cong. 3–4 (2015) (statement of Jeffrey Shuren, Director of Ctr. for Devices and Radiological Health, U.S. Food & Drug Admin.).

12. See U.S. Food & Drug Admin., Draft Guidance For Industry, Clinical Laboratories, And FDA Staff: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) 5 (Oct. 3, 2014), <http://www.fda.gov/downloads/medical-devices/deviceregulationandguidance/guidancedocuments/ucm416685.pdf> [<https://perma.cc/ZX68-4S3X>] [hereinafter LDT Draft Guidance].

13. See *infra* Part IV.

14. See *id.*

I. THE SCIENCE OF PERSONALIZED MEDICINE

Rapid advancements in the field of genomics have enabled scientists to develop tests to assess an individual's risk of developing a wide range of diseases. The advent of these increasingly sophisticated diagnostics continues to disrupt the traditional health care model, thus making way for personalized medicine.

A. GENETICS

Deoxyribonucleic acid (DNA) is the blueprint of our genetic makeup, or genome.¹⁵ A gene is a segment of DNA that encodes a specific protein or trait.¹⁶ DNA coding is made up of four chemical bases: adenine, guanine, cytosine, and thymine.¹⁷ DNA bases pair with each other in a zipper-like double helix structure.¹⁸ The human genome consists of three billion base pairs, ninety-nine percent of which are the same in all people.¹⁹ Except for rare somatic mutations,²⁰ an individual's genome sequence does not change.²¹

Inheritable, or "Mendelian," disorders such as cystic fibrosis and Huntington's disease can be caused by a single genetic mutation.²² These diseases are generally highly penetrant, meaning the mutation highly correlates with disease risk.²³ Other common diseases such as cancer and diabetes are much more complex and much less penetrant; they are likely associated with the interplay of numerous genetic and environmental factors and are thus more difficult to predict.²⁴

15. *Deoxyribonucleic Acid (DNA) Fact Sheet*, NAT'L HUMAN GENOME RES. INST. (June 16, 2015), <https://www.genome.gov/25520880> [<https://perma.cc/7TYV-TJ55>].

16. *Id.*

17. *Id.*

18. *Id.*

19. *What is DNA?*, NAT'L INSTS. OF HEALTH (Mar. 7, 2016), <http://ghr.nlm.nih.gov/handbook/basics/dna> [<https://perma.cc/J7ZE-N6N9>].

20. Somatic mutations are non-inherited genetic mutations. They are frequently caused by environmental factors such as ultraviolet radiation exposure. *See Somatic Mutation*, NAT'L INSTS. OF HEALTH (Mar. 7, 2016), <http://ghr.nlm.nih.gov/glossary=somaticmutation> [<https://perma.cc/57DD-T8WZ>].

21. *See* Williams E. Evans & Howard L. McLeod, *Pharmacogenomics—Drug Disposition, Drug Targets, and Side Effects*, 348 N. ENGL. J. MED. 538, 546 (2003).

22. *See* Wenfei Jin et al., *A Systematic Characterization of Genes Underlying Both Complex and Mendelian Diseases*, 21 HUM. MOLECULAR GENETICS 1611, 1611 (2012).

23. *See* Kari Hemminki et al., *The Balance Between Heritable and Environmental Aetiology of Human Disease*, 7 NATURE 958, 958 (2006).

24. Jin, *supra* note 22.

B. DIAGNOSTIC TESTS

In vitro molecular diagnostic tests are laboratory procedures used to detect and analyze genetic sequences and other biomarkers in collected patient samples.²⁵ Diagnostics play an increasingly important role in the practice of medicine, impacting as high as seventy percent of health care decision making.²⁶ Notably, genetic testing is likely the fastest growing field in diagnostics.²⁷ DNA sequencing provides information that can reveal underlying genetic causes of diseases, in turn enabling the development of increasingly sophisticated diagnostic tests.²⁸ While early genetic tests were developed to detect rare, relatively straightforward single-gene variations highly correlated with a specific disease (i.e. “Mendelian” diseases), today’s genetic tests examine more common, complex diseases by detecting multiple, often novel genes.²⁹

In particular, next generation sequencing (NGS) is widely expected to transform the nature of genetic testing.³⁰ NGS generally refers to new high-throughput technologies that generate millions of sequences simultaneously for whole-genomic analysis from a single sample.³¹ Whole-genome sequencing technology promises to have a striking impact on genomic research and clinical diagnostics by “allow[ing] any lab to test any sequence for any purpose.”³² Because a single NGS test can generate a vast amount of genetic information, high-power computational analysis is a crucial aspect of NGS technology.³³

25. See KEWAL K. JAIN, TEXTBOOK OF PERSONALIZED MEDICINE 91–96 (2d. ed. 2015) (ebook).

26. *Id.* at 35.

27. Douglas A. Grimm, FDA, CLIA, or a “Reasonable Combination of Both”: Toward Increased Regulatory Oversight of Genetic Testing, 41 U.S.F. L. REV. 107, 107 (2006).

28. See U.S. FOOD & DRUG ADMIN., PAVING THE WAY FOR PERSONALIZED MEDICINE 30 (2013) (“Volumes of information arising out of the human genome project combined with a dramatic decrease in costs of DNA sequencing . . . are giving way to an explosion of publications linking particular genetic markers to diseases or conditions and a rapid application of this information in the development of new molecular diagnostic tests.”).

29. Michael M. Hopkins & Paul Nightingale, The Economic Dynamics of Modern Biotechnology 142 (Maureen D. McKelvey et al. eds., 2004).

30. See Gail H. Javitt & Katherine Strong Carner, *Regulation of Next Generation Sequencing*, 42 J.L. MED. & ETHICS 9, 9 (2014).

31. Ayman Grada & Kate Weinbrecht, *Next-Generation Sequencing: Methodology and Application*, 133 J. INVESTIGATIVE DERMATOLOGY 1, 1 (2013).

32. See Collins & Hamburg, *supra* note 7, at 2371.

33. See Jun Zhang et al., *The Impact of Next-Generation on Genomics*, 38 J. GENETICS & GENOMICS 95, 100–01 (2011) (“The benefits of NGS sequencing will not be fully

Though it has had little clinical impact so far, NGS is now transitioning from laboratory research to clinical use.³⁴ With significantly higher throughput and dramatically lower costs, the technology has advanced to the point of the near-widespread availability.³⁵ By offering an efficient, cost-effective means of identifying a wide range of genetic variants within a single test, NGS technologies will be a cornerstone in the success of personalized medicine.³⁶

C. HEALTH CARE MODELS

Health care is traditionally performed by a “one-size-fits-all” approach, whereby diagnosis and treatment selections are based on broad population averages.³⁷ In other words, a physician traditionally attributes a set of symptoms to a generally associated disease. Physical symptoms, however, can mask a whole range of causes.³⁸ As a result, a doctor must prescribe various medications and treatments associated with a disease in a trial-and-error manner without particular specificity to the underlying cause.³⁹

Personalized medicine, on the other hand, allows for “the right drug at the right dose at the right time.”⁴⁰ For example, pharmacogenomics—perhaps the most emblematic field in personalized medicine—uses genomic information to study an individual’s response to drugs.⁴¹ Different genetic mutations can cause a disease that, despite similar symptoms, responds to different treatments.⁴² Genetic tests can uncover the mutations underlying a disease, enabling physicians to deliver the most effective treatment strategy and thus potentially sparing patients unnecessary expenses and

appreciated until extremely high-performance computing and intensive bioinformatics support is available. The information accrued by NGS may lead to a paradigm shift in the way that genetics and bioinformatics converge.”).

34. See Jason M. Rizzo & Michael J. Buck, *Key Principles and Clinical Applications of “Next-Generation” DNA Sequencing*, 5 *CANCER PREVENTION RES.* 887, 990 (2012).

35. See Turna Ray, *With \$999 Whole-Genome Sequencing Service, Veritas Embarks on Goal to Democratize DNA Information*, GENOMEWEB (Mar. 6, 2016), <https://www.genomeweb.com/sequencing-technology/999-whole-genome-sequencing-service-veritas-embarks-goal-democratize-dna> [<https://perma.cc/ZBS4-XP72>].

36. See Leslie G. Biesecker & Robert C. Green, *Diagnostic Clinical Genome and Exome Sequencing*, 370 *N. ENGL. J. MED.* 2418, 2418 (2014).

37. Nat’l Insts. of Health, *supra* note 2.

38. See Evans & McLeod, *supra* note 21, at 538.

39. See *id.*

40. Hamburg & Collins, *supra* note 6.

41. *What is Pharmacogenomics?*, NAT’L INSTS. OF HEALTH (Mar. 7, 2016), <https://ghr.nlm.nih.gov/handbook/genomicresearch/pharmacogenomics> [<https://perma.cc/AJ7X-J2M9>].

42. Evans & McLeod, *supra* note 21, at 538.

adverse side effects.⁴³ Because of their profound impact on the health care model, DNA sequencing diagnostics play a fundamental role in personalized medicine.⁴⁴ Furthermore, personalized medicine has a more preventive focus as compared to the traditional health care model, which essentially reacts to the onset of disease.⁴⁵ As a result, physicians increasingly rely on genetic test results in making crucial treatment decisions.

II. CURRENT FEDERAL REGULATORY OVERSIGHT OF DIAGNOSTIC TESTS

Two federal regulatory agencies currently oversee diagnostic tests: FDA and the Centers for Medicare and Medicaid Services (CMS). Both agencies differ significantly in the frameworks used to regulate these tests.

A. FDA REGULATION

FDA is responsible for protecting and promoting public health by assuring “the safety, effectiveness, [and] quality”⁴⁶ of medical drugs and devices. Congress continues to modify FDA’s statutory authority to help safeguard public health as technologies become more complex and prevalent.⁴⁷ Accordingly, FDA’s role has shifted from that of a mere policeman of fraudulent medical products to a powerful gatekeeper of medical products.

1. *History of FDA’s Authority over Medical Devices*

In 1938, the Federal Food, Drug, and Cosmetic Act (FDCA) authorized FDA to regulate medical devices for the first time.⁴⁸ Under the FDCA, Congress authorized FDA to regulate any medical device

43. See PERSONALIZED MEDICINE COAL., *supra* note 1, at 4 (“The genotyping of drug-metabolizing enzymes has produced improved dosing of drugs for conditions as wide-ranging as depression and anxiety, coronary and peripheral artery disease, inflammatory bowel disease, and cancer.”).

44. JAIN, *supra* note 25, at 17.

45. See Leroy Hood & Stephen H. Friend, *Predictive, Personalized, Preventive, Participatory (P4) Cancer Medicine*, 8 NATURE 184, 184 (2011).

46. *FDA Fundamentals*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm192695.htm> [<https://perma.cc/MLK8-VRXY>].

47. See Carol Rados, *Medical Device and Radiological Health Regulations Come of Age*, U.S. FOOD & DRUG ADMIN. (Oct. 7, 2010), <http://www.fda.gov/aboutfda/whatwedo/history/productregulation/medicaldeviceandradiologicalhealthregulationscomeofage/default.htm> [<https://perma.cc/EQW6-5TR9>].

48. *Id.*

introduced into interstate commerce.⁴⁹ FDA's enforcement power, however, was still limited to policing fraudulent devices via post-market regulation.⁵⁰

Congress addressed this regulatory gap by passing the Medical Device Amendments of 1976 (MDA). By the mid-1960s, medical devices had grown increasingly more sophisticated and complex.⁵¹ Reports of faulty devices such as pacemaker failures and problems with intrauterine devices, which caused 10,000 injuries including 731 deaths,⁵² incentivized efforts to strengthen regulation of medical devices. Congress thus passed MDA, fundamentally altering the way medical devices entered the market. MDA granted FDA authority to regulate medical devices the same way it regulated drugs—through pre-market approval to ensure the safety and efficacy of medical devices.⁵³

2. FDA's Regulation of *in Vitro* Diagnostic Tests

FDA regulates *in vitro* diagnostic tests (IVDs) as a subset of medical devices. The FDCA defines “medical device” broadly. Generally, FDA considers as medical devices “any health care product that does not achieve its principal intended purposes by chemical action in or on the body.”⁵⁴ Three regulatory classes—Classes I, II, and III—determine the level of oversight of devices based on their intended use and the degree of risk they pose to the public.⁵⁵ Class I includes low-risk devices and Class III includes high-risk devices.⁵⁶ Class I devices are generally exempt from pre-market

49. See 21 U.S.C. § 331(a) (2012) (prohibiting “[t]he introduction or delivery for introduction into interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded”).

50. Rados, *supra* note 47.

51. See *id.*

52. S. REP. NO. 94-33, at 6 (1975).

53. See *id.*

54. Grimm, *supra* note 27, at 118–19.

55. *Classify Your Medical Device*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice> [<https://perma.cc/P4TB-3B5V>] (“The class to which your device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market Device classification depends on the *intended use* of the device and also upon *indications for use* In addition, classification is risk based, that is, the risk the device poses to the patients and/or the user is a major factor in the class it is assigned.”).

56. *Id.*

approval; class III devices generally require more stringent pre-market approval before marketing.⁵⁷

The FDCA defines IVDs as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is . . . *intended for use* in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.”⁵⁸ FDA further defines IVDs as “those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease.”⁵⁹

FDA’s pre-market approval of IVDs involves both analytical and clinical validation.⁶⁰ Analytical validation is assessed by the test’s laboratory performance characteristics based on its ability to detect a known sample whose detection has a known intended use.⁶¹ In other words, FDA ensures that the test accurately identifies the sample. Clinical validation is assessed by evidence linking a particular variant to a specific disease or clinical action.⁶² In other words, FDA ensures that the test results correctly identify a patient’s relevant disease or condition.

B. CMS REGULATION

CMS currently regulates clinical laboratories under the Clinical Laboratory Improvement Amendments of 1988 (CLIA).⁶³ Congress passed CLIA’s 1988 amendments to unify the previous patchwork of inconsistent regulation of laboratories under a single, strengthened regulatory mechanism.⁶⁴ CLIA regulations ensure the reliability and accuracy of laboratory test results by “establish[ing] quality standards for laboratory testing performed on specimens from humans . . . for the purpose of

57. *Id.*; *Class III Exemptions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051549.htm> [<https://perma.cc/CKH6-NZQ8>].

58. 21 U.S.C. § 321(h)(2) (2012) (emphasis added).

59. In Vitro Diagnostic Products for Human Use, 21 C.F.R. § 809.3(a) (2015).

60. *CLIA Overview*, CMS, LDT AND CLIA FAQs (Oct. 22, 2013), https://www.cms.gov/regulations-and-guidance/legislation/clia/downloads/ltd-and-clia_faqs.pdf [<https://perma.cc/4XWU-9KS6>].

61. *Id.*

62. *Id.*

63. PETER M. KAZON, *Laboratory Developed Tests*, IN VITRO DIAGNOSTICS: THE COMPLETE REGULATORY GUIDE 115, 115 (Scott D. Danzis & Ellen J. Flannery eds., 2010).

64. *See* S. REP. NO. 100-561, at 3 (1988); H.R. REP. NO. 100-899, at 12 (1988).

diagnosis, prevention, or treatment of disease, or assessment of health.”⁶⁵ These standards focus on the overall operation of the laboratory by assessing training of lab personnel, proficiency testing, and quality control systems.⁶⁶ Diagnostic tests are considered high complexity tests and therefore clinical laboratories performing such tests are subject to stringent CLIA requirements.⁶⁷

While CLIA ensures analytical validity of diagnostic tests performed by a specific laboratory, it does not address clinical validity.⁶⁸ Ultimately, CLIA oversight focuses on “intra-laboratory processes as opposed to the clinical uses of test results.”⁶⁹ Furthermore, oversight occurs post-market—after a laboratory has already started testing—during a laboratory’s routine biennial inspections assessing compliance with CLIA standards.⁷⁰

III. REGULATORY CHALLENGES: LABORATORY-DEVELOPED TESTS

As laws regulating medical devices and diagnostic tests predate health care’s recent focus on personalized medicine, current regulatory mechanisms were not designed to accommodate today’s sophisticated, ubiquitous diagnostic tests.⁷¹ As such, gaps in federal oversight of these rapidly advancing technologies continue to widen.⁷² These gaps are most evident in the current oversight of LDTs.

65. *CLIA Law & Regulations*, CTRS. FOR DISEASE CONTROL & PREVENTION (Mar. 16, 2015), <http://wwwn.cdc.gov/clia/Regulatory/default.aspx> [<https://perma.cc/XH7V-AHBZ>].

66. KAZON, *supra* note 63, at 116.

67. *CLIA Overview*, *supra* note 60.

68. *Id.*

69. Sec’y’s Advisory Comm. on Genetic Testing, NIH, *Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT 9* (2000), http://osp.od.nih.gov/sites/default/files/oversight_report.pdf [<https://perma.cc/EX77-ZUF5>] [hereinafter SACGT RECOMMENDATIONS].

70. *CLIA Overview*, *supra* note 60.

71. Gail H. Javitt, *In Search of a Coherent Framework: Options for FDA Oversight of Genetic Tests*, 62 *FOOD & DRUG L.J.* 617, 617 (2007).

72. See Gail H. Javitt et. al., *Direct-to-Consumer Genetic Tests, Government Oversight, and the First Amendment: What the Government Can (and Can't) Do to Protect the Public's Health*, 57 *OKLA. L. REV.* 251, 253–54 (2004) (“Government oversight of genetic testing services . . . currently falls between several regulatory ‘cracks’ within the federal government, and is therefore arguably both ambiguous and insufficient.”).

A. LABORATORY-DEVELOPED TESTS

Laboratories often develop and market their own diagnostic tests⁷³ using generally available testing reagents and equipment.⁷⁴ FDA defines LDTs as tests “intended for clinical use and designed, manufactured and used within a single laboratory.”⁷⁵ While a laboratory may not commercially distribute an IVD test kit, it can commercially sell its services as an LDT. Traditionally, a health care provider such as a physician orders these tests. Recently, however, LDTs are increasingly offered directly to consumers.⁷⁶

Thus diagnostic tests can be marketed in two ways. First, a test can be developed, manufactured, packaged, and sold for distribution as an IVD commercial test kit.⁷⁷ Second, a test can be developed by and used in-house as an LDT.⁷⁸ While FDA regulates IVDs, the agency does not currently regulate LDTs. Although FDA considers LDTs as medical devices, the agency maintains that it has exercised “enforcement discretion,” meaning it chose not to enforce regulatory requirements with respect to LDTs.⁷⁹ As such, LDTs are currently only regulated under the less-stringent CLIA framework.

While a small handful of diagnostics are sold as IVDs, a vast majority of tests are offered as LDTs.⁸⁰ As these increasingly complex tests transition into routine clinical practice, they are expected to play a key role in personalized medicine. Current regulation over these complex LDTs, however, lags behind the technology.⁸¹ After previously shying away from regulating genetic tests and LDTs,⁸² FDA now plans to enforce regulatory requirements over these tests.⁸³ Many stakeholders, however, heavily dispute FDA’s authority to regulate LDTs.⁸⁴ While it is generally accepted

73. These tests are referred to as “LDTs,” “home brews,” or “in-house” tests. LDT DRAFT GUIDANCE, *supra* note 12, at 4 n.2.

74. *Id.* at 5.

75. *Id.*

76. *E.g.*, 23ANDME, <https://www.23andme.com> [<https://perma.cc/RX3T-XACC>]; THERANOS, <https://www.theranos.com> [<https://perma.cc/V7JX-VDT6>].

77. KAZON, *supra* note 63.

78. *Id.*

79. *See* LDT DRAFT GUIDANCE, *supra* note 12, at 6–7.

80. PERSONALIZED MEDICINE COAL., *supra* note 1, at 22.

81. *See generally* Javitt, *supra* note 71.

82. *See* Neil A. Holtzman, *FDA and the Regulation of Genetic Tests*, 41 JURIMETRICS J. 53, 61 (2000) (“Fearing that it will be deluged with new tests, FDA has maintained that it lacks the resources to extend its full power to regulate devices to genetic tests marketed as services.”).

83. LDT DRAFT GUIDANCE, *supra* note 12.

84. *See infra* Part IV.

that LDT regulation must be modernized to provide appropriate oversight,⁸⁵ various interested parties argue over the proper degree and manner of oversight.

B. EVOLUTION OF FDA'S APPROACH TO LDTs

FDA has historically exercised “enforcement discretion” over LDTs and thus did not actively regulate these tests. The increasing complexity and prevalence of LDTs—and their increasingly pervasive business models—however, have recently provoked FDA to end its enforcement discretion altogether.

1. *Enforcement Discretion*

FDA historically did not regulate LDTs because they were initially relatively simple, well-understood tests used only for rare diseases.⁸⁶ These tests were typically used within the health care institution responsible for the patient⁸⁷ and were viewed merely as low-risk enhancements to medical care.⁸⁸ As the LDT market grew, however, FDA began expressing concern over the quality of LDTs by noting an emerging trend of sophisticated laboratories developing their own tests to diagnose a wide range of medical conditions.⁸⁹ In 1996, despite this concern, FDA believed LDTs fulfilled niche clinical needs and thus ultimately chose to continue enforcement discretion.⁹⁰

2. *Early Approach: Analyte-Specific Reagents*

In 1997, FDA began regulating the “active ingredients,” called analyte-specific reagents (ASRs), used in LDTs rather than the tests themselves.⁹¹ The ASR category differentiates between general-purpose reagents, which include equipment, collection systems, and chemicals used broadly in various tests, and “active ingredients” including antibodies and nucleic acid probes designed for diagnostic purposes.⁹² Since FDA “believed that

85. See Turna Ray, *Amid Competing LDT Regulatory Proposals, Common Ground but Key Disagreements for Congress to Consider*, GENOMEWEB (Sep. 28, 2015), <https://www.genomeweb.com/molecular-diagnostics/amid-competing-ldt-regulatory-proposals-common-ground-key-disagreements> [<https://perma.cc/7TDDK-TNMC>].

86. LDT DRAFT GUIDANCE, *supra* note 12, at 7.

87. *Id.*

88. *See id.*

89. 61 Fed. Reg. 10,484 (proposed Mar. 14, 1996).

90. *See id.* (recognizing that LDTs play an important clinical role “as a mechanism for providing novel, highly specialized tests in a relatively short time”).

91. *See* 21 C.F.R. § 864.4020 (2015).

92. *See id.*

laboratories certified as high complexity under [CLIA] . . . have demonstrated expertise and ability to use ASRs in test procedures and analysis,” the agency chose to regulate ASRs rather than the tests as a whole to minimize regulatory burden.⁹³ FDA noted that “at a future date,” however, it “may reevaluate whether additional controls over [LDTs] may be needed to provide an appropriate level of consumer protection.”⁹⁴

The LDT landscape continues to grow more complex since the completion of the Human Genome Project in 2003.⁹⁵ DNA sequencing technologies have evolved from single-gene to multi-gene testing. As such, LDTs increasingly rely on complex instrumentation and software to generate results.

After several prominent committees had become concerned about the lack of oversight of genetic tests,⁹⁶ FDA began increasing scrutiny over LDTs. In February 2004, FDA halted the release of OvaCheck, a diagnostic test for ovarian cancer.⁹⁷ OvaCheck differed from previous genetic tests by analyzing multiple biomarkers and utilizing “black-box” algorithmic technology.⁹⁸ While acknowledging general enforcement discretion over LDTs, FDA asserted that the software was a medical device, as the software was intended to diagnose a disease.⁹⁹

3. *Breaking Enforcement Discretion: In Vitro Multivariate Index Assays*

In 2006, FDA first broke its enforcement discretion policy by announcing its intent to regulate in vitro multivariate index assay

93. Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays, 71 Fed. Reg. 52,800, 52,801 (Sept. 7, 2006).

94. 61 Fed. Reg. at 10,484.

95. In 2003, the international scientific community working on the Human Genome Project completed the first sequencing of the human genome. This gave rise to genomic research and the commercialization of DNA technologies. *The Human Genome Project Completion: Frequently Asked Questions*, NAT'L HUM. GENOME RES. INST. (Oct. 30, 2010), <https://www.genome.gov/11006943> [<https://perma.cc/BD27-5VKH>].

96. See, e.g., SACGT RECOMMENDATIONS *supra* note 69, at ix–x (“Based on the rapidly evolving nature of genetic tests, their anticipated widespread use, and extensive concerns expressed by the public about their potential for misuse or misinterpretation, additional oversight is warranted for all genetic tests . . . FDA should be the federal agency responsible for the review, approval, and labeling of all new genetic tests that have moved beyond the basic research phase.”).

97. Javitt, *supra* note 71, at 634.

98. *Id.*

99. *Id.*

(IVDMIA) LDTs as medical devices.¹⁰⁰ Like OvaCheck, the growing IVDMIA category included use of non-standard LDT components such as proprietary algorithms relying on multiple biomarkers to diagnose a disease or condition.¹⁰¹ FDA grew concerned over the safety and effectiveness of “black box” algorithms because they are “not within the ordinary ‘expertise and ability’ of laboratories that FDA referred to when it issued the ASR rule.”¹⁰² In other words, clinicians could not independently interpret IVDMIA test results without the test developer’s assessment of clinical significance. Because FDA believed these LDTs posed new, significant public health risks, it asserted that IVDMIA “do not fall within the scope of laboratory-developed tests over which FDA has generally exercised enforcement discretion.”¹⁰³ FDA, however, never finalized this enforcement plan.

4. *Facing Changes in LDT Business Models*

Simultaneous advances in everyday consumer-oriented technologies such as overnight shipping and the Internet hugely impacted laboratory business models, increasing FDA’s concern over LDTs.¹⁰⁴ In contrast to traditional LDT providers in 1976 such as hospital laboratories offering tests for its own patients, many of today’s LDT providers are large corporations that nationally market complex, high-risk tests independent of any health care institution.¹⁰⁵ Concern over the potential for widespread consequences of LDTs heightened with OvaSure, an algorithm-based LDT.¹⁰⁶ In June 2008, LabCorp, one of the largest clinical laboratory companies in the U.S., began marketing OvaSure as an ovarian cancer risk detection test.¹⁰⁷ Because patients who catch the disease in its early stages

100. See U.S. Food & Drug Admin., Draft Guidance For Industry, Clinical Laboratories, And FDA Staff: In Vitro Diagnostic Multivariate Index Assays (2007).

101. *Id.*

102. Draft Guidance for Industry, Clinical Laboratories, and FDA Staff on In Vitro Diagnostic Multivariate Index Assays, 71 Fed. Reg. 52,800, 52,801 (Sept. 7, 2006).

103. *Id.* at 52,801.

104. A single laboratory can now provide services nationwide due to overnight shipping and electronic delivery of test results. LDT DRAFT GUIDANCE, *supra* note 12, at 8.

105. LDTs are now a multibillion-dollar-a-year industry. See Thomas M. Burton, *Is Lab Testing the ‘Wild West’ of Medicine?*, WALL ST. J. (Dec. 10, 2015), <http://www.wsj.com/articles/is-lab-testing-the-wild-west-of-medicine-1449800707> [<https://perma.cc/2QCD-SAKG>].

106. See Andrew Pollack, *F.D.A. Says Cancer Test Failed to Get Its Approval*, N.Y. TIMES (Oct. 8, 2008), <http://www.nytimes.com/2008/10/09/business/09cancer.html> [<https://perma.cc/BKD3-5AXV>].

107. Louise M. Slaughter, *FDA Oversight of Laboratory Developed Tests Essential for Patient Health and Safety*, 20 AM. J. MANAGED CARE SP393, SP421 (2014).

have a much higher chance of survival, many preemptively removed their ovaries based on OvaSure's test results.¹⁰⁸ Yet the test was not clinically validated and was later found to have a high false positive rate, which possibly led healthy women to unnecessarily undergo highly invasive surgery.¹⁰⁹ In October 2008, FDA effectively halted the sale of OvaSure.¹¹⁰

The rise of the Internet also fostered the direct-to-consumer (DTC) genetic testing market. In 2007, laboratory companies such as 23andMe and Pathway Genomics began offering personal genetic testing directly to consumers.¹¹¹ Due to rising demand, increasing complexity of health reports, and lack of physician intermediary, FDA began exercising jurisdiction over DTC genomic services. In 2010, FDA effectively blocked a partnership between Pathway Genomics and Walgreens.¹¹² In 2013, FDA sent a warning letter to 23andMe instructing the company to discontinue its unapproved health report service.¹¹³ The agency later again emphasized its jurisdictional exercise over DTC services, stating that it "generally does not exercise enforcement discretion for [DTC] tests regardless of whether they meet the definition of an LDT Therefore . . . FDA's usual enforcement policies apply to DTC tests."¹¹⁴

5. *Uniform Regulation of LDTs*

In June 2010, in lieu of issuing a final guidance on IVDMLA regulation, FDA announced its intention to revoke enforcement discretion over LDTs altogether.¹¹⁵ The agency now plans to replace its previous ad hoc regulatory approach with uniform regulation of LDTs.

108. *Id.*

109. *Id.*

110. *Responding to FDA, LabCorp Discontinues Offering OvaSure Test*, GENOMEWEB (Oct. 27, 2008), <https://www.genomeweb.com/responding-fda-labcorp-discontinues-offering-ovasure-test> [<https://perma.cc/3CJ3-JRM8>].

111. Sancy A. Leachman et al., *Direct-to-Consumer Genetic Testing: Personalized Medicine in Evolution*, 29 AM. SOC'Y CLINICAL ONCOLOGY 34, 36 (2011).

112. Andrew Pollack, *Walgreens Delays Selling Personal Genetic Test Kit*, N.Y. TIMES (May 12, 2010), <http://www.nytimes.com/2010/05/13/health/13gene.html> [<https://perma.cc/A8ZS-CMH7>].

113. Letter from Alberto Gutierrez, Director, Office of In Vitro Diagnostics and Radiological Health, to Ann Wojcicki, CEO, 23andMe, Inc. (Nov. 22, 2013), <http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm> [<https://perma.cc/QWY7-E3WD>].

114. LDT DRAFT GUIDANCE, *supra* note 12, at 4 n.4.

115. Turna Ray, *FDA Shelves IVDMLA Final Guidelines in Order to Focus on Overall LDT Regulation*, GENOMEWEB (June 23, 2010), <https://www.genomeweb.com/dxpgx/fda-shelves-ivdmia-final-guidelines-order-focus-overall-ldt-regulation> [<https://perma.cc/NC43-4KU9>].

In October 2014, FDA released the draft guidance document for LDT oversight.¹¹⁶ FDA noted the changes in the complexity and use of LDTs and the associated increased risks, particularly in the context of personalized medicine.¹¹⁷ The agency also noted changes in the laboratory industry, such as the shift from local use of LDTs to nationwide marketing.¹¹⁸ FDA stated that due to these drastic changes in the LDT landscape, it “has serious concerns regarding the lack of independent review of the evidence of clinical validity of LDTs.”¹¹⁹

FDA also grew concerned over the “unbalanced playing field” between LDT and traditional IVD companies: IVD manufacturers performing rigorous, resource-intensive clinical studies for FDA approval must compete with LDT companies offering similar tests that are only subject to minimal CLIA requirements.¹²⁰ The current discrepancy between LDT and test kit regulation has led many diagnostic testing companies to base their business model on the LDT model.¹²¹ The public is also growing more aware of this “LDT loophole” as media scrutiny over certain prominent LDT companies intensifies.¹²² To address this business model trend—and growing public concern—FDA reasons that tests should be regulated “based on their use, not how they were developed.”¹²³

The LDT draft guidance proposes to regulate LDTs under a risk-based framework.¹²⁴ FDA’s requirements include registration and listing,

116. LDT DRAFT GUIDANCE, *supra* note 12, at 4.

117. FDA believes that LDTs not validated for their intended use put patients at risk of missed diagnoses, inaccurate diagnoses, or failure to receive proper treatment. *Id.* at 10–11.

118. *Id.* at 8.

119. *Id.* at 9.

120. See U.S. FOOD & DRUG ADMIN., THE PUBLIC HEALTH EVIDENCE FOR FDA OVERSIGHT OF LABORATORY DEVELOPED TESTS: 20 CASE STUDIES 4 (2015), <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf> [<https://perma.cc/M4WL-VXWA>] [hereinafter FDA CASE STUDIES].

121. See Nick Stockton, *Fixing the Laws That Let Theranos Hide Data Won't Be Easy*, WIRED (Oct. 20, 2015), <http://www.wired.com/2015/10/fixing-the-laws-that-let-theranos-hide-data-wont-be-easy> [<https://perma.cc/P2TN-D2B7>].

122. See, e.g., *id.*; Arielle Duhaime-Ross, *Theranos Isn't the Only Diagnostic Company Exploiting Regulatory Loopholes: Avoiding Pre-Market Verification Is Downright Easy*, VERGE (Nov. 11, 2015), <http://www.theverge.com/science/2015/11/11/9706356/fda-theranos-health-diagnostics-cancer-tests-regulation-loophole-ldt> [<https://perma.cc/LCE6-77WR>]; *In Modern-Day Gold Rush of Genetic Testing, Profit Placed Above Proof*, CBS NEWS (Feb. 10, 2016), <http://www.cbsnews.com/news/cbs-news-investigation-genetic-tests-pathway-genomics-profit-over-evidence> [<https://perma.cc/4TZX-ED7L>].

123. Andrew Pollack, *F.D.A. Acts on Lab Tests Developed In-House*, N.Y. TIMES (July 31, 2014) <http://www.nytimes.com/2014/08/01/business/fda-to-regulate-lab-developed-test-kits.html> [<https://perma.cc/G9KT-Y2Y5>].

124. LDT Draft Guidance, *supra* note 12, at 11–13.

notification, adverse event reporting, and pre- and post-market review for LDTs based on risk-classification.¹²⁵ To give laboratories time to comply, enforcement over moderate- and high-risk LDTs will be phased in over nine years, beginning with high-risk tests.¹²⁶ FDA does not plan to regulate all forms of LDT. Under the proposed framework, the agency will continue to exercise enforcement discretion over LDTs that diagnose rare diseases, address unmet needs, or pose low risks.¹²⁷

The draft guidance was predictably met with heavy opposition, with many stakeholders arguing against FDA's jurisdiction over LDTs. Consequently, before FDA can successfully move forward with its plan to regulate LDTs, it must first establish its jurisdiction over these tests.

IV. FDA'S AUTHORITY TO REGULATE LDTs

FDA's jurisdiction over LDTs has been consistently contested. At the heart of this decades-long debate is whether an LDT is a medical "device." FDA maintains that LDTs are devices and thus the 1976 Medical Device Amendments grant it authority to regulate LDTs.¹²⁸ Many stakeholders, however, argue that LDTs are services, not devices, and are thus outside the purview of FDA's jurisdiction.¹²⁹ The legal questions at play in this dispute highlight broader policy questions—particularly the feasibility of applying FDA's current regulatory framework to rapidly evolving technologies. In essence, stakeholders argue over the right balance between protecting public health and innovating the clinical tools necessary for the success of personalized medicine.¹³⁰

125. *Id.*

126. Jeffrey Shuren, *Curbing Risk, Not Medical Innovation, in Personalized Medicine*, FDA VOICE (July 31, 2014), <http://blogs.fda.gov/fdavoices/index.php/2014/07/curbing-risk-not-medical-innovation-in-personalized-medicine> [<https://perma.cc/92YV-VJSX>]; LDT DRAFT GUIDANCE, *supra* note 12, at 14.

127. LDT DRAFT GUIDANCE, *supra* note 12, at 22–23.

128. *Id.* at 6.

129. Paul D. Clement & Laurence H. Tribe, *Laboratory Testing Services, as the Practice of Medicine, Cannot Be Regulated as Medical Devices*, AM. CLINICAL LABORATORY ASS'N 2 (Jan. 7, 2015), <http://www.acla.com/acla-releases-white-paper-detailing-legal-arguments-against-fdas-proposal-to-regulate-laboratory-developed-tests-ldts-as-medical-devices> [<https://perma.cc/F2ZT-7DNG>].

130. Congress is currently examining the policy issues regarding LDT regulation. *See, e.g., 21st Century Cures: Examining the Regulation of Laboratory Developed Tests*, H. COMM. ON ENERGY & COM. (Sept. 9, 2014), <https://energycommerce.house.gov/hearings-and-votes/hearings/21st-century-cures-examining-regulation-laboratory-developed-tests> [<https://perma.cc/3MJV-5QEN>].

A. FDA'S AUTHORITY UNDER THE FDCA

The FDCA mandates that FDA regulate “[t]he introduction or delivery for introduction into interstate commerce of any . . . device . . . that is adulterated or misbranded.”¹³¹ Therefore, FDA’s jurisdiction depends on the presence of both a device and interstate commerce.

1. *Device Versus Service*

A product’s “intended use” is critical to the definition of “device.”¹³² Similar to IVD test kits manufactured by traditional device companies, LDTs are test systems comprised of instruments, apparatus, in vitro reagents, and other related articles “intended for use in the diagnosis of disease or other conditions.”¹³³

A straightforward reading of the FDCA thus arguably supports FDA’s interpretation of LDTs as devices. FDA argues that attempts to distinguish LDTs from IVDs boil down to a difference without distinction: because both IVD test kits and LDTs are functionally the same, the location of manufacturing should not affect their regulation. This functional similarity is illustrated by the fact that some laboratories offer LDTs diagnosing the same conditions as FDA-approved IVDs.¹³⁴

Opponents argue that LDTs are outside FDA’s jurisdiction because they are medical *services* rather than *devices*.¹³⁵ This distinction emphasizes

131. 21 U.S.C. § 331(a) (2012).

132. Jessica Elizabeth Palmer, Genetic Gatekeepers: Regulating Direct-to-Consumer Genomic Services in an Era of Participatory Medicine, 67 FOOD & DRUG L.J. 475, 496 (2012).

133. 21 U.S.C. § 321(h)(2) (2012). LDTs such as genetic tests arguably do not diagnose but simply provide information—putting them outside of FDA’s jurisdiction. The term “diagnose,” however, is a broadly inclusive term. Courts have generally considered products that aid in the detection and screening of a health condition, even if results are inconclusive or a disease or condition is not ultimately determined, as a diagnosis. *See, e.g.*, United States v. 25 Cases, More or Less, of an Article of Device, 942 F.2d 1179, 1181–83 (7th Cir. 1991) (recognizing that the term “diagnosis” in 21 U.S.C. § 321(h)(2) brings within the definition of “device” an article that screens for possible symptoms of disease but does not provide final identification of condition); United States v. Undetermined No. of Unlabeled Cases, 21 F.3d 1026, 1028–29 (10th Cir. 1994) (holding that specimen containers used as part of a protocol identifying the presence of HIV antibodies for insurance risk assessment purposes constituted “diagnosis”).

134. *See, e.g.*, Charlie Schmidt, *Challenges Ahead for Companion Diagnostics*, 104 J. NAT’L CANCER INST. 14, 15 (2012) (highlighting the availability of the FDA-approved Cobas test and similar LDTs testing for the same mutations).

135. Clement & Tribe, *supra* note 129, at 2.

the common usage of the term “device” as an article or tangible product.¹³⁶ This interpretation is arguably supported by MDA’s legislative history, which consistently referred to “devices” as “articles” and “products.”¹³⁷ Compared to IVD test kits, LDTs can be viewed as proprietary methodologies or protocols for performing diagnostic tests.¹³⁸ No article is ever labeled or sold as a product. As such, opponents argue that FDA’s effort to exert jurisdiction over LDTs requires an unnatural reading of the statute.¹³⁹

Broad, even purportedly unnatural reading of the FDCA, however, does not necessarily defeat FDA’s assertion of authority. In the past, FDA has been generally successful in expanding its jurisdiction in analogous situations. Before Congress enacted MDA, and thus before FDA had pre-market authority over devices, courts liberally construed the term “drug” to grant FDA broad jurisdiction over non-drug products. In *AMP, Inc. v. Gardner*, the Second Circuit upheld FDA’s classification of a nylon ligature loop used during surgery as a “drug.”¹⁴⁰ While the more natural understanding of the ligature loop is as a device, the court was “reluctant to give a narrow construction to this statute, touching the public health as it does.”¹⁴¹ The following year, the Supreme Court reaffirmed this broad reading in *United States v. An Article of Drug . . . Bacto-Unidisk*.¹⁴² The Court upheld FDA’s liberal interpretation of “drug” to include an antibiotic disc used as a screening test. As a result, courts allowed FDA to regulate certain device-like products as if they were drugs.

Just as courts were highly cognizant of public health concerns—and thus deferred to FDA’s liberal construction of the term “drug”—courts will likely be similarly cognizant of public health concerns in evaluating FDA’s interpretation of “device.” FDA, various medical societies,¹⁴³ and patient

136. See, e.g., *American Heritage Dictionary Entry: Device*, AM. HERITAGE DICTIONARY, <https://www.ahdictionary.com/word/search.html?q=device> [<https://perma.cc/DS6G-3NWX>] (defining “device” as “[a]n object designed and manufactured to perform one or more functions”).

137. H.R. REP. NO. 94–853, at 6 (1976).

138. Clement & Tribe, *supra* note 129, at 10.

139. *Id.*

140. 389 F.2d 825, 830 (2d Cir. 1968).

141. *Id.*

142. 394 U.S. 784, 801 (1969).

143. E.g., American Society of Clinical Oncology, American Cancer Society, American Heart Association, Open letter to FDA (Dec. 10, 2014), https://www.heart.org/idc/groups/ahaecc-public/@wcm/@adv/documents/downloadable/ucm_470484.pdf [<https://perma.cc/M5FM-5VGE>].

advocacy groups¹⁴⁴ cite the need for stronger evidentiary support for diagnostics, particularly when such tests directly guide clinical decision making. The agency recently released a report of twenty case studies of problematic LDTs to support its new enforcement policy.¹⁴⁵ FDA believes its regulatory demand for rigorous evidence will help address these potential complications.¹⁴⁶ Proponents of FDA regulation further stress that “[i]t is paramount that patients and their physicians know that regardless of how or where a test is manufactured or performed, they can trust the information produced by that test.”¹⁴⁷

In light of FDA’s public health rationale, a court may agree with FDA that apparent “manufacturing” factual distinctions, while perhaps significant from a regulatory standpoint, are immaterial from a consumer standpoint.¹⁴⁸ Thus due to the increase in complexity and prevalence of LDTs, a court may accept FDA’s interpretation of “device.”

2. *Interstate Commerce*

Congress delegated statutory power under the Commerce Clause to FDA through the FDCA’s enforcement provisions.¹⁴⁹ Thus, as a prerequisite to its jurisdiction, FDA must show that LDTs are “in interstate commerce.”¹⁵⁰ IVD test kits easily fall under FDA’s jurisdiction because they are a collection of physical objects that are bundled and sold across state lines. On the other hand, LDTs by definition are performed in-house and

144. *NHC’s Comments on Oversight of Laboratory-Developed Tests*, NAT’L HEALTH COUNCIL (Aug. 15, 2010), http://www.nationalhealthcouncil.org/sites/default/files/NHC_Letter_LDT.pdf [<https://perma.cc/Z5NF-BNTF>].

145. FDA CASE STUDIES, *supra* note 120, at 2. FDA claims that LDTs that have not been validated for their intended use can put patients at risk of missed diagnosis, inaccurate diagnosis, failure to receive proper treatment, or suffering unnecessarily uncomfortable or dangerous procedures. *Id.* at 4. The Association for Molecular Pathology, however, disputes the strength of FDA’s case study report. *Facts FDA Ignored: An Analysis of the FDA Report, “The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies,”* ASS’N FOR MOLECULAR PATHOLOGY (Dec. 13, 2015), <http://amp.org/emailads/documents/AMPResponseFDACaseReportFinal.pdf> [<https://perma.cc/4JW6-C6Q9>].

146. FDA CASE STUDIES, *supra* note 120, at 30.

147. *FDA Report Cites Benefits of LDT Oversight*, AM. CANCER SOC’Y CANCER ACTION NETWORK (Nov. 16, 2015), <https://www.acscan.org/content/media-center/fda-report-cites-benefits-of-ldt-oversight> [<https://perma.cc/KW25-PC4G>].

148. See Anny Huang, *FDA Regulation of Genetic Testing: Institutional Reluctance and Public Guardianship*, 53 FOOD & DRUG L.J. 555, 557 (1998).

149. See 21 U.S.C. § 331.

150. *Id.*

are thus necessarily intrastate activities. The issue then is whether these intrastate activities constitute interstate commerce.

LDTs likely fulfill the interstate commerce requirement because of their substantial economic effect on interstate commerce and their interstate clientele and components. Commerce Clause jurisprudence grants Congress expansive powers to regulate activities substantially affecting interstate commerce. The Supreme Court notably held in *Wickard v. Filburn* that “[e]ven if [an] activity be local and though it may not be regarded as commerce, it may still . . . be reached by Congress if it exerts a substantial economic effect on interstate commerce.”¹⁵¹ LDTs most likely fall within this broad category, as these services are a significant commercial industry within the health care system.¹⁵² This reach over intrastate activities was recently supported in *United States v. Regenerative Sciences, LLC*, where the D.C. Circuit held that FDA had jurisdiction over “the mixture” of a patient’s stem cells and various reagents and antibiotics.¹⁵³ The court found that although the procedure was entirely intrastate, the mixture had sufficient connection to interstate commerce under the Commerce Clause.¹⁵⁴

Furthermore, the D.C. Circuit held that the FDCA does not require the entire product to have been shipped in interstate commerce for FDA to have statutory jurisdiction.¹⁵⁵ The court found that because the FDCA defines the term “drug” to include the product’s components as well as the finished product itself, the mere use of an ingredient that travelled in interstate commerce sufficiently triggered the interstate commerce element.¹⁵⁶ Similarly, the FDCA defines “device” to include the components of the product. As such, FDA jurisdiction over LDTs can be based on materials laboratories receive in interstate commerce in assembling

151. 317 U.S. 111, 125 (1942) (holding that the Commerce Clause allows Congress to regulate wheat produced solely for a farmer’s personal use); *see also* *Gonzales v. Raich*, 545 U.S. 1, 17 (2005) (recognizing that Congress has the authority to regulate even “purely local activities that are part of an economic ‘class of activities’ that have a substantial effect on interstate commerce”).

152. *See* *Burton*, *supra* note 105.

153. 741 F.3d 1314, 1323 (D.C. Cir. 2014).

154. *Id.* at 1320–21.

155. *Id.* at 1320.

156. *Id.* Again the D.C. Circuit chose to broadly construe a statutory scheme “designed to regulate the safety of drugs at every stage of their distribution.” *Id.*; *see also* *Baker v. United States*, 932 F.2d 813, 814 (9th Cir. 1991) (“[S]hipment in interstate commerce’ requirement is satisfied even when only an ingredient is transported interstate.”).

the tests, such as ASRs.¹⁵⁷ Thus, a court will likely find that LDTs satisfy the interstate commerce requirement even though no final product is sold and delivered across state lines.

B. PRACTICE OF MEDICINE LIMITATION

The FDCA contains an implicit practice of medicine limitation. FDA acknowledges that it cannot interfere with the practice of medicine, as Congress traditionally left regulation of the practice of medicine to the states.¹⁵⁸ The line between FDA's jurisdiction and the practice of medicine, however, has always been subject to controversy.¹⁵⁹ Stakeholders argue that LDTs, as laboratory testing procedures, are "part and parcel" to the practice of medicine and are thus beyond FDA's reach.¹⁶⁰ The practice of medicine limitation, however, does not completely shield medical practice from FDA regulation.

FDA cannot regulate how a physician uses available medical tools, such as the prescription of legally marketed drugs or diagnosis based on IVD results. For example, both FDA and courts protect a physician's off-label use of drugs or devices—that is, the ability to use FDA-approved drugs and devices for unapproved uses when appropriate—as the practice of medicine.¹⁶¹ Yet, pre-market regulation is distinct from the practice of medicine: FDA clearly has the authority to regulate the initial marketing of medical products.¹⁶² In this sense, FDA can indirectly regulate the practice of medicine.

FDA's regulation of LDTs is arguably in the same vein. FDA cannot interfere with how a physician uses LDT results in diagnosing a patient—and the agency does not seek to regulate a physician's post-market diagnostic use of LDTs. On the other hand, the agency has the authority to

157. Juliana Han, *The Optimal Scope of FDA Regulation of Genetic Tests: Meeting Challenges and Keeping Promises*, 20 HARV. J. LAW & TECH. 423, 434 (2007).

158. *Id.* at 434–35.

159. *See id.* at 435–36; *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 349–50 (2001) (recognizing that FDA, under its statutory and regulatory framework, must balance "difficult (and often competing) objectives" to fulfill "the difficult task of regulating the marketing and distributing of medical devices without intruding upon decisions statutorily committed to the discretion of health care professionals").

160. Clement & Tribe, *supra* note 129, at 4.

161. *E.g.*, *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989) (allowing off-label drug use); *Femrite v. Abbott Nw. Hosp.*, 568 N.W.2d 535, 541 (Minn. Ct. App. 1997) (allowing off-label device use).

162. *United States v. Evers*, 643 F.2d 1043, 1048 (5th Cir. 1981) ("[W]hile the [FDCA] was not intended to regulate the *practice of medicine*, it was obviously intended to control the *availability of drugs* for prescribing by physicians.").

regulate which LDTs, as medical devices, are available to physicians in the first place. FDA regulation necessarily affects the practice of medicine by deciding which tools are safe and effective for use. Thus while it might be true that the use of LDTs is an integral part of the practice of medicine, the development of LDTs themselves arguably does not constitute the practice of medicine.¹⁶³ Furthermore, the argument that LDTs are part and parcel to the practice of medicine potentially also implicates CMS's authority to regulate LDTs under CLIA, as medical practice regulation is left to states. This argument thus risks bringing about the very opposite result that those opposing FDA's authority over LDTs hope to achieve.¹⁶⁴

LDTs are also arguably outside the scope of the practice of medicine because such tests are increasingly developed and performed in laboratories having no relation to a particular patient.¹⁶⁵ Additionally, claiming that LDTs constitute the practice of medicine arguably implies that physicians perform such laboratory services. Yet non-physicians, including scientists, are authorized to direct clinical laboratories.¹⁶⁶ Congress also did not believe that a medical degree alone assured the requisite competence to manage a clinical laboratory.¹⁶⁷ To say that the practice of medicine extends to technicians and non-physicians arguably improperly stretches the traditional understanding of medical practice. Thus, a court may find reasonable grounds to view the practice of medicine and laboratory services as distinct.

163. See *U.S. v. Regenerative Scis., LLC*, 741 F.3d 1314, 1319 (D.C. Cir. 2014) (“Notwithstanding appellants’ attempt to characterize this case as an effort by the FDA to ‘restrict[] the use of an autologous stem cell procedure,’ . . . the focus of the FDA’s regulation is the Mixture. That is, the FDA does not claim that the procedures used to administer the Mixture are unsafe; it claims that the Mixture itself is unsafe. Appellants’ arguments about the practice-of-medicine exemption are therefore wide of the mark.”)

164. E.g., *ACLA Expresses Concern with FDA Guidance on Laboratory Developed Tests (LDTs)*, AM. CLINICAL LABORATORY ASS’N (July 31, 2014), <http://www.acla.com/acla-expresses-concern-with-fda-guidance-on-laboratory-developed-tests-ldts> [<https://perma.cc/W338-PEBP>] (supporting enhancement of the CLIA regulatory framework, rather than imposing FDA regulation, to improve regulation of LDTs).

165. See, e.g., *Lab Services*, DOUGLAS COUNTY HOSP., <http://www.dchospital.com/alexclinic/services/lab-services> [<https://perma.cc/JGH6-J9DY>] (“Individualized laboratory testing is not conducted within Alexandria Clinic. All testing services are referred to external reference labs such as Douglas County Hospital, LabCorp or Mayo Medical Laboratories.”).

166. See H.R. REP. NO. 100-899, at 28 (1988).

167. *Id.*

C. OVERALL REGULATORY SCHEME: FDCA AND CLIA

LDTs are currently regulated by CMS under CLIA. Neither CLIA nor the MDA mention each other in either statutory text or legislative history. Nor does either statute facially limit the other. Thus, it is unclear whether Congress intended to delegate LDT oversight exclusively to CMS.

In passing the 1976 MDA, Congress noted, “[i]f present regulatory controls are sufficient, the Committee does not intend that the proposed legislation result in promulgation of duplicative regulations.”¹⁶⁸ Congress first passed the Clinical Laboratory Improvement Act in 1967, which it later amended in 1988 to strengthen federal oversight of laboratories after reports of poor-quality laboratory services.¹⁶⁹ Many stakeholders claim that since LDTs are already regulated under CLIA, FDA regulation would be duplicative.¹⁷⁰

Overlapping regulations over LDTs, however, are not necessarily duplicative. FDA regulation of LDTs is arguably complementary to CMS regulation because the two regulatory schemes differ in focus, scope, and purpose.¹⁷¹ CMS regulates clinical laboratories by setting general quality standards.¹⁷² Specifically, CLIA requirements focus on certifying good laboratory practice standards.¹⁷³ These standards, which are not directed to any specific test, provide only analytical validation through a biennial, post-market survey.¹⁷⁴ The legislative history of CLIA illustrates that Congress was focused on low-quality administration of laboratory tests. Congress specifically noted that dangerously inaccurate pap smear results were, “[i]n too many instances . . . the result of overworked and undersupervised cytotechnologists charged with the crucial responsibility of examining and

168. H.R. REP. NO. 94-853, at 15 (1976).

169. *See* S. REP. NO. 100-561, at 3 (1988).

170. *E.g.*, Clement & Tribe, *supra* note 129, at 15 (The “enactment of the CLIA amendments in 1988 would be well-nigh inexplicable if Congress had intended in the 1976 MDA . . . to subject laboratory-developed testing services to the FDCA’s device regulations” and would render CLIA “utterly pointless.”).

171. *CLIA Overview*, *supra* note 60; *see also* Jeffrey Shuren & Patrick H. Conway, *FDA and CMS Form Task Force on LDT Quality Requirements*, FDA VOICE (Apr. 16, 2015), <http://blogs.fda.gov/fdavoices/index.php/2015/04/fda-and-cms-form-task-force-on-ldt-quality-requirements> [<https://perma.cc/NPB9-5YL9>] (noting that the FDA-CMS task force will be “working together to clarify responsibilities for laboratories that fall under the purview of both agencies”).

172. Grimm, *supra* note 27, at 120.

173. *See CLIA Overview*, *supra* note 60 (“Analytical validation [of tests] is limited . . . to the specific conditions, staff, equipment and patient population of the particular laboratory.”).

174. *See id.*

categorizing cervical slides.”¹⁷⁵ Congress reiterated this point in 1997 by noting that “[t]he purpose of CLIA quality control, proficiency testing, and personnel requirements is to ensure consistent, reliable, and appropriate use of a test system by users of the test.”¹⁷⁶

FDA, on the other hand, regulates specific devices. As such, FDA regulation arguably differs from CMS regulation by focusing on the test itself rather than general laboratory practices. More significantly, unlike CMS, FDA clinically validates tests.¹⁷⁷ In the context of personalized medicine, accurate analysis of a patient’s clinical symptoms is essential to effective treatment. Rapid technological advances and a decreasing tolerance for test error can impose non-negligible risks to public safety.¹⁷⁸ Thus the distinction between analytical and clinical validity can have important consequences. Notably, CMS itself states that FDA is the agency with the scientific capability to handle clinical validation.¹⁷⁹ Moreover, FDA can provide more robust post-market surveillance compared to CMS by implementing an adverse event reporting system.¹⁸⁰ As such, a court may find an overriding public need for heightened regulation and thus deem mere post-market analytical validation under CLIA inadequate.

In construing the FDCA, courts generally presume that “unless they explicitly forbid it, the purpose of a statutory provision is the best test of the meaning of the words chosen.”¹⁸¹ Courts are conscious of the FDCA’s overriding purpose of protecting public health and FDA’s expertise in defining public health risks.¹⁸² The FDCA arguably does not explicitly prohibit FDA’s jurisdiction over LDTs, and CLIA does not compel preemption.¹⁸³ Thus given the public health concerns voiced by FDA and various medical and patient advocacy groups, a court would have reasonable

175. S. REP. NO. 100-561, at 26–27 (1988).

176. H.R. REP. NO. 105-310, at 76 (1997).

177. *CLIA Overview*, *supra* note 60.

178. *See* FDA CASE STUDIES, *supra* note 120, at 4.

179. *Examining the Regulation of Diagnostic Tests and Laboratory Operations: Hearing Before the H. Comm. on Energy & Com., Subcomm. on Health*, 114th Cong. 7 (2015) (statement of Patrick Conway, Chief Med. Officer, Ctrs. for Medicare & Medicaid Serv.).

180. *See id.*

181. *AMP, Inc. v. Gardner*, 389 F.2d 825, 827 (2d Cir. 1968) (quoting Judge Learned Hand in broadly construing the term “drug”); *see also* *United States v. Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 799 (1969) (quoting the same language).

182. Han, *supra* note 157, at 432.

183. *Clinical Reference Lab., Inc. v. Sullivan*, 791 F. Supp. 1499, 1509 (D. Kan. 1992) (holding that FDCA and CLIA are not inconsistent, and “Congress intended to leave some regulatory overlap between” the two statutory schemes), *partially rev’d on other grounds*, *United States v. Undetermined No. of Unlabeled Cases*, 21 F.3d 1026 (10th Cir. 1994).

grounds to view FDA and CMS regulation as complementary rather than duplicative.

D. *BROWN & WILLIAMSON* AND THE ABSURDITY DOCTRINE

Even if a court agrees with FDA's reading of the FDCA, it may nonetheless be reluctant to infer Congress's intent to give FDA authority over LDTs due to potential "absurd results" such regulation could produce. In *FDA v. Brown & Williamson*, the Supreme Court rejected FDA's attempt to regulate tobacco products.¹⁸⁴ The Court acknowledged that though nicotine seemed to fall within the FDCA's definition of "drug," FDA's regulation of tobacco products would lead to results clearly not intended by Congress.¹⁸⁵ Thus based on the inconsistent results between Congress's inferred intent and the FDCA's overall regulatory scheme, the Court rejected FDA's interpretation of "drug."¹⁸⁶

Similarly, whether a court is willing to accept FDA's asserted jurisdiction over LDTs—which include NGS tests and individualized tests—will likely depend on FDA's ability to modernize its regulatory framework to accommodate personalized medicine. FDA currently regulates diagnostic tests based on a "one-test, one-disease" framework. That is, a test developer must prove that a claimed variant is accurately identified and clinically linked to the disease or condition the test is intended to diagnose.¹⁸⁷ This necessarily requires that a test developer have an intended disease or condition in mind prior to FDA approval.

NGS tests, however, fundamentally differ from traditional diagnostic tests by the sheer volume of data they generate, the lack of a priori intended use, and the unlimited number of clinical interpretations possible from a single sample.¹⁸⁸ These fundamental differences do not fit within FDA's regulatory framework for traditional diagnostic tests.

First, NGS tests challenge FDA's current approach to analytical validation. A single NGS test sequencing a whole genome can detect over

184. 529 U.S. 120, 161 (2000).

185. The Court held nicotine regulation under the FDCA would lead to a complete ban on tobacco products, while tobacco-specific legislation enacted subsequent to the FDCA implied that Congress did not intend to ban them. *Id.* at 137.

186. *Id.* at 126.

187. *See supra* Section II.A.2.

188. *Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests—Preliminary Discussion Paper*, U.S. FOOD & DRUG ADMIN. (2014), <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM427869.pdf> [<https://perma.cc/3VA7-Z7KW>] [hereinafter *Optimizing FDA's Regulatory Oversight of NGS*].

three billion bases, including up to three million genetic variants. Assessing the analytical validity of all three billion bases detected, as required under FDA's current framework, is unfeasible.¹⁸⁹

Second, NGS tests present clinical validation challenges as well. Whole-genome NGS tests may have broad or undefined intended uses.¹⁹⁰ This possibility strains FDA's "one-test, one-disease" framework because a single NGS test can be intended to diagnose a wide range of diseases or conditions or not be intended to diagnose any particular disease at all prior to testing. Moreover, if an NGS test is intended to diagnose a particular disease or condition, it might do so by detecting rare variants specific to an individual or family.¹⁹¹ Proving clinical validity for rare variants, however, places a heavy burden on test developers: because the variant is rare, the test developer likely will not have sufficient data or information to demonstrate clinical significance required for approval.¹⁹² These various bottlenecks in pre-market review could thus effectively ban patient access to valuable tests.

Furthermore, FDA oversight of LDTs could potentially have negative consequences contrary to the agency's intentions. Laboratories update their tests in response to a patient's need or developments in scientific research and technology—a practice that will only increase with the use of NGS.¹⁹³ FDA's additional layer of regulatory requirements, however, may impede laboratories that literally cannot afford to comply with FDA requirements from developing or improving tests, or at the very least introduce lag time in test updates, making tests obsolete.¹⁹⁴ This may have the undesired effect of stifling the very innovations that are leading the health care industry towards personalized medicine. FDA regulation may also have the undesirable effect of leaving LDT development to large laboratory

189. Developing Analytical Standards for NGS Testing, U.S. FOOD & DRUG ADMIN. (2015), <http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM468521.pdf> [<https://perma.cc/QX9R-LNQP>] ("NGS-based tests have the capacity to produce, in a single test, data for up to billions of individual analytes. This large number of analytes, and even larger number of possible results, makes it infeasible for test developers to provide and FDA to review performance data for each analyte."); Lander, *supra* note 10, at 1186 ("FDA's regulatory framework might lead to a *reduction ad absurdum*.").

190. *Optimizing FDA's Regulatory Oversight of NGS*, *supra* note 188.

191. *See id.*

192. *Id.*

193. *See* Gail Javitt, *Which Way for Genetic-Test Regulation?*, 446 NATURE 816, 818 (2010) ("A particular challenge for the regulators of genetic testing . . . is that geneticists' understanding of the clinical significance of markers is evolving rapidly.").

194. *See* James P. Evans & Michael S. Watson, *Genetic Testing and FDA Regulation: Overregulation Threatens the Emergence of Genomic Medicine*, 313 J. AM. MED. ASS'N 669, 669 (2015).

corporations that have the resources to meet FDA requirements. This sort of monopoly could hinder patient access to necessary tests due to cost.¹⁹⁵

Given personalized medicine's reliance on nimble NGS and individualized tests,¹⁹⁶ FDA's current regulatory approach—which is modeled for traditional commercial device manufacturers—is an inappropriate framework for LDTs. FDA oversight may thus lead to the “absurd result” of effectively banning laboratory tests necessary to the success of personalized medicine. As such, even if FDA's interpretation of “device” is accepted, a court may infer that Congress intended LDTs to be regulated by the more flexible CLIA framework.

FDA's ability to account for these potential negative consequences, however, may help the agency avoid these absurd results. In *Medical Center Pharmacy v. Mukasey*,¹⁹⁷ the Fifth Circuit dealt with an analogous question of whether a pharmacist's compounding of medication to meet an individual patient's needs constitutes a “new drug” under the FDCA.¹⁹⁸ The pharmacists argued that their compounded drugs were exempt from “new drug” approval requirements because the FDCA does not reach traditional pharmacy practice. Moreover, they invoked the absurd-result argument, claiming that “few would undergo the costly and arduous approval process” of meeting FDA's requirements for each individualized compounded drug product, thus making nearly all compounding effectively unlawful under the FDCA.¹⁹⁹ The court acknowledged that such a result “appear[ed] inconsistent with the likely expectation that compounding would and

195. *Id.* at 670 (“Prior to [*Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013)], only a single laboratory was permitted to offer sequencing of those clinically important [BRCA1/2] genes, leading to a situation in which improvements in testing were stifled, women and their physicians had no options to obtain independent second opinions, and patient access to testing was limited. Immediately following elimination of this monopoly, numerous laboratories began offering [expanded, higher-quality, cheaper] testing Should [FDA regulate LDTs], monopolies in laboratory medicine may reappear, affecting not just genetic testing but diagnostic testing more broadly.”).

196. Andrew Pollack, *F.D.A. Acts on Lab Tests Developed In-House*, N.Y. TIMES (July 31, 2014), <http://www.nytimes.com/2014/08/01/business/fda-to-regulate-lab-developed-test-kits.html> [<https://perma.cc/26ZZ-ALWR>] (“The ability of laboratories to develop custom diagnostic tests has been critical to the growth of personalized medicine and keeping pace with the changing face of disease.”).

197. 536 F.3d 383 (5th Cir 2008).

198. FDA asserted it previously exercised enforcement discretion over drug compounding and only began enforcing the “new drug” requirements when it believed a pharmacist engaged in drug manufacturing “under the guise of compounding” to avoid FDA's oversight. *Id.* at 389–99.

199. *Id.* at 389.

should persist.”²⁰⁰ Similarly for LDTs, arguably few would be willing to undergo the additional approval process for every individualized test update.

The *Medical Center* court, however, believed it should not infer an absurd result from a “maximalist interpretation” of FDA’s authority when it is “tempered” by enforcement discretion.²⁰¹ That is, FDA’s authority over compounded drugs did not lead to absurd results where FDA’s continued enforcement discretion did not completely outlaw all drug compounding. As such, the court affirmed FDA’s jurisdiction over compounded drugs.²⁰²

Courts may similarly accept FDA’s “tempered” jurisdiction over LDTs. The agency has already made strides in modernizing its regulatory approach to accommodate personalized medicine.²⁰³ The 2014 draft guidance includes proposed discretionary carve-outs for LDTs that are inherently individualized,²⁰⁴ traditional, low-risk, or that detect rare diseases or address unmet needs.²⁰⁵ It also proposes a phased-in nine-year timeframe to give laboratories time to comply as well as to address concern over patient access to necessary tests in the short term.²⁰⁶ Moreover, FDA has already approved the first NGS test in 2013²⁰⁷ and is actively exploring ways to modernize its regulatory framework to adapt to the complexity and data-richness of rapidly evolving NGS tests.²⁰⁸ Thus FDA’s continued enforcement

200. *Id.* at 398.

201. *Id.* at 399.

202. *Id.* at 389–99.

203. Examining the Regulation of Diagnostic Tests and Laboratory Operations: Hearing Before the H. Comm. on Energy & Com., Subcomm. on Health, 114th Cong. 2 (2015) (statement of Jeffrey Shuren, Director of Ctr. for Devices and Radiological Health, U.S. Food & Drug Admin.).

204. *E.g.*, LDT DRAFT GUIDANCE, *supra* note 12, at 16 (“Consistent with a 2011 recommendation from the Secretary’s Advisory Committee on Organ Transplantation, FDA intends to continue to exercise enforcement discretion in full over LDTs used in CLIA-certified, high-complexity histocompatibility laboratories, when those LDTs are used in connection with organ, stem cell, and tissue transplantation These devices are often individualized within each medical facility They also are rapidly evolving.”).

205. *Id.* at 20–23.

206. *Id.* at 24, 26; Joshua Sharfstein, *FDA Regulation of Laboratory-Developed Diagnostic Tests: Protect the Public, Advance the Science*, 313 J. AM. MED. ASS’N ONCOLOGY 667, 668 (2015).

207. Collins & Hamburg, *supra* note 7.

208. FDA has hosted several public workshops beginning in 2011 to discuss potential regulatory schemes for NGS platforms and tests and will continue to host workshops in the future. FDA also recently launched precisionFDA, a curated database to help address clinical validation challenges. Taha A. Kass-Hout & Elaine Johanson, *FDA Launches precisionFDA to Harness the Power of Scientific Collaboration*, FDA VOICE (Dec. 15, 2015), <http://blogs.fda.gov/fdavoices/index.php/2015/12/fda-launches-precisionfda-to-harness-the-power-of-scientific-collaboration> [<https://perma.cc/37FS-S2BS>].

discretion and the flexibility the agency is attempting to display in its proposed guidance and public workshops may help mitigate a court's concern over potentially absurd results of the agency's jurisdiction over LDTs.

E. NOTICE-AND-COMMENT RULEMAKING

As a final note, FDA's choice of procedural tool to enforce regulatory requirements for LDTs may impact the agency's authority in court. The rigorous notice-and-comment procedure is meant to ensure "public transparency, responsiveness, and reason-giving."²⁰⁹ Although a thorough discussion of the Administrative Procedure Act is beyond the scope of this Note, FDA is likely legally obligated to promulgate LDT regulation through the notice-and-comment rulemaking procedure, as opposed to its current use of less rigorous guidance documents.²¹⁰

FDA contends that its guidance document is merely a policy statement on its allegedly pre-existing jurisdiction and thus it is not imposing any new requirements on the LDT industry.²¹¹ On the other hand, considering FDA's long exercise of enforcement discretion for LDTs, "a policy shift of this magnitude" likely would require notice-and-comment rulemaking.²¹² Imposing regulatory requirements would constitute a drastic departure from FDA's longstanding position and would thus fundamentally alter the LDT landscape. The agency's shifts in policy due to changes in technology and medical practice "are exactly the sorts of changes in fact and circumstance which notice and comment rulemaking is meant to inform."²¹³ Furthermore, it is disputable whether FDA's LDT guidance document carries the force of law and is thus unclear whether a court would owe the agency *Chevron*²¹⁴ deference in a challenge to FDA enforcement.²¹⁵ If FDA were to proceed with notice-and-comment rulemaking, however, it would

209. Cass R. Sunstein, *Chevron Step Zero*, 92 VA. L. REV. 187, 211 (2006).

210. Gail Javitt & Katherine Carner, *Must FDA Engage in Rulemaking to Regulate Laboratory-Developed Tests?*, 1 FOOD & DRUG L. INST. 1, 1 (2011).

211. Turna Ray, *Q&A: FDA's Alberto Gutierrez Fields Questions On Evolving LDT, CDx Regulations*, GENOMEWEB (Dec. 30, 2014), <https://www.genomeweb.com/molecular-diagnostics/qa-fdas-alberto-gutierrez-fields-questions-evolving-ldt-cdx-regulations> [<https://perma.cc/4EXD-2RW7>].

212. Javitt & Carner, *supra* note 210.

213. *Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 95 (D.C. Cir. 1997).

214. *Chevron, U.S.A., Inc. v. NRDC, Inc.*, 467 U.S. 837 (1984).

215. *Chevron* deference is owed to agency rules carrying the force of law. Whether a guidance document carries the force of law, however, is contestable—both courts and scholars debate whether formal notice-and-comment rulemaking is necessary to constitute the force of law. *See generally* Kristen E. Hickman, *Unpacking the Force of Law*, 66 VAND. L. REV. 465 (2013).

undoubtedly benefit from heightened deference under *Chevron*—an advantage needed in this long-contentious debate over the agency’s interpretation.²¹⁶

V. CONCLUSION

Due to rapidly advancing DNA sequencing technologies such as NGS, the long-awaited promise of personalized medicine is now an attainable reality. Genomic-based diagnostic tests will play an increasingly important role in fostering this new health care reality. At the same time, these tests continue to grow in complexity and prevalence and thus also potentially present increased risks to public safety. As such, proper regulatory oversight of these sophisticated diagnostic tests must be addressed.

FDA is constantly playing catch up to these quickly evolving diagnostic tests. While it is important to ensure public confidence in these tests, premature oversight may lead to undesirable, “absurd” results. Without a new flexible framework adapted for the profoundly different emerging field of personalized medicine, FDA risks cutting off the health care model it seeks to support. FDA should consider establishing clear evidentiary standards for analytical and clinical validation for new diagnostic technologies before moving forward with its plan to regulate LDTs. The agency should also work closely with stakeholders through the notice-and-comment rulemaking procedure to understand the appropriate scope of enforcement discretion it should exercise. Otherwise, FDA, despite its good intentions, risks contravening its obligation to protect and promote public health by cutting off patient access to the promise of personalized medicine.

216. Specifically, agencies are owed *Chevron* deference to their interpretation of statutory ambiguity regarding the scope of their jurisdiction. *City of Arlington v. FCC*, 133 S. Ct. 1863, 1871 (2013).