
Direct-to-Consumer Genetic Testing: The FDA's Dual Role as Safety and Health Information Regulator

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DIRECT-TO-CONSUMER GENETIC TESTING: THE FDA'S DUAL ROLE AS SAFETY AND HEALTH INFORMATION REGULATOR

*Catherine M. Sharkey**

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A brave new world of genetic testing and personalized medicine—one in which vast amounts of patient genetic raw data can be readily produced and analyzed in light of rapid technological advances in whole genome sequencing and large-scale research and testing of the effects of genetics on human health—is upon us. The proliferation of

* Crystal Eastman Professor of Law, New York University School of Law. I received helpful comments from participants at Law Faculty Workshops at University of Iowa, University of Connecticut, and NYU. Thanks also to Kathy Strandburg and Rochelle Cooper Dreyfuss. Chase Weidner (NYU Law 2019) provided extraordinary research assistance.

direct-to-consumer (DTC) genetic testing poses new regulatory challenges as genetic testing and information, once within the exclusive domain of medical institutions, has migrated into the private commercial sector.

The FDA's traditional "protective" medical device model threatens to stifle the burgeoning industry supporting personalized medicine, and it is increasingly at odds with a patient-driven participatory health movement grounded in patient autonomy and empowerment. While the pull towards a more consumer-oriented "libertarian" or deregulatory model is strong, if taken to an extreme it would transform hitherto medical relationships into purely commercial transactions with potentially adverse health and safety consequences for patients.

The FDA is on the cusp of articulating a new flexible regulatory paradigm that maintains the FDA's oversight role in ensuring the accuracy of "diagnostic" genetic testing and interpretation of results, while at the same time lowering regulatory barriers to market entry of "informational" genetic testing and enabling consumers to order such testing on their own initiative. At this critical juncture for regulatory design and oversight, it is important to consider not only the FDA's role in promoting health and safety but also its complementary role in innovation policy, in particular in creating and overseeing incentives for the production and use of medical information.

Part I presents the saga of 23andMe to illustrate the shifting regulatory regime for DTC genetic testing over the past decade. 23andMe burst onto the scene in 2007 when it began marketing its flagship Personal Genome Service. At that time, 23andMe operated largely outside the purview of the FDA, against an ambiguous and uncertain regulatory landscape. This continued until 2013, when the FDA demanded 23andMe (and other DTC testing companies) cease marketing their products—the apogee of the FDA's precautionary paternalistic regulatory response. This moment took on added salience in contrast with the company's successful launch of DTC genetic testing with approval by the Medicines and Healthcare Products Regulatory Agency in the United Kingdom in 2014. The FDA seemed to signal a shift in its regulatory approach with its approval of 23andMe's DTC carrier screening test for Bloom Syndrome in February 2015. In the years since, the signal has intensified, with the FDA approving ten genetic health risk tests (including Alzheimer's risk, Parkinson's disease, and hereditary thrombophilia) in April 2017, the first genetic cancer health risk test (for selected variants on BRCA1/BRCA2) in

March 2018, and pharmacogenetic tests for variants associated with metabolism of some therapeutic drugs in October 2018.

Part II generalizes from this case study to characterize the FDA's emerging regulatory model as a hybrid, combining elements from the traditional "protective" medical device model and its contrasting consumer-based "libertarian" model. What is perhaps most surprising, given the Trump Administration's overall deregulatory thrust and the conservative and libertarian attacks on the regulation of information-based technologies, is that the FDA continues to assert the need for oversight, albeit pursuant to a new and evolving regulatory model.

Part III focuses on the dual roles of the FDA as safety regulator and as health information regulator by highlighting the less well-recognized (albeit traditional) role of the FDA in medical information production and then considering new challenges posed by DTC genetic testing. The FDA is well poised to play a small (albeit significant) part in the wider effort to gather and disseminate data in the health sector; its emergent hybrid regulatory model has potential implications for ensuring the creation of underlying evidence and substantiation of "big data" medical claims.

INTRODUCTION

The realms of genetic testing, personalized medicine, and consumer health are developing at breakneck speed made possible by the confluence of large-scale research on the effects of genetics on human health, increased consumer demand, and greater commercial competition. The Human Genome Project, proceeding alongside the technological revolution in big data processing, has opened up an entirely new world of genetic testing: one in which vast amounts of patient genetic information can be quickly and cheaply produced and analyzed.¹ "Next generation sequencing" promises a further revolution in terms of the potential information it will provide patients, doctors,

1. Genotyping, the process 23andMe uses to identify genetic variants, gives a limited view of an individual's genetic makeup and generally looks for pre-established or known genetic signifiers. See, e.g., *What Is the Difference Between Genotyping and Sequencing?*, 23ANDME, <https://customer.care.23andme.com/hc/en-us/articles/202904600-What-is-the-difference-between-genotyping-and-sequencing> (last visited Nov. 24, 2018). Genotyping chips "require prior identification of the variants of interest," whereas "sequencing can be used to genotype someone for known variants, as well as identify variants that may be unique to that person." *Id.* See also Barbara J. Evans et al., *The FDA and Genomic Tests—Getting Regulation Right*, 372 *NEW ENG. J. MED.* 2258, 2258 (2015) (noting that older "technologies for detecting genetic variants," including single-nucleotide-polymorphism arrays, "are designed to capture predefined data points that are known in advance of testing").

and researchers.² These developments portend a future where medicine is tailored to a specific patient's needs.³ Moreover, aggregating massive amounts of genetic data promises a time in the near future when public health officials, pharmaceutical companies, doctors, insurance companies, and biotechnology companies can effectively harness big data to uncover previously unknown sources of illness and disease.⁴

Genome sequencing has become increasingly affordable,⁵ while a user-driven participatory health movement grounded in patient empowerment has gained momentum. One significant aspect of these developments posing acute regulatory challenges is that, with the rise of direct-to-consumer (DTC) genetic testing, genetic information is increasingly moving out of medical institutions and into the private commercial sector.⁶

2. High throughput genome sequencing, also known as “next-generation sequencing,” can sequence an individual's entire genome, thereby producing vast amounts of information about an individual's genes. *See* Evans et al., *supra* note 1, at 2258 (“Examples include next-generation sequencing assays that detect any variant present in a specific set of genes, whole-exome and whole-genome sequencing tests, and copy-number variant arrays.”); *see also* U.S. FOOD & DRUG ADMIN., UCM427869, OPTIMIZING FDA'S REGULATORY OVERSIGHT OF NEXT GENERATION SEQUENCING DIAGNOSTIC TESTS—PRELIMINARY DISCUSSION PAPER (2014), <https://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM427869.pdf> (“Next generation sequencing (NGS) comprises a collection of new technologies that allow rapid sequencing of large segments of an individual's DNA and even an individual's entire genome.”). NGS opens the door for interested parties to study a vast number of genetic variants through techniques like genome-wide association studies. Such studies promise to uncover the genetic origins of various health problems, thereby enabling pharmaceutical companies and doctors to address them. That this process can identify associations is clear. *See, e.g., For the Scientific Community, 23ANDME*, <https://www.23andme.com/publications/for-scientists/> (last visited Nov. 24, 2018) (listing numerous scientific papers finding associations between phenotypes and genes). What is less assured is that those associations will always lead to actionable steps. *See, e.g., Evans et al., supra* note 1, at 2259.

3. *See, e.g.,* Rebecca S. Eisenberg, *Shifting Institutional Roles in Biomedical Innovation in a Learning Healthcare System*, 14 J. INST. ECON. 1139, 1145 (2018).

4. *See, e.g.,* Evans et al., *supra* note 1, at 2260; *see also* Erika Cule et al., *Significance Testing in Ridge Regression for Genetic Data*, BMC BIOINFORMATICS, Sept. 19, 2011, at 1–2.

5. The costs of genetic testing have dropped precipitously. *See, e.g.,* Megan A. Allyse et al., *Direct-to-Consumer Testing 2.0: Emerging Models of Direct-to-Consumer Genetic Testing*, 93 MAYO CLINIC PROC. 113, 114 (2018) [hereinafter *DTC Testing 2.0*] (“In 2007, the cost of a DTC panel hovered around \$1000. Three years later it dropped to between \$300 and \$400. By 2012, it dropped to \$99 and 23andMe announced their goal of collecting 1 million users.”).

6. *See* SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, DIRECT-TO-CONSUMER GENETIC TESTING: REPORT OF THE SECRETARY'S ADVISORY COMMITTEE ON GENETICS, HEALTH, AND SOCIETY 5 (Apr. 2010), https://osp.od.nih.gov/wp-content/uploads/2013/11/SACGHS_DTC_Report_2010.pdf [hereinafter REPORT OF THE SECRETARY'S ADVISORY COMMITTEE] (“As of February 2010, more than 30 Web-based companies sell DTC genetic services; however, the volume of business is unknown. . . . Some companies provide a limited number of genetic tests in a particular area, such as drug response or for a particular subset of health conditions such as cancer. Other companies offer genetic tests for a large number of health conditions

The current consumer genomics landscape is a mix of trusted, reliable data and practices along with prematurely deployed market offerings based on weak science. According to Dr. Eric Topol, a geneticist and cardiologist at Scripps Translational Science Institute: “There’s a big, I guess, divergence of companies that are peddling things that have no evidence basis—like nutrigenomics, weight management, sports genomics, all kinds of things, and on the other hand, lots of hard, impressive data for drug DNA interactions and risks of major diseases.”⁷ Topol concludes: “So there is data that is terrific and continues to be evolving, but [it’s] not widely commercialized, and then there’s these very questionable entities selling data services that have no basis.”⁸ The U.S. Food and Drug Administration (FDA) concurs: “Direct-to-consumer tests have varying levels of evidence that support their claims. Some [DTC] tests have a lot of scientific and clinical data to support the information they are providing, while other tests do not have as much supporting data.”⁹ Kenneth Offit, Chief of the Clinical Genetics Service at Sloan Kettering Institute, has warned that “the public health may be as much at risk from the premature deployment of de-medicalized, commercialized testing for genetic predisposition, as it is from the health threats of the syndromes of cancer predisposition themselves.”¹⁰ In a similar vein, a group representing genetic testing companies, more than one hundred patient and advocacy groups, genetic test manufacturers, and other parties has called for revamping

or traits and for different purposes such as diagnosis.”); *see also* Antonio Regalado, *2017 Was the Year Consumer DNA Testing Blew Up*, MIT TECH. REV. (Feb. 12, 2018), <https://www.technologyreview.com/s/610233/2017-was-the-year-consumer-dna-testing-blew-up/> (“The number of people who have had their DNA analyzed with direct-to-consumer genetic genealogy tests more than doubled during 2017 and now exceeds 12 million, according to industry estimates.”); *cf.* Anelka M. Phillips, *Only a Click Away—DTC Genetics for Ancestry, Health, Love . . . and More: A View of the Business and Regulatory Landscape*, 8 APPLIED & TRANSLATIONAL GENOMICS 16, 17 tbl.1 (2016) (finding 246 companies “offer some form of DNA test online,” including some companies outside of the United States). Ancestry’s website explains that the company has “samples from over 10 million people.” *Our Story*, ANCESTRY, <https://www.ancestry.com/corporate/about-ancestry/our-story> (last visited Dec. 23, 2018).

7. Heather Mack, *In-Depth: Consumer Genomics and the Road to Legitimacy*, MOBIHEALTHNEWS (Nov. 23, 2016), <https://www.mobihealthnews.com/content/depth-consumer-genomics-and-road-legitimacy> (quoting an interview with Dr. Topol). Companies continue to make dubious claims. *See, e.g.*, Nick Webbon et al., *Direct-to-Consumer Genetic Testing for Predicting Sports Performance and Talent Identification: Consensus Statement*, 49 BRIT. J. SPORTS MED. 1486, 1486 (2015), <https://bjsm.bmj.com/content/49/23/1486.full.pdf> (refuting companies’ claims that genetic tests can predict athletic ability).

8. Mack, *supra* note 7.

9. *Direct-to-Consumer Tests*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm624726.htm> (last updated Nov. 1, 2018).

10. Kenneth Offit, *The Future of Clinical Cancer Genomics*, 43 SEMINARS ONCOLOGY 615, 619 (2016).

regulation of genetic tests on the ground that “while accurate, reliable, and timely genetic testing offers enormous promise to help shape our healthcare system to meet the challenges of the 21st century, ‘poor quality testing can harm patients and waste scarce resources.’”¹¹

What, then, is the optimal regulatory framework for DTC genetic testing?¹² The debate over FDA regulation of genetic testing feeds into a wider debate of governmental paternalism versus patient autonomy and the right to information about oneself.

This Article begins with the story of the rise, fall, and rise of 23andMe as the predominant DTC genetic testing company. This saga provides an illustrative case study of the shifting sands of the regulatory landscape for DTC genetic testing. It provides a lens into the deeper exploration in Part II of the emergence of the FDA’s hybrid flexible regulatory model that moves away from the traditional “protective” medical device model and towards the consumer-based “libertarian” model especially as applied to innovative information-based technology. But at the same time, it resists full-stop embrace of the libertarian model, which, taken to the extreme, would transform medical relationships into purely commercial ones.

Part III then turns to considering the dual role of the FDA as a regulator of safety as well as of health information, specifically its appropriate role in the production and dissemination of this medical information. The FDA has traditionally regulated medical products such as prescription drugs and medical devices as well as the accompanying

11. Press Release, Genetics & Pub. Policy Center and Coal. for 21st Century Med., Overhaul of Genetic and Other Advanced Diagnostic Testing Regulations Necessary for Personalized Medicine, HHS Secretary Told (May 5, 2009), http://www.geneticalliance.org/sites/default/files/pressreleasearchive/sebelius_letter_release.pdf.

12. To tackle this question fully, one would need to consider regulation by tort law, state and federal statutory law and regulations, and the market. One would also have to consider the extent to which federal regulation should preempt state tort law. *Cf. generally* Catherine M. Sharkey, *States Versus FDA*, 83 *GEO. WASH. L. REV.* 1609 (2015).

My focus in this Article is limited to how the federal regulatory model should evolve, but of course this cannot be fully considered in isolation. Several states, for example, have prohibited or limited DTC genetic testing in the past. *See Survey of Direct-to-Consumer Testing Statutes and Regulations*, GENETICS & PUB. POL’Y CTR. (June 2007), <https://repository.library.georgetown.edu/bitstream/handle/10822/511162/DTCStateLawChart.pdf?sequence=1&isAllowed=y>; *see also 23andMe Genetic Service Now Fully Accessible to Customers in New York and Maryland*, 23ANDME (Dec. 4, 2015), <https://mediacenter.23andme.com/press-releases/23andme-genetic-service-now-fully-accessible-to-customers-in-new-york-and-maryland/> (23andMe “was not able to process saliva samples collected in or mailed from the state of New York due to New York Department of Health regulations designating the 23andMe Personal Genome Service as a test requiring direct physician involvement. In Maryland, state law prohibited residents from buying any direct-to-consumer tests that provided health related information. Those tests had to be ordered by a doctor, according to state law.”). According to 23andMe, these state law bans no longer applied once the FDA approved 23andMe’s tests as suitable for over-the-counter use.

labeling. The FDA's newly emergent flexible regulatory model recognizes the significance of the fact that the product being sold is "medical information" posing health and safety risks due to false positives and false negatives. But the FDA also serves a critical regulatory function to intervene to correct market failures in the privatization and commercialization of consumer genetic information. A significant component of the FDA's review for safety and efficacy of these medical products is to evaluate the data submitted to substantiate the claims made to diagnose, treat, or manage diseases and medical conditions. The FDA is thus poised to play an enhanced role, most likely in partnership with other agencies such as the National Institute of Health, in the creation and exploitation of aggregate genetic databases.

I. A SHIFTING REGULATORY REGIME FOR DTC GENETIC TESTING: THE CASE OF 23ANDME

DTC genetic testing—which provides a means of allowing patients to access genetic information without the involvement of a physician—emerged in the 2000s.¹³ And "[i]n Silicon Valley, at the height of the dotcom boom, 23andMe was at the vanguard of a wave of interest in personal genomics."¹⁴ In 2007, 23andMe began marketing its flagship Personal Genome Service (PGS). In certain respects, 23andMe's business model mirrors that of a company like Facebook.¹⁵

13. Physicians have used genetic testing, in some form, for nearly fifty years. See Ricki Lewis, *A Brief History of Genetic Testing: What the First Generation of Tests Can Tell Us About the Latest*, SCI. PROGRESS: GENETICS (May 5, 2008), <https://scienceprogress.org/2008/05/a-brief-history-of-genetic-testing/>; see also *Genetic Testing: How it is Used for Healthcare*, NIH, <https://report.nih.gov/NIHfactsheets/ViewFactSheet.aspx?csid=43> (last updated June 30, 2018). In addition to eliminating the physician as learned intermediary, modern DTC genetic tests go well beyond the earlier iterations that tested for well-defined genetic variations with well-established causalities. See, e.g., Lewis, *supra*; Siobhan M. Dolan, *Personalized Genomic Medicine and Prenatal Genetic Testing*, 312 JAMA 1203 (2014); Siobhan M. Dolan, *Prenatal Genetic Testing*, 38 PEDIATRIC ANNALS 426, 426 (2009) ("Prenatal genetic testing options have grown tremendously over the past 25 years. What began as testing of maternal blood to screen for neural tube defects and chromosomal abnormalities has evolved to include a spectrum of screening and diagnostic tests which can be performed on the mother, father, and fetus both before and during pregnancy."); Jessica Elizabeth Palmer, *Genetic Gatekeepers: Regulating Direct-to-Consumer Genomic Services in an Era of Participatory Medicine*, 67 FOOD & DRUG L.J. 475, 479 (2012) ("Huntington's disease is highly penetrant, meaning that almost all individuals with a mutated gene will eventually develop the disease. A genetic test for Huntington's disease is thus highly predictive: the presence of a mutated gene correlates with an estimated lifetime disease risk of 100%. But most diseases are significantly less penetrant.").

14. *DTC Testing 2.0*, *supra* note 5, at 113.

15. See, e.g., Kayte Spector-Bagdady, "The Google of Healthcare": Enabling the Privatization of Genetic Bio/Databanking, 26 ANNALS EPIDEMIOLOGY 515, 515 (2016) ("Since 2007, 23andMe has offered an inexpensive product to consumers (personalized genetic analysis) to generate

On the one hand, just as Facebook is best known for its social media platform, 23andMe is best known for a consumer-facing product—its Personal Genome Service. On the other hand, just as Facebook sells user data to third parties, 23andMe sells its user “data” to third parties. 23andMe has made several deals with pharmaceutical companies where it sells access to its genetic database.¹⁶

Products like 23andMe’s saliva-testing kit paved the way for consumer genomics by getting people curious about their ancestry and their health. Since then, 23andMe has dominated the health-related DTC genetic testing market.¹⁷ In 2015, it surpassed its goal of one million customers,¹⁸ and today touts having “more than five million genotyped customers around the world.”¹⁹ And *Forbes Magazine* reported that investors estimated its value at \$1.1 billion.²⁰

A. *The Ambiguous Regulatory Backdrop*

When 23andMe emerged on the scene, it capitalized on an ambiguous regulatory landscape in making a business decision to market its genetic testing service largely outside the purview of the FDA.

Under the Clinical Laboratory Improvement Act (CLIA), the FDA is tasked—along with the states, the Federal Trade Commission (FTC), and the Centers for Medicaid and Medicare Services (CMS)—with ensuring the safety and efficacy of medical tests and interventions by monitoring laboratories that process medical samples and ensuring testing validity.²¹ But, as of 2007, the FDA had declined to exercise its prerogative to regulate so-called laboratory-developed

broader consumer data and then leveraged that data to generate profit, becoming—as board member Patrick Chung put it—“the Google of personalized health care.”

16. *See, e.g.*, Press Release, GlaxoSmithKline, GSK and 23andMe Sign Agreement to Leverage Genetic Insights for the Development of Novel Medicines (July 25, 2018), <https://www.gsk.com/en-gb/media/press-releases/gsk-and-23andme-sign-agreement-to-leverage-genetic-insights-for-the-development-of-novel-medicines/>; *Company*, 23ANDME, <https://medical.23andme.com/company/#research> (last visited July 10, 2018) (“Research is conducted independently, in collaboration with third parties, including academic institutions[,] . . . companies such as Pfizer and Genentech, and nonprofits . . .”).

17. Several other companies, such as Ancestry.com and Family Tree DNA provide ancestry-related genetic testing.

18. Anne Wojcicki, *Power of One Million*, 23ANDME BLOG (June 18, 2015), <https://blog.23andme.com/news/one-in-a-million/>.

19. *Ancestry*, 23ANDME, <https://www.23andme.com/dna-ancestry/> (last visited Dec. 23, 2018).

20. *See* Spector-Bagdady, *supra* note 15, at 515.

21. *See, e.g.*, Kayte Spector-Bagdady & Elizabeth R. Pike, *Consuming Genomics: Regulating Direct-to-Consumer Genetic and Genomic Information*, 92 NEB. L. REV. 677, 727 (2014). There is some debate regarding whether the FDA, CMS, and state regulations are duplicative. *See, e.g.*, Sarah Y. Kwon, *Regulating Personalized Medicine*, 31 BERKELEY TECH. L.J. 931, 953 (2016). The FTC has regulatory oversight over public claims about regulated products. For further discussion of the role of the FTC with respect to DTC genetic testing companies, *see infra* note 136.

tests (LDTs).²² The FDA's decision to absent itself from oversight of LDTs allowed for the rapid development of physician-ordered carrier tests, such as those for cystic fibrosis and Tay-Sachs disease. Thus, when 23andMe burst onto the scene, there were no clear regulatory mechanisms in place to assess analytical validity,²³ clinical validity,²⁴ or clinical utility²⁵ of DTC genetic tests.

B. *The FDA's Precautionary Approach*

Faced with the rapid development and marketing of DTC genetic testing kits against an ambiguous regulatory backdrop, the FDA (with a few years' time lag) took a precautionary approach. In 2010, the U.S. Government Accountability Office (GAO) published a report entitled "Direct-to-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices."²⁶ As part of its investigation, the GAO sent identical DNA samples to four DTC genetic testing companies—selected for being "frequently cited as being credible by the media and in scientific publications"²⁷—and compared their respective results and interpretations with those of genetics experts. The GAO concluded that the reported test results were "misleading and of little or no practical use to consumers."²⁸ Moreover, its investigation uncovered "10 egregious examples of deceptive marketing."²⁹

In the wake of the GAO's report, in May and June 2010, the FDA sent letters to the four largest DTC testing companies, notifying them that the FDA considered DTC genetic tests to be "medical devices"

22. The FDA has taken various positions on whether and to what extent it can or should regulate *in vitro* diagnostics and laboratory developed tests. For further discussion, see *infra* notes 74–79 and accompanying text.

23. Analytical validity concerns whether a genetic test accurately and reliably captures and conveys the genes for which it is testing. See, e.g., Evans, *supra* note 1, at 2258; Spector-Bagdady & Pike, *supra* note 21, at 719.

24. Clinical validity concerns whether an association that a DTC genetic testing company claims exists between a variation and presentation is accurate. See, e.g., Spector-Bagdady & Pike, *supra* note 21, at 719. In other words, clinical validity ensures that the identified genetic variant is predictive of a certain health condition.

25. Clinical utility describes whether the information the genetic test provides is useful in some fashion or has a "positive impact on a patient's health and wellbeing." Audrey Huang, *Who Regulates Genetic Tests?*, GENETICS & PUB. POL'Y CTR., <http://research.policyarchive.org/9644.pdf> (last updated May 30, 2008).

26. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-10-847T, DIRECT-TO-CONSUMER GENETIC TESTS: MISLEADING TEST RESULTS ARE FURTHER COMPLICATED BY DECEPTIVE MARKETING AND OTHER QUESTIONABLE PRACTICES (2010).

27. *Id.* at 2.

28. *Id.* at 4.

29. *Id.*

subject to the FDA's pre-market approval process.³⁰ The FDA's letter to 23andMe recounts how 23andMe failed to respond after the FDA raised various concerns in a meeting with 23andMe in July 2009.³¹

Close on the heels of these FDA letters, in July 2010, the House Committee on Commerce and Energy convened a hearing on DTC genetic testing. Chairman Representative Henry Waxman did not mince words, calling for governmental regulation to "ensure the public is protected against exaggerated claims, abusive marketing, and practices that threaten individual health and safety."³²

In November 2013, the FDA took decisive action, sending cease and desist letters to several DTC genetic testing companies, including 23andMe, ordering them immediately to stop marketing and selling their health-related genetic testing services.³³ The FDA sharply criticized 23andMe for ignoring the analytical validity and clinical validity requirements the FDA had established for the company's disease-re-

30. See, e.g., Letter from Alberto Gutierrez, Dir., Office of *In Vitro* Diagnostic Device Evaluation & Safety, to Anne Wojcicki, President & Co-Founder, 23andMe, Inc. (June 10, 2010), <https://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM215240.pdf> [hereinafter FDA June 2010 Letter to 23andMe]; Letter from James L. Woods, Deputy Dir. of Patient Safety & Product Quality, Office of *In Vitro* Diagnostic Device Evaluation & Safety, to James Plante, Founder & CEO, Pathway Genomics Corp. (May 10, 2010), <https://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM211875.pdf>.

31. FDA June 2010 Letter to 23andMe, *supra* note 30.

32. *Direct-to-Consumer Genetic Testing and the Consequences to the Public Health: Hearing Before the Subcomm. on Oversight & Investigations of the H. Comm. on Energy & Commerce*, 111th Cong. 20, 23 (2010) (statement of Rep. Henry A. Waxman, Chairman, H. Comm. on Energy & Commerce).

33. The cease and desist letter to 23andMe reads in relevant part:

This product is a device . . . because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure or function of the body. For example, your company's website . . . markets the PGS for providing "health reports on 254 diseases and conditions," including categories such as "carrier status," "health risks," and "drug response," and specifically as a "first step in prevention" that enables users to "take steps toward mitigating serious diseases" such as diabetes, coronary heart disease, and breast cancer. Most of the intended uses for PGS listed on your website . . . are medical device uses Most of these uses have not been classified and thus require premarket approval or de novo classification

Letter from Alberto Gutierrez, Dir. Office of *In Vitro* Diagnostics & Radiological Health, to Anne Wojcicki, CEO, 23andMe, Inc. (Nov. 22, 2013), <http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm> [hereinafter FDA Nov. 2013 Warning Letter to 23andMe].

Immediately following the FDA's Warning Letter, a group of plaintiffs filed a class action against 23andMe alleging "unfair business practices, breach of warranty, and misrepresentations about the health benefits of 23AndMe's services." *Tompkins v. 23andMe, Inc.*, 840 F.3d 1016, 1021 (9th Cir. 2016). The Ninth Circuit Court of Appeals held that the class action must be conducted in arbitration. *Id.* at 1033.

lated claims as well as its proposed labeling revisions.³⁴ The FDA also flagged the potential health consequences that could result from inaccurate health risk assessments, highlighting in particular how a false positive BRCA-related assessment of breast or ovarian cancer risk could lead a patient to undergo prophylactic surgery.³⁵

In response to the FDA's actions, several DTC genetic testing companies changed their business models to require physician participation, narrowed their services to offer DNA sequencing without interpretation and analysis, or ceased operating altogether.³⁶ Consumers of DTC genetic testing companies that offered sequencing but no longer provided interpretation or analysis could take advantage of platforms such as OpenSNP, which "markets itself as allowing 'customers of direct-to-customer genetic tests to publish their test results, find others with similar genetic variation, learn more about their results, get the latest primary literature on their variants and help scientists find new associations.'" ³⁷ While shut down in the United States, 23andMe launched its PGS in the UK in 2014 after working closely

34. The FDA appears to have been willing to allow 23andMe to proceed under the de novo review regulatory pathway (discussed further below) and possibly to allow classification as a Class II medical device (also discussed below). According to its letter, the FDA worked "diligently . . . to help [23andMe] comply with regulatory requirements regarding safety and effectiveness and obtain marketing authorization." FDA Nov. 2013 Warning Letter to 23andMe, *supra* note 33. Moreover, in 2013, the FDA approved MiSeqDx, a "next-generation [gene] sequencing platform," as a Class II medical device, albeit not one sold directly to consumers. See Nicholas S. Downing & Joseph S. Ross, *Innovation, Risk, and Patient Empowerment: The FDA-Mandated Withdrawal of 23andMe's Personal Genome Service*, 311 JAMA 793, 793 (2014).

The 23andMe shut-down by the FDA may thus have had as much (or more) to do with the company's stonewalling and non-responsiveness than with the FDA's precautionary approach. Note in this regard that, after at least fourteen meetings between the FDA and 23andMe and several years of back-and-forth communication, 23andMe went radio silent for six months (May 2013 until November 2013) leading up to the FDA's cease-and-desist letter.

35. FDA Nov. 2013 Warning Letter to 23andMe, *supra* note 33.

36. See, e.g., Spector-Bagdady & Pike, *supra* note 21, at 728–30. Color Genomics, ostensibly a competitor of 23andMe, offers several genetic tests for which 23andMe lacks FDA approval. For example, Color Genomics tests an individual's "risk for common cancers and heart conditions." See *Individuals: Overview*, COLOR GENOMICS, <https://www.color.com/product/overview> (last visited Jan. 30, 2019). While an individual ordering one of these tests through Color is not required to obtain a prescription *per se*, Color "require[s] that test requisition be approved either by a patient's own doctor or by a company-associated physician, and that patients learn about their results through that doctor or from a genetic counsellor." Molika Ashford, *Episona Adds DTC Option for Epigenetic Male Infertility Test, Enters Shifting Regulatory Landscape*, GENOMEWEB (Oct. 18, 2017), <https://www.genomeweb.com/molecular-diagnostics/episona-adds-dtc-option-epigenetic-male-infertility-test-enters-shifting>. See also *Hereditary Cancer Test*, COLOR GENOMICS, <https://www.color.com/product/hereditary-cancer-genetic-test> (last visited Jan. 30, 2019) ("All Color tests are ordered by a physician—either your own or an independent physician who can review your information and order testing on your behalf. . . . Your ordering physician will automatically get a copy of your test results.").

37. Spector-Bagdady & Pike, *supra* note 21, at 729.

with the UK Medicines and Healthcare Products Regulatory Agency.³⁸

The high-profile 23andMe PGS shutdown in the United States led to protests that the FDA was being overly cautious and stifling innovation.³⁹

C. *The FDA Changes Course*

23andMe seemed to have a reversal of fortune in February 2015, when the FDA authorized, as a Class II medical device with “special controls,” marketing of its first DTC genetic test screening for genetic predisposition to Bloom Syndrome.⁴⁰ 23andMe touted that it was “[t]he first and only genetic service available directly to individuals in the United States that includes reports that meet FDA standards for being scientifically and clinically valid.”⁴¹ As part of its premarket submission to the FDA, 23andMe conducted extensive analytical validation of its test as well as extensive user-comprehension research.⁴² In its marketing authorization decision, the FDA specifically noted that the company submitted scientific evidence of analytic validity as well as consumer usability evidence establishing that members of the

38. See Samuel Gibbs, *DNA-Screening Test 23andMe Launches in UK After US Ban*, GUARDIAN (Dec. 1, 2014, 7:01 PM), <https://www.theguardian.com/technology/2014/dec/02/google-genetic-testing-23andme-uk-launch>. Moreover, “British availability won’t be a workaround for Americans looking to get the benefits of the system—23andMe will only ship to a UK IP address and a UK shipping address.” Jonah Comstock, *Still Facing FDA Opposition in the US, 23andMe Heads Across the Pond*, MOBIHEALTHNEWS (Dec. 2, 2014), <http://www.mobihealthnews.com/38662/still-facing-fda-opposition-in-the-us-23andme-heads-across-the-pond/>.

39. See, e.g., Robert C. Green & Nita A. Farahany, *The FDA is Overcautious on Consumer Genomics*, 505 NATURE 286, 286 (2014) (“[A]s scholars who study how individuals respond to their own genetic information, we contend that the FDA’s precautionary approach may pose a greater threat to consumer health than the harms that it seeks to prevent.”); Richard Epstein, *Manhattan Moment: FDA Overreach Has Heavy Costs*, WASH. EXAMINER (Nov. 29, 2013, 12:00 AM), <http://www.washingtonexaminer.com/manhattan-moment-fda-overreach-has-heavy-costs/article/2539939>.

40. See U.S. FOOD & DRUG ADMIN., DEN14004, EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR THE 23ANDME PERSONAL GENOME SERVICE CARRIER SCREENING TEST FOR BLOOM SYNDROME: DECISION SUMMARY (2015), https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf [hereinafter FDA BLOOM SYNDROME DECISION SUMMARY].

41. *23andMe and the FDA*, 23ANDME, <https://customercare.23andme.com/hc/en-us/articles/211831908-23andMe-and-the-FDA> (last visited Jan. 30, 2019).

42. FDA BLOOM SYNDROME DECISION SUMMARY, *supra* note 40, at 5–19 (detailing the results of two studies, one with human cell line samples and a second with human saliva samples, conducted to substantiate analytical performance of the test). See also *id.* at 23–24 (describing a user comprehension study that addressed the “purpose of the PGS, limitations of the test (variants covered), relevant ethnicities for the test, meaning of test results, and appropriate follow-up actions”).

public were capable of interpreting its test report at a 90% comprehension level.⁴³

In April 2017, the FDA authorized 23andMe to market DTC Genetic Health Risk (GHR) tests for genetic predisposition to ten diseases (including Alzheimer's risk, Parkinson's disease, and hereditary thrombophilia) as Class II medical devices, again with "special controls."⁴⁴ In 2016, 23andMe had submitted a de novo application for premarket approval. As part of its submission, 23andMe provided "data from peer-reviewed, scientific literature that demonstrated a link between specific genetic variants and each of the 10 health conditions."⁴⁵

43. According to the FDA's press release noting its approval:

23andMe performed two separate studies to demonstrate that their test is accurate in detecting Bloom syndrome carrier status. One study conducted at two laboratories tested a total of 70 unique samples, including samples from known carriers of the disease. An additional study evaluated 105 samples at the same two laboratories. Both studies showed equivalent results in detecting carrier status of Bloom syndrome when the same samples were tested.

The company also conducted a usability study with 302 people not familiar with the 23andMe saliva collection device to demonstrate consumers could understand the test instructions and collect an adequate saliva sample.

Finally, the company conducted a user study comprised of 667 randomly recruited participants representing the U.S. general population in age, gender, race and education level to show the test instructions and results were easy to follow and understand.

Press Release, U.S. Food & Drug Admin., FDA Permits Marketing of First Direct-to-Consumer Genetic Carrier Test for Bloom Syndrome (Feb. 23, 2015), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm435003.htm> [<https://web.archive.org/web/20150301075100/http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435003.htm>].

44. See U.S. FOOD & DRUG ADMIN., DEN160026, EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR THE 23ANDME PERSONAL GENOME SERVICE (PGS) GENETIC HEALTH RISK TEST FOR HEREDITARY THROMBOPHILIA, ALPHA-1 ANTITRYPSIN DEFICIENCY, ALZHEIMER'S DISEASE, PARKINSON'S DISEASE, GAUCHER DISEASE TYPE 1, FACTOR XI DEFICIENCY, CELIAC DISEASE, G6PD DEFICIENCY, HEREDITARY HEMOCHROMATOSIS AND EARLY-ONSET PRIMARY DYSTONIA: DECISION SUMMARY (2017), https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN160026.pdf [hereinafter FDA GHR DECISION SUMMARY].

45. The FDA's press release elaborated:

Authorization of the 23andMe GHR tests was supported by data from peer-reviewed, scientific literature that demonstrated a link between specific genetic variants and each of the 10 health conditions. The published data originated from studies that compared genetic variants present in people with a specific condition to those without that condition. The FDA also reviewed studies, which demonstrated that 23andMe GHR tests correctly and consistently identified variants associated with the 10 indicated conditions or diseases from a saliva sample.

Press Release, U.S. Food & Drug Admin., FDA Allows Marketing of First Direct-to-Consumer Tests That Provide Genetic Risk Information for Certain Conditions (Apr. 6, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm> [hereinafter FDA DTC Press Release]. See also FDA GHR DECISION SUMMARY, *supra* note 44, at 7–28 (detailing the results from analytical performance studies for each of the 10 health conditions); *id.* at 28–50 (detailing the clinical studies consulted for each of the 10 health conditions); *id.* at 50–52 (describing results of user comprehension study conducted by 23andMe finding "average com-

23andMe had certainly turned over a new leaf in terms of cooperating and submitting to the FDA premarket clearance process. But was the FDA likewise signaling a shift in its regulatory approach, perhaps fueled by a change in presidential administration? Earlier in 2015, the FDA had announced that it would classify DTC genetic carrier screens as lower-risk devices, thus opening up a more rapid path to market for additional genetic tests for additional autosomal recessive conditions. And in 2017, the FDA announced a further shift to approving GHR tests on a device-wide basis. Namely, tests for additional conditions would be exempt from premarket review, provided the tests meet the requirements of the new GHR category.⁴⁶

23andMe has continued to ride the wave of favorable momentum. On March 6, 2018, with surprisingly little fanfare, the FDA authorized 23andMe to market the first cancer health risk test to provide information to users on their status with respect to three out of more than one thousand BRCA1/BRCA2 mutations.⁴⁷ According to the FDA, the test report “describes if a woman is at increased risk of developing breast and ovarian cancer, and if a man is at increased risk of developing breast cancer or may be at increased risk of developing prostate cancer.”⁴⁸ As part of its *de novo* review application, 23andMe submitted evidence to the FDA that the test accurately identifies the BRCA genes and it produces reproducible results.⁴⁹ In the FDA’s press release, the Acting Director of the Office of *In Vitro* Diagnostics and Radiological Health in the FDA’s Center for Devices and Radiologi-

prehension rates per core comprehension concept ranged from 73.3% to 100%” and “overall comprehension score for all concepts across all test reports studied as greater than 90%”).

46. FDA DTC Press Release, *supra* note 45. See also generally FDA GHR DECISION SUMMARY, *supra* note 44.

47. See Letter from Reena Philip, Dir., Office of *In Vitro* Diagnostics & Radiological Health, U.S. Food & Drug Admin., to Lisa Charter, Dir. Regulatory Affairs & Quality Assurance, 23andMe, Inc. (Mar. 6, 2018), https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170046.pdf; see also U.S. FOOD & DRUG ADMIN., DEN170046, EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR THE 23ANDME PERSONAL GENOME SERVICE (PGS) GENETIC HEALTH RISK REPORT FOR BRCA1/BRCA2 (SELECTED VARIANTS): DECISION SUMMARY (2018), https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN170046.pdf [hereinafter FDA BRCA1/BRCA2 DECISION SUMMARY].

48. FDA BRCA1/BRCA2 DECISION SUMMARY, *supra* note 47, at 2.

49. Press Release, U.S. Food & Drug Admin., FDA Authorizes, with Special Controls, Direct-to-Consumer Test That Reports Three Mutations in the BRCA Breast Cancer Genes (Mar. 6, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599560.htm> [hereinafter FDA BRCA Press Release]. See also FDA BRCA1/BRCA2 DECISION SUMMARY, *supra* note 47, at 4–8 (detailing analytical performance, including precision and reproducibility studies); *id.* at 9–11 (describing clinical data and studies relating to BRCA1 and BRCA2 variants); *id.* at 12 (noting that “[s]pecific user comprehension studies were not performed to specifically assess the comprehension of the Genetic Health Risk report for BRCA1/BRCA2 (Selected Variants)”).

cal Health, explained: “This test provides information to certain individuals who may be at increased breast, ovarian or prostate cancer risk and who might not otherwise get genetic screening, and is a step forward in the availability of DTC genetic tests.”⁵⁰ But, the Acting Director cautioned, given the limited amount of information the test provides, it “should not be used as a substitute for seeing [a] doctor for cancer screenings or counseling on genetic and lifestyle factors that can increase or decrease cancer risk.”⁵¹

23andMe has also made headway into the field of pharmacogenetics, the study of the link between genetics and patient reaction to drugs. According to the FDA, “[t]he use of some drugs can be aided by pharmacogenetic testing; there is sufficient scientific evidence demonstrating a relationship between certain drugs and genetic variants.”⁵² On October 31, 2018, the FDA permitted marketing, with “special controls,” 23andMe’s pharmacogenetic test to detect 33 variants for multiple genes that may be associated with a patient’s ability to metabolize drugs.⁵³ According to the Director of the Office of *In Vitro* Diagnostics and Radiological Health, “This test is a step forward in making information about genetic variants available directly to consumers We know that consumers are increasingly interested in genetic information to help make decisions about their health care.”⁵⁴ At the same time, the Director added the caveat: “This test should be used appropriately because it does not determine whether a medication is appropriate for a patient, does not provide medical advice and does not diagnose any health conditions.”⁵⁵ As part of its *de novo* premarket review application, 23andMe submitted scientific data to

50. FDA BRCA Press Release, *supra* note 49.

51. *Id.* These variants are found most often in people of Ashkenazi Jewish descent and “for non-Ashkenazi women and men, the test would miss more than 99% of all BRCA mutations.” Robert Resta, *23andMe to Offer BRCA Genetic Testing, but Should I Take This Test?*, SWEDISH: BLOG (Mar. 8, 2018), <https://www.swedish.org/blog/2018/03/23andme-to-offer-brca-genetic-testing-but-should-i-take-this-test>.

52. Press Release, U.S. Food & Drug Admin., Jeffrey Shuren, M.D., J.D., Director of the FDA’s Center for Devices and Radiological Health, and Janet Woodcock, M.D., Director of the FDA’s Center for Drug Evaluation and Research on Agency’s Warning to Consumers About Genetic Tests That Claim to Predict Patients’ Responses to Specific Medications (Nov. 1, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624794.htm> [hereinafter Shuren & Woodcock FDA Press Release].

53. See U.S. FOOD & DRUG ADMIN., DEN180028, EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR THE 23ANDME PERSONAL GENOME SERVICE (PGS) PHARMACOGENETIC REPORTS: DECISION SUMMARY (Oct. 31, 2018), https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN180028.pdf [hereinafter FDA PHARMACOGENETIC DECISION SUMMARY].

54. Press Release, U.S. Food & Drug Admin., FDA Authorizes First Direct-to-Consumer Test for Detecting Genetic Variants That May Be Associated with Medication Metabolism (Oct. 31, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm624753.htm>.

55. *Id.*

demonstrate analytical validity as well as user comprehension studies.⁵⁶

II. AN EMERGING HYBRID REGULATORY MODEL FOR DTC GENETIC TESTING

The FDA has recognized the need for regulatory reform and modernization to accommodate the rapidly changing genetic test landscape. Indeed, FDA Commissioner Scott Gottlieb aims to position the FDA as a facilitator of laboratory test innovation.⁵⁷ Moreover, according to Gottlieb, “these technologies are also prompting FDA to rethink our own mandate, and how we enable safe, effective innovation in this novel area.”⁵⁸

The FDA has jurisdiction to regulate a medical device—which is defined broadly in the Federal Food, Drug, and Cosmetic Act (FDCA) as “an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article . . . which is . . . intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease.”⁵⁹ The FDA’s medical device framework under the Medical Device Amendments to the FDCA was developed in 1976 with traditional, tangible devices in mind. At that time, few devices were controlled by, or even incorporated, software. “But by 2006, more than half of all medical devices on the U.S. market incorporated software.”⁶⁰ Moreover, “[t]his shift occurred with very little change in the FDA’s statutory authority or approach to regulating medical devices.”⁶¹

56. See FDA PHARMACOGENETIC DECISION SUMMARY, *supra* note 53, at 5–9 (detailing data submitted to demonstrate analytical performance and reproducibility of studies); *id.* at 11 (describing user comprehension study results).

57. See generally Scott Gottlieb, Comm’r, U.S. Food & Drug Admin., Remarks at the American Clinical Laboratory Association Annual Meeting (Mar. 6, 2018), <https://www.fda.gov/NewsEvents/Speeches/ucm599551> [hereinafter Gottlieb, Remarks at ACLA Annual Meeting].

58. Scott Gottlieb, Comm’r, U.S. Food & Drug Admin., Remarks at Academy Health’s 2018 Health Datapalooza: Transforming the FDA’s Approach to Digital Health (Apr. 26, 2018), <https://www.fda.gov/NewsEvents/Speeches/ucm605697.htm> [hereinafter Gottlieb, Transforming the FDA’s Approach].

59. 21 U.S.C. § 321(h), (h)(2) (2012).

60. Nathan Cortez, *Substantiating Big Data in Health Care*, 14 I/S: J.L. & POL’Y FOR INFO. Soc’y 61, 77 (2017).

61. *Id.* Congress’s 21st Century Cures Act of 2016 amended the statutory definition of “device” to exempt from FDA jurisdiction certain types of software—including software used for administrative purposes, wellness and lifestyle purposes, patient record purposes, and some clinical decision support purposes. See 21 U.S.C. § 360j(o) *et seq.* (2012 & Supp. V 2018). The exemption carves out clinical decision support software unless the professional using it cannot “independently review” the basis for its recommendations and the professional is intended to rely on the recommendation as a primary point for diagnosing or treating a specific patient. See *id.* § 360j(o)(1)(E)(iii); see also U.S. FOOD & DRUG ADMIN., CLINICAL AND PATIENT DECISION

The traditional medical device model for regulating genetic testing rests upon expert knowledge and structural elements of the health care system. It would seem to fit the traditional setting whereby a physician, with a patient-provider relationship, orders clinically indicated genetic testing. Thereafter, licensed, board-certified medical genetic counselors interpret and deliver the results to the patient.

The FDA, however, is moving away from the traditional “protective” medical device regulatory model. As Commissioner Gottlieb explained:

The old posture at the FDA is we have all the authority we need, and we can adapt our current review processes to whatever new technology comes about. So if it meets the definition of [a] medical device, we can somehow apply the 510(k) [pre-market clearance based on “substantial equivalence” to existing predicate device on the market] construct to it.⁶²

Moreover, he continued, “I think what you are hearing now from FDA is a clearer recognition that even if we could do that, and we tried to do that in the past, it’s probably not the right thing to do.”⁶³

At the same time, notwithstanding its endorsement of the promise of technological innovation unencumbered by overly burdensome regulations, the FDA has not embraced full stop the consumer-based libertarian model that focuses instead on patient autonomy and empowerment. Instead, we see the emergence of a new hybrid model: a flexible regulatory paradigm beginning to take shape.

A. *The Traditional “Protective” Medical Device Model*

The FDA has regulatory authority over all medical devices, which it classifies according to risk, with correspondingly stringent levels of

SUPPORT SOFTWARE: DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 7–8 (Dec. 8, 2017), <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm587819.pdf>. The new definition exempts software intended to transfer, store, or display data from patient records, laboratory tests, or other device inputs, unless it is “intended to interpret or analyze” these data. *See id.* § 360j(o)(1)(C)–(D). The new definition, however, does not exempt most software that processes, interprets, or analyzes data from medical images, *in vitro* diagnostics, clinical laboratory tests, or signal and pattern acquisition systems. *See id.* § 360j(o)(1)(D)–(E). Thus, as Nathan Cortez points out, “predictive analytics that generate customized treatment recommendations might qualify as medical ‘devices’ subject to FDA review.” Cortez, *supra* note 60, at 75. Moreover, the “FDA can, through notice-and-comment in the *Federal Register*, assert jurisdiction over software that would otherwise be exempt if the agency finds that it ‘would be reasonably likely to have serious adverse health consequences.’” Cortez, *supra* note 60, at 76 (quoting 21 U.S.C. § 360j(o)(3)).

62. *FDA Should Facilitate Lab Test Innovation, Craft Long-Term Regulatory Overhaul, Gottlieb Says at ACLA, GENOMEWEB* (Mar. 8, 2018), https://www.genomeweb.com/regulatory-news/fda-should-facilitate-lab-test-innovation-craft-long-term-regulatory-overhaul#.Wxv_KIMvwWr.

63. *Id.*

regulatory oversight. More specifically, under the 1976 Medical Device Amendments (MDA) to the FDCA, the FDA sets premarket clearance or approval requirements for manufacturers by placing devices into one of three categories based on the health risks associated with their use: Class I, low-risk devices subject to general controls;⁶⁴ Class II, medium-risk devices subject to special controls; and Class III, high-risk devices subject to premarket approval.

Class III medical devices “present[] a potential unreasonable risk of illness or injury” or are “purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health.”⁶⁵ Such devices are subject to the FDA’s premarket approval (PMA) process, a rigorous process that requires the manufacturer to submit substantial data to provide “reasonable assurance” to the FDA that its device is safe and effective for its intended use before introducing it to the market.⁶⁶

The MDA also outlined a “grandfathering” process for devices already on the market as of 1976; and it thus provided for a streamlined pre-market notification (PMN) process (also called the 510(k) process after the then-existing statutory provision) for devices that are “substantially equivalent” to pre-existing devices.⁶⁷ This streamlined PMN process loosely resembles the streamlined pathway for generic drugs (known as the Abbreviated New Drug Application) that can rely on “bioequivalence” with approved brand-name drugs (which must sub-

64. General controls typically associated with Class I medical devices include registration, listing, current good manufacturing practice, and medical device reporting.

65. 21 U.S.C. § 360c(a)(1)(C)(ii)(I)–(II) (2012).

66. See e.g., *id.* § 360c(a)(1)(C)(i) (noting, *inter alia*, that a Class III device is one that “(I) cannot be classified as a class I device because insufficient information exists to determine that the application of general controls are sufficient to provide *reasonable assurance of the safety and effectiveness* of the device, and (II) cannot be classified as a class II device because insufficient information exists to determine that the special controls described in subparagraph (B) would provide *reasonable assurance of its safety and effectiveness*”) (emphasis added); see also 21 U.S.C. § 360e *et seq.* (2012 & Supp. V 2018) (describing certain PMA requirements); 21 C.F.R. § 814 *et seq.* (2018) (elaborating on PMA requirements).

In *Riegel v. Medtronic, Inc.*, the U.S. Supreme Court held that the MDA to the FDCA preempted state law design-defect and failure-to-warn claims involving a medical device that had undergone rigorous FDA pre-approval scrutiny. 552 U.S. 312, 324–25 (2008). *Riegel* certainly narrows (but does not entirely foreclose) the scope of state law claims of allegedly defective FDA-approved Class III medical devices that can withstand a federal preemption challenge. See generally Catherine M. Sharkey, *Tort-Agency Partnerships in an Age of Preemption*, 15 THEORETICAL INQUIRIES L. 359, 362–69 (2014) (elaborating upon the “new (or resurrected) species of tort claims” that have arisen “in the shadow of preemption” enforcing state requirements that are “parallel” to federal statutory schemes).

67. See 21 U.S.C. §§ 360c(f)(1)(A)(ii), 360c(i) (2012).

mit a full New Drug Application with clinical trial evidence) to enter the market once patent protection ends.⁶⁸

In Vitro Diagnostics (IVDs) are defined as:

[T]hose 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 or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body.⁶⁹

IVDs are regulated like other medical devices. That is, the FDA classifies them as Class I, II, or III depending on its determination of what kind of scientific data and additional controls are required to ensure safety and effectiveness.⁷⁰ A device that is not substantially equivalent to a pre-1976 device is classified by statute into Class III without any FDA rulemaking proceedings.

When it comes to genetic testing, the potential targets of the FDA's regulatory reach include: (1) the container in which the DNA is held or shipped to the lab; (2) the device that is reading the DNA (e.g., the actual machine as well as the reagents or chemicals that allow it to work); (3) the laboratory conducting the tests; (4) the tests used to demonstrate testing validity; and (5) the software that translates raw read-outs into comprehensible medical information.⁷¹ The FDA's pre-

68. Compare *id.* § 360c(i)(1), with 21 U.S.C. § 355(j)(2) (2012). For discussion of the implications for federal preemption of state tort law, see Catherine M. Sharkey, *What Riegel Portends for FDA Preemption of State Products Liability Claims*, 102 Nw. U. L. REV. 415, 422–23 (2008) (“The contrast between FDA’s PMA process (at issue in *Riegel*) and its premarket notification process (at issue in *Lohr*) is twofold. Premarket notification is a streamlined process, which is completed in an average of 20 hours (as compared to the PMA’s 1,200-hour average). So, measured by average manpower hours, this type of regulatory review is sixty times more lax. Even more germane is the distinction the Court draws between the FDA’s premarket notification ‘equivalence’ review, which essentially ‘grandfathers’ devices that are equivalent to those existing on the market at the time of the MDA’s enactment, versus the full-blown PMA ‘safety’ review.”).

69. 21 C.F.R. § 809.3 (2018).

70. See *Overview of IVD Regulation*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRegulatoryAssistance/ucm123682.htm> (last updated July 9, 2018).

71. Companies seeking FDA approval of their IVDs may also be required to obtain Investigational Device Exemptions (IDE) in order to perform clinical investigations. It is through IDEs that the FDA may regulate, to a certain degree, genetic testing research studies. NGS companies fear that the FDA may unnecessarily interject itself into such studies. It seems, however, that NGS companies are in the clear subject to the following constraint:

In deciding whether FDA can regulate research, there is a crucial legal distinction between sequencing people’s genes for general genetic and biomedical research purposes (for example, to study which variants appear in the human genome, or to study the medical significance of specific gene variants, or to study optimal procedures for communicating and utilizing genetic information in clinical settings, or to study the psychological impact of genetic disclosures on patients) *versus* sequencing people’s genes in

rogative to regulate (1)–(3) is relatively uncontroversial. As to (1) and (2), the FDA has authority to regulate these as medical devices or “other similar or related article[s].”⁷² As to (3), IVDs are subject to CLIA, which “establishes quality standards for laboratory testing and an accreditation program for clinical laboratories,” based on the complexity of the tests performed.⁷³

A key controversial question had been whether a genetic test is an IVD subject to FDA regulation or instead a Laboratory Developed Test (LDT) subject to the FDA’s “homebrew” exception. While all LDTs are IVDs, the FDA has traditionally exercised “enforcement discretion” with respect to LDTs.⁷⁴ LDTs were initially exempt from FDA regulation because the FDA viewed them as straightforward tests conducted largely in-house at research labs.⁷⁵ Whereas IVDs can be sold to laboratories, hospitals, clinics, or directly to patients, LDTs are technically for research purposes only, and are created and ex-

order to study the analytical and clinical performance characteristics of the sequencing technology itself.

Barbara J. Evans, *The Limits of FDA’s Authority to Regulate Clinical Research Involving High-Throughput DNA Sequencing*, 70 *FOOD & DRUG L.J.* 259, 263 (2015).

72. See 21 U.S.C. § 321(h) (2012) (“The term device . . . means an instrument, apparatus, implement, machine, contrivance, implant, *in vitro* reagent, or other similar or related article, including any 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, in man . . . or . . . intended to affect the structure or any function of the body of man . . .”).

73. *Overview of IVD Regulation*, *supra* note 70. States and CMS also play roles in regulating testing laboratories. A state can exempt its labs by demonstrating that it meets or goes beyond what CLIA requires, and CMS (at least in the FDA’s view) plays a role complementary to that of the FDA. Whereas the FDA regulates clinical and analytic validity, CMS ensures clinical utility primarily, and analytical validity to a lesser extent in certain circumstances. See, e.g., *Discussion Paper on Laboratory Developed Tests (LDTs)*, U.S. FOOD & DRUG ADMIN. (Jan. 13, 2017), <https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf> [hereinafter FDA, *Discussion Paper on LDTs*]; see also *CLIA Overview*, CMS.GOV (Oct. 22, 2013), https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf.

74. See e.g., REPORT OF THE SECRETARY’S ADVISORY COMMITTEE, *supra* note 6, at 16. Although the FDA (and some commentators) view the FDA as having clear statutory authority to regulate LDTs, others disagree. Compare Evans et al., *supra* note 1, at 2258 (“Skeptics raise important concerns, but there is little doubt that the FDA has ample power to impose at least some new regulatory requirements on genomic testing—enough, in any event, to make laboratory directors squirm.”), and Palmer, *supra* note 13, at 512, with, e.g., PAUL D. CLEMENT & LAURENCE H. TRIBE, LABORATORY TESTING SERVICES, AS THE PRACTICE OF MEDICINE, CANNOT BE REGULATED AS MEDICAL DEVICES (2015), <http://www.acla.com/wp-content/uploads/2015/01/Tribe-Clement-White-Paper-1-6-15.pdf>, and Patricia Zettler, *Pharmaceutical Federalism*, 92 *IND. L.J.* 845, 890–92 (2017).

75. *Laboratory Developed Tests*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm> (last updated Oct. 12, 2018) (“The FDA has generally not enforced premarket review and other applicable FDA requirements because LDTs were relatively simple lab tests and generally available on a limited basis.”).

aminated within a single lab.⁷⁶ Traditionally exempt from FDA regulation, LDTs create what some have called a “regulatory black hole.”⁷⁷

But regardless of the status of LDT tests as exempt from FDA regulation:⁷⁸

The FDA has made clear that DTC tests do not fall within that [LDT enforcement discretion] policy, which means that manufacturers of such tests are subject to enforcement action if they do not submit information about their tests to the FDA for premarket review and do not comply with other FDA regulatory controls, even if they otherwise would be considered LDTs.⁷⁹

B. The Consumer-Based “Libertarian” Critique

In recent years, there has been increasing backlash against the FDA’s protective medical device regulatory model. Richard Epstein has long bemoaned the heavy hand of the risk-averse FDA in the traditional realms of medical device and drug regulation. Epstein has advocated a laissez-faire approach that would liberate such medical products from upstream regulatory control and place control downstream in the hands of physicians who can make individual-based assessments.⁸⁰ But he has been joined more recently by liberal critics, highlighting the potential suffocating effect of regulation on technology-fueled innovation.

Stephan Landsman and Michael Saks argue in a forthcoming book that the medical model innovates too slowly because of regulation as well as professional resistance to new practices.⁸¹ The authors use the

76. See Palmer, *supra* note 13, at 498, 500–01.

77. See Bruce Patsner, *New “Home Brew” Predictive Genetic Tests Present Significant Regulatory Problems*, 9 HOUS. J. HEALTH L. & POL’Y 237, 239 (2009).

78. In 2014, the FDA issued draft guidance on the regulation of LDTs, which was subsequently shelved. In January 2017, however, the FDA issued a discussion paper addressing the feedback it had received on its 2014 document and offered some insight into how the FDA is thinking about LDT regulation. FDA, *Discussion Paper on LDTs*, *supra* note 73. As detailed therein, the FDA asserts: (1) it can regulate LDTs; (2) it plans to take a risk-based approach to LDT oversight; (3) it may outsource some of the work; and (4) it will implement LDT regulation over a few years, grandfathering in many LDTs currently on the market. See *id.*

79. See, e.g., Nancy K. Stade et al., *FDA Challenges Direct-to-Consumer Genetic Tests*, LAW360 (Mar. 22, 2016, 11:47 AM), <https://www.law360.com/articles/772679/fda-challenges-direct-to-consumer-genetic-tests>.

80. See, e.g., Richard A. Epstein, *Against Permittitis: Why Voluntary Organizations Should Regulate the Use of Cancer Drugs*, 94 MINN. L. REV. 1 (2009); Richard A. Epstein, *Rational Basis Review and FDA Regulation: Why the Two Do Not Mix*, 14 GEO. J.L. & PUB. POL’Y 417 (2016); Richard A. Epstein, *Regulatory Paternalism in the Market for Drugs: Lessons from Vioxx and Celebrex*, 5 YALE J. HEALTH POL’Y, L., & ETHICS 741 (2005).

81. STEPHAN LANDSMAN & MICHAEL J. SAKS, *CLOSING DEATH’S DOOR: LEGAL INNOVATIONS TO STEM THE EPIDEMIC OF HEALTHCARE HARM* (forthcoming 2020) (manuscript at 1) (on file with DePaul L. Rev.) (examining medicine’s resistance to technological steps that have the potential to enable patients to make decisions and to provide a check on unsafe practices).

case study of 23andMe and the FDA to illustrate the medical establishment's resistance to the provision of medical information directly to consumers and the potential of such a practice to alter the balance between medical professionals and the recipients of medical care. They claim that medical professionals are overly concerned with preserving their own authority and revenue streams.⁸² Moreover, they charge that the empirical evidence simply does not support the exaggerated concerns about consumer anxiety or negative changes in health behavior.⁸³ Of particular relevance here, they challenge the FDA's role, chastising its "rigorous use of governmental regulatory powers to curtail the flow of such information."⁸⁴ Moreover, they decry that the "professional establishment's primary strategy in its effort to retain control will be calls for regulation by the FDA and other government agencies."⁸⁵

Proponents of the libertarian model tout its potential to promote preventative and individualized medicine, while simultaneously reducing costs to individuals and the health care system. Their vision is populated by patient consumers, engaged with online social media platforms, with an ability to respond voluntarily to follow-up surveys

82. *Id.* at 488 ("A good bit of doctors' anxiety about information technology perhaps finds its basis in this threat to upend traditional bases of treatment and devalue doctors' substantial investments in their training in the art of medicine.").

83. *Id.* at 475 ("The alleged risks that justified this level of protection were the speculative possibilities of consumer anxiety and a heightened level of requests for medical advice. Direct-to-consumer delivery of healthcare information was perceived as so threatening that a solution akin to a death sentence was proposed for the activity."); *id.* at 480–81 ("Medicine's tools in its holding action against change will include claims that supplying information directly to patients will cause anxiety and that patients are incompetent to manage the necessary response. Those claims will not, generally, wait for empirical evidence before advancing armed only with anecdote and supposition."); *id.* at 474 ("While the authors [of a JAMA article sharply criticizing DTC genetic testing] saw no need to shore up the empirical basis for their criticisms, they were at pains to stress the substantial empirical burden that should be imposed on direct-to-consumer companies.").

In 2011, Scripps Research Institute surveyed individuals before and after accessing a DTC testing product; the study reported "no significant differences in the level of anxiety, dietary fat intake, or exercise behavior between baseline and follow-up for the sample as whole." Cinnamon S. Bloss et al., *Effect of Direct-to-Consumer Genomewide Profiling to Assess Disease Risk*, 364 *NEW ENG. J. MED.* 524, 529 (2011). A subsequent 2013 study found that 24.6% of DTC genetic testing customers reported a change in levels of anxiety—and of these, 85.3% claimed their anxiety was reduced. Corin Egglestone et al., *Effect of Direct-to-Consumer Genetic Tests on Health Behaviour and Anxiety: A Survey of Consumers and Potential Consumers*, 22 *J. GENETIC COUNSELING* 565, 565 (2013).

84. LANDSMAN & SAKS, *supra* note 81, at 474–75.

85. *Id.* at 481.

and health reports in order to interpret raw data.⁸⁶ It is a vision enabled by the information technology revolution in medicine.⁸⁷

C. *The FDA's Hybrid Model: Flexible Regulatory Paradigm*

The FDA has launched “Innovation Pathway 2.0,” a series of initiatives designed to promote the development of breakthrough devices by reducing the timeline and cost of generating safety and efficacy data.⁸⁸ In a 2018 public workshop, the FDA Director of the Center for Devices and Radiological Health bemoaned that the FDA’s standard of reasonable assurance of safety and effectiveness is “one of the highest standards in the world [and] it often entails the generation of much more evidence . . . that can create disincentives for innovators to bring their technologies to the US early, if at all.”⁸⁹ And FDA Commissioner Gottlieb has sounded a consistent theme:

[W]e must also recognize that FDA’s usual approach to medical product regulation is not always well suited to emerging technologies like digital health, or the rapid pace of change in this area. If we want American patients to benefit from innovation, FDA itself must be as nimble and innovative as the technologies we’re regulating.⁹⁰

There is a recognition that the existing traditional regulatory regime for medical devices and pharmaceutical drugs may not be right for genetic testing (regulated either as IVDs or LDTs).⁹¹ The FDA is embracing “flexible regulatory paradigms”: “The idea is rather than take technologies and put them down in cookie cutter pathways, design the regulatory paradigm around the technology. What are its unique evi-

86. *Id.* at 480 (advocating that “[p]atients [be] empowered to become the assessors of their own condition and collectors of critical information about it”). “The direct-to-consumer genetic testing story provides important lessons for efforts to disseminate information to customers that can put them in charge of monitoring their health and addressing potential problems.” *Id.*

87. See generally ERIC TOPOL, *THE PATIENT WILL SEE YOU NOW* (2015) (crediting improvements in information technology that will sidestep professional control and empower patients to pursue and secure better and safer care on their own initiative).

88. See *Innovation Pathway*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/InnovationPathway/default.htm> (last updated Aug. 18, 2016).

89. Jeffrey Shuren, Dir., Ctr. for Devices & Radiological Health, U.S. Food & Drug Admin., Remarks at Fostering Digital Health Innovation: Developing the Software Precertification Program Public Workshop 11 (Jan. 30, 2018) [hereinafter Shuren, Remarks at Fostering Digital Health Innovation] (transcript available at <https://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM600093.pdf>).

90. Gottlieb, Transforming the FDA’s Approach, *supra* note 58.

91. *Cf.*, e.g., Cortez, *supra* note 60, at 81 (“If predictive analytics does not fit well into existing frameworks governing medical products, medical professionals, or medical information, what would a more appropriate framework look like? There is a fair bit of skepticism of traditional regulation by traditional regulators; conversely, there is a fair bit of optimism in private certifiers and technology-enabled intermediation.”).

dence generation needs, patient access needs, innovation cycles?”⁹² Increasingly,

[i]t seems clear that the emerging regulatory system will need to develop a hybrid strategy that includes some aspects of the responsibility of medical information providers to ensure the quality of their information, their responsibility to facilitate user comprehension and interpretation of test results, the freedom of consumers to order testing on their own initiative, and the expectation that data will be managed appropriately.⁹³

The first of three pillars of the FDA’s more flexible regulatory model is greater use of the so-called expedited *de novo* process for regulatory approval of DTC genetic tests.⁹⁴ Introduced as part of the 2012 Food and Drug Safety and Innovation Act, the “direct *de novo*” process allows medical device sponsors to submit a *de novo* application in the first instance without submitting a prior 510(k) “substantial equivalent” application.⁹⁵ It is a preclearance regulatory pathway designed for novel, low-to-moderate risk devices for which there is no existing predicate on the market.

In 2016, the FDA issued a guidance document entitled “Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications.”⁹⁶ The FDA’s *de novo* review process is still somewhat in flux. Regulatory expectations for DTC genetic testing companies are patterned after the

92. Shuren, Remarks at Fostering Digital Health Innovation, *supra* note 89, at 11.

93. *DTC Testing 2.0*, *supra* note 5, at 119.

94. The FDA Modernization Act of 1997 created the *de novo* process—an expedited review process for low to moderate risk devices that could bypass the PMA process, even without substantially equivalent predicates on the market. *See, e.g.*, U.S. FOOD & DRUG ADMIN., FDA-2011-D-0689, DE NOVO CLASSIFICATION PROCESS (EVALUATION OF AUTOMATIC CLASS III DESIGNATION): GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF 4 (2017), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf> [hereinafter FDA 2017 DE NOVO GUIDANCE] (describing the creation and nature of the *de novo* process in 1997). The 2012 Food and Drug Safety and Innovation Act built on the earlier 1997 *de novo* initiative.

95. *See, e.g., id.* (creating “an alternative mechanism for submitting a *De Novo* request that does not require that a device be reviewed first under a 510(k) and found NSE [not substantially equivalent] prior to submission of a *De Novo* request”). While 2012 marked the final Congressional action to date on *de novo* review, the FDA has continued to refine the process. In 2017, the FDA finalized a guidance document (originally issued in draft form in 2014) entitled “*De Novo* Classification Process (Evaluation of Automatic Class III Designation)” that seeks to clarify which kinds of information device sponsors need to submit to help ensure the success of their *de novo* application. *See id.*

96. U.S. FOOD & DRUG ADMIN., FDA-2011-D-0577, GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: FACTORS TO CONSIDER WHEN MAKING BENEFIT-RISK DETERMINATIONS IN MEDICAL DEVICE PREMARKET APPROVAL AND DE NOVO CLASSIFICATIONS 4 (2016), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM517504.pdf> [hereinafter FDA 2016 DE NOVO GUIDANCE].

FDA's April 2017 market authorization of 23andMe's Genetic Health Risk (GHR) tests, which were submitted under the direct de novo process.⁹⁷

The second pillar is a new genetic testing approval pathway for GHR tests that the FDA announced in November 2017. FDA Commissioner Gottlieb has advocated for the creation of a precertification program for diagnostics: "In the setting of these DTC tests, we realized that if we had enough confidence in the validity of the lab's underlying system, we could exempt from premarket review many individual tests that met pre-specified standards."⁹⁸ Building on the proposed firm-based, pre-certification model that the FDA developed for digital health technologies,⁹⁹ it allows "manufacturers of these types of [GHR] tests . . . to come to FDA for a one-time review to ensure that they meet the FDA's requirements, after which they [can] enter the market with new GHR tests without further review."¹⁰⁰ As FDA Director of the Center for Devices and Radiological Health elaborated:

In 2017 [the FDA] put out an approach for direct to consumer genetic health risk tests [The FDA] essentially said you have these tests . . . rather than coming in for every single claim, if the developer comes to us once with one claim and can show they meet expectations for demonstrating their accuracy and identifying the relevant genetic variance, that they are meeting expectations in assessing the clinical evidence to support the claim, and they can conduct good user comprehension studies, thereafter they don't come back to [the FDA].¹⁰¹

The third pillar of the new hybrid approach is third-party accreditation, which Commissioner Gottlieb has touted as "designed to reduce the burden on test developers and streamline the regulatory assess-

97. See *Evaluation of Automatic Class III Designation (De Novo) Summaries*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHTransparency/ucm232269.htm> (last updated Jan. 11, 2019) (listing current *de novo* applications as well as those that have been approved).

98. Gottlieb, Remarks at ACLA Annual Meeting, *supra* note 57.

99. As Gottlieb explained:

The goal of this [digital health technologies] program is to develop a tailored and pragmatic framework that trusts the excellence of organizations, but also continually verifies the safety, effectiveness, and performance of software as a medical device. It leverages the transparency of a sponsor's culture of quality and its evidence of organizational excellence.

Gottlieb, Transforming the FDA's Approach, *supra* note 58.

100. Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on Implementation of Agency's Streamlined Development and Review Pathway for Consumer Tests That Evaluate Genetic Health Risk (Nov. 6, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583885.htm>.

101. Shuren, Remarks at Fostering Digital Health Innovation, *supra* note 89, at 19.

ment of eligible innovative projects.”¹⁰² The FDA recently accredited the New York State Department of Health as a third-party reviewer of certain IVDs.¹⁰³ In announcing the accreditation, Commissioner Gottlieb explained that it was “another example of [] the FDA [] working to find creative and flexible approaches to regulation that spurs development and efficient delivery of innovative technology.”¹⁰⁴

III. EVALUATING THE FDA’S DUAL ROLE AS SAFETY AND HEALTH INFORMATION REGULATOR

The FDA has reached a critical juncture for institutional design and regulatory control over DTC genetic testing. Under the recently proposed Diagnostic Accuracy and Innovation Act (Act), DTC genetic tests classified as *in vitro* clinical tests (IVCTs) would not be regulated as devices, drugs, or biologics, but would instead constitute a “new category and regulatory structure” under the FDCA.¹⁰⁵ IVCT oversight would be segmented by agency and by function: (1) the FDA’s oversight would be limited to development and manufacturing; (2) CMS would regulate laboratory operations; and (3) the states along with health care professionals and related medical consultants would oversee medical use and interpretation.

Reform efforts such as the recently proposed Act, which would largely remove the FDA from regulating medical diagnostic information, should be resisted on two separate (albeit related) grounds. First, the FDA has signaled its commitment to its role as safety regulator in the emerging hybrid regulatory model for DTC genetic testing. The FDA’s prime *raison d’être* is to protect public health and safety.¹⁰⁶ This is indeed significant, but it is not the whole story. This conventional view of the FDA fails to appreciate the second important role

102. Gottlieb, Remarks at ACLA Annual Meeting, *supra* note 57.

103. Press Release, U.S. Food & Drug Admin., FDA Unveils a Streamlined Path for the Authorization of Tumor Profiling Tests Alongside Its Latest Product Action (Nov. 15, 2017), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm585347.htm>.

104. *Id.* This third-party accreditation mirrors the third-party certification for digital health technology mentioned in Gottlieb’s newest budget proposal. Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on Administration’s Request for New FDA Funding to Promote Innovation and Broaden Patient Access Through Competition (Feb. 13, 2018), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm596554.htm>.

105. *The Diagnostic Accuracy and Innovation Act: Advancing Innovation and Safety for Patients in Diagnostics*, HOUSE.GOV, <https://bucshon.house.gov/sites/bucshon.house.gov/files/documents/daia%20summary.pdf> (last visited Jan. 31, 2019).

106. *What We Do*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/aboutfda/whatwedo/> (last updated Mar. 28, 2018).

that FDA regulation plays in promoting innovation by incentivizing the generation of credible information about medical products.¹⁰⁷

In this Part, after exploring the role of the FDA as safety regulator, I turn to the argument in favor of the FDA's regulation of DTC genetic testing on information production grounds.¹⁰⁸ I explore the FDA's role as a regulator of health information, responsible for aspects of its quality, creation, interpretation, delivery, protection, and implications. If DTC genetic testing is subject to FDA oversight, the agency will ensure that the tests are analytically accurate and reliable and that companies' claims are truthful and not misleading—all of which requires substantiation via scientific data and clinical trials.

A. *The FDA as Safety Regulator*

In the current deregulatory climate, it is hardly a surprise that the FDA has signaled a policy shift away from the protective medical device regulatory model. What is perhaps more surprising is its insistence on keeping its regulatory hand in oversight of DTC genetic tests.¹⁰⁹ The FDA has consistently maintained that “since 2012 our strategic priorities have been focused around how we can sufficiently reduce the time and cost of the total product enterprise and life cycle such that innovators view the US marketplace more favorably, but not

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

108. Potentially harsh trade-offs arise in this particular context, namely whether “[l]ooser access restrictions will enhance data quality in the long term by increasing the number of participants willing and able to share DNA and information—but at the risk of misinforming and harming individuals in the meantime.” Anna B. Laakmann, *The New Genomic Semicommons*, 5 U.C. IRVINE L. REV. 1001, 1032 (2015).

109. Indeed, in prior writings, now-FDA Commissioner Gottlieb signaled a more deregulatory approach. See, e.g., Scott Gottlieb, *FDA Fear of Printed Word Threatens Our Health*, AEI (Dec. 11, 2013), <http://www.aei.org/publication/fda-fear-of-the-printed-word-threatens-our-health> (“Licensing schemes like FDA’s are ordinarily reserved for high-risk products. Most other products in commerce are regulated, if at all, by government rules addressing reliability and self-testing. . . . Congress should consider a similar method when it comes to new tech medical information tools like consumer gene tests, medical apps, and clinical decision software.”); see also Scott Gottlieb, *Will Regulation Thwart the Personalization of Medicine?*, HEALTH POL’Y OUTLOOK, Oct. 2010, at 1–2, <http://www.aei.org/wp-content/uploads/2011/10/2010-10-No-3-g.pdf> (“[W]hen it comes to safety, the [molecular diagnostics] industry has a fairly good track record. If the FDA steps in to impose regulations that are too costly, time consuming, or burdensome, it could stall much of the investment and entrepreneurship that have fueled recent innovations.”); *id.* at 5 (“[T]he increased regulatory costs and time involved in satisfying the PMA process[] will discourage investors from making new bets on diagnostics. . . . If the costs of developing diagnostics continue to rise, and if the FDA regulates diagnostics using a scheme meant to regulate drugs, investing in many of these endeavors simply becomes unviable. . . . By requiring a PMA trial, the FDA will stifle the market framework that helps drive education and the adoption of tests among clinicians.”); *id.* at 7–8 (“The question is how much innovation we are willing to trade in exchange for greater certainty about the performance of the resulting tests.”).

sacrifice that standard of reasonable assurance of safety and effectiveness.”¹¹⁰ More specifically, according to FDA Commissioner Gottlieb: “While [DTC genetic tests] can offer significant amounts of personal risk information, they’re not without their own risks—especially if they provide consumers with incorrect or misleading information that may be used to make health choices without considering the advice of a medical professional.”¹¹¹ Thus, “[i]n its consideration of [DTC genetic] tests, the FDA seeks to strike a balance that provides for an efficient pathway to bring these tests to consumers, without sacrificing the assurances offered by FDA oversight.”¹¹²

The key distinction between unregulated LDTs and DTC genetic tests, which the FDA brought under its regulatory purview, is the absence of a physician as learned intermediary. One of the FDA’s chief concerns regarding unregulated DTC genetic tests is that consumers may act on incorrect information to the detriment of their health and safety. DTC genetic tests pose three distinct risks to health and safety: (1) incorrect test results; (2) incorrect interpretation of test results; and (3) incorrect action based on test results.¹¹³ A study by Ambry

110. Shuren, Remarks at Fostering Digital Health Innovation, *supra* note 89, at 11.

111. Press Release, U.S. Food & Drug Admin., Statement from FDA Commissioner Scott Gottlieb, M.D., on Implementation of Agency’s Streamlined Development and Review Pathway for Consumer Tests That Evaluate Genetic Health Risks (Nov. 6, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm583885.htm>.

112. *Id.*

113. DTC genetic tests might pose additional risks such as the emotional impact of test results upon consumers. See Gina Kolata, *The Online Gene Test Finds a Dangerous Mutation. It May Well Be Wrong.*, N.Y. TIMES (July 2, 2018), <https://www.nytimes.com/2018/07/02/health/genetic-testing-disease-nyt.html>; Gina Kolata, *When Reporting on Mail-In Genetic Testing Comes Home*, N.Y. TIMES (July 3, 2018), <https://www.nytimes.com/2018/07/03/insider/23andme-genetic-testing-disorders.html>. Various studies have sought to better understand how consumers use and internalize DTC genetic test information. See, e.g., J. Scott Roberts & Jenny Ostergren, *Direct-to-Consumer Genetic Testing and Personal Genomics Services: A Review of Recent Empirical Studies*, 1 CURRENT GENETIC MED. REP. 182, 185–86 (2013). Suffice it to say, there is no consensus on this issue; nor does it form the crux of the FDA’s case for regulation.

DTC genetic testing raises significant privacy concerns—which I am putting aside for purposes of this Article—that provide additional grounds for opposing a market-driven libertarian response. Indeed, de-identified genetic data apparently can be re-identified. See, e.g., Arti K. Rai, *Risk Regulation and Innovation: The Case of Rights-Encumbered Biomedical Data Silos*, 92 NOTRE DAME L. REV. 1641, 1652 n.59 (2017) (collecting studies). The increased use of biometrics as privacy mechanisms, moreover, heightens the risk that criminals might seek to obtain this information. See Andelka Phillips & Jan Charbonneau, Am. Fed. Trade Comm’n’s PrivacyCon, Presentation: Giving Away More Than Your Genome Sequence?: Privacy in the Direct-to-Consumer Genetic Testing Space (Jan. 2016), https://www.ftc.gov/system/files/documents/public_comments/2015/10/00057-98101.pdf.

A further danger is the possibility of discrimination resulting from genetic test results. A handful of statutes have been passed at the state and federal level to address this. See, e.g., Rebecca S. Eisenberg & W. Nicholson Price, II, *Promoting Healthcare Innovation on the Demand Side*, 4 J.L. & BIOSCIENCES 3, 26 n.148, 35 n.199 (2017). Nevertheless, loopholes apparently still exist.

Genetics (published in *Genetics in Medicine*) found that about 40% of variants reported in raw data from DTC genetic tests may be wrong.¹¹⁴

With respect to incorrect test results, the FDA wants to guard against both false positive results and false negative results. “*False positive* results may prompt unnecessary additional testing, . . . could lead to unnecessary therapies (e.g., inappropriate prophylactic therapy or dietary restriction)[, could] . . . cause or enhance anxiety or depression[, or could cause users to] . . . make inappropriate lifestyle changes.”¹¹⁵ Such false positives can pose serious morbidity and mortality risks. For example, with respect to the BRCA1/BRCA2 test, “[f]alse positive results could subject patients to morbidity and mortality due to earlier and more frequent radiological screening and/or unnecessary surgery or medications . . . or erroneous entry into clinical investigations of cancer prevention.”¹¹⁶ Moreover, “[t]o avoid passing the variants to their children, some users could make inappropriate reproductive choices or receive unnecessary prenatal testing, which may include amniocentesis or chorionic villus sampling. Such invasive procedures carry a risk of spontaneous abortion.”¹¹⁷

See, e.g., Gregory Katz & Stuart O. Schweitzer, *Implications of Genetic Testing for Health Policy*, 10 YALE J. HEALTH POL’Y, L., & ETHICS 92, 108 (2010).

To date, the FTC has been more attuned to privacy implications than the FDA. *Compare* Lesley Fair, *DNA Test Kits: Consider the Privacy Implications*, FED. TRADE COMMISSION: CONSUMER INFO. (Dec. 12, 2017), <https://www.consumer.ftc.gov/blog/2017/12/dna-test-kits-consider-privacy-implications> (“We’ve brought dozens of cases challenging deceptive or unfair practices related to consumer privacy and data security—including a settlement with a business that sold products based on at-home genetic testing, but allegedly failed to provide reasonable security for consumers’ personal information.”), *with* FDA GHR DECISION SUMMARY, *supra* note 44, at 59 (“The risks associated with genetic privacy violation are mitigated by the manufacturer providing a privacy statement on their website.”), *and* FDA BRCA1/BRCA2 DECISION SUMMARY, *supra* note 47, at 19 (repeating the same boilerplate sentence).

114. This study was based on 49 cases that came to Ambry for confirmation testing between January 2014 and December 2017, largely for testing of cancer genes. Some DTC genetic testing firms give consumers their raw genotyping data; consumers can then send for additional testing if DTC results indicate they harbor a disease-linked variant. Two out of every five samples sent to Ambry for confirmation testing were false positives.

115. FDA GHR DECISION SUMMARY, *supra* note 44, at 55–56. The FDA noted that these issues were mitigated, in part, by virtue of (a) labeling that “recommend[s] . . . consulting healthcare professionals, genetic counselors, board-certified clinical molecular geneticist[s], or [the] equivalent” and (b) the fact that “[h]ealthcare professionals routinely review a patient’s personal and family medical history and perform physical examinations before ordering additional diagnostic tests.” *Id.* at 58 tbl.

116. FDA BRCA1/BRCA2 DECISION SUMMARY, *supra* note 47, at 14. “False positive results could also unnecessarily cause or enhance anxiety or depression. If the false positive results are associated with diseases with significant morbidity or mortality, the users may develop severe anxiety, depression or make inappropriate lifestyle changes.” *Id.*

117. *Id.*

False negative results “can delay the identification of genetic risk[s].”¹¹⁸ With respect to the BRCA1/BRCA2 test, “[f]alse negative results could lead to inappropriate follow-up, premature death and/or severe morbidity. Users receiving a false negative result may fail to initiate known effective preventive measures including appropriate lifestyle changes, risk reducing surgery, therapeutic options and/or targeted surveillance.”¹¹⁹ Whereas the existence of the physician intermediary may mitigate certain false positive risks, the same cannot be said for false negatives which may never be presented to a physician.

Certain of the tests implicate heightened risk of incorrect interpretation of test results. For example, the BRCA1/BRCA2 test reports only on three mutations commonly found in individuals of Ashkenazi Jewish descent, but there are over 1,000 BRCA mutations identified that are associated with increased risk of developing cancer. Thus, as the FDA has recognized, “users may misinterpret negative results from the report to indicate that they are negative for all variants in the BRCA1/BRCA2 genes.”¹²⁰ Moreover, removing the physician as learned intermediary, available to interpret results or detect errors, increases the risk and harm of such errors.¹²¹

The FDA’s hybrid approach embraces direct consumer access to some types of health-related genetic information while maintaining stricter regulatory oversight over diagnostic and other more clearly medical results. The FDA seems to be forging a distinction between “diagnostic” tests and those showing a genetic predisposition. While the FDA has not been clear on what constitutes a diagnostic test, it has suggested that diagnostic tests are “tests [that] are often used as the sole basis for major treatment decisions.”¹²² In a press release describing its April 2017 approval of 23andMe’s GHR tests, the FDA elaborated:

Excluded from today’s marketing authorization and any future, related exemption are GHR tests that function as diagnostic tests. Diagnostic tests are often used as the sole basis for major treatment decisions, such as a genetic test for BRCA, for which a positive re-

118. FDA GHR DECISION SUMMARY, *supra* note 44, at 56.

119. FDA BRCA1/BRCA2 DECISION SUMMARY, *supra* note 47, at 14.

120. *Id.* at 15.

121. See, e.g., Diane R. Koeller et al., *Utilization of Genetic Counseling After Direct-To-Consumer Genetic Testing: Findings from the Impact of Personal Genomics (PGen) Study*, 26 J. GENETIC COUNSELING 1270 (2017); see also June C. Carrol et al., *Primary Care Providers’ Experiences with and Perceptions of Personalized Genomic Medicine*, 62 CANADIAN FAM. PHYSICIAN e626 (2016), <http://www.cfp.ca/content/cfp/62/10/e626.full.pdf>.

122. Press Release, U.S. Food & Drug Admin., FDA Allows Marketing of First Direct-to-Consumer Tests That Provide Genetic Risk Information for Certain Conditions (Apr. 6, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm551185.htm>.

sult may lead to prophylactic (preventative) surgical removal of breasts or ovaries.¹²³

But this is somewhat perplexing in light of the FDA's March 2018 approval of 23andMe's cancer health risk test to provide information to users on their status with respect to three out of more than one thousand BRCA1/BRCA2 mutations.¹²⁴ The FDA did nonetheless impose a "special condition for use statement(s)" to specify that "[t]he test does not diagnose cancer or any other health condition and should not be used to make medical decisions."¹²⁵

Perhaps instead of attempting to maintain the diagnostic boundary line, the FDA should instead emphasize the risk-based classification for specific genetic associations.¹²⁶ History could provide a guide. Two decades ago, the FDA set up a framework to regulate the use of analyte specific reagents (ASRs), raw materials, and components used in certain IVDs used in laboratory tests.¹²⁷ The majority of ASRs

123. *Id.* The FDA also singled out tests for cancer, prenatal tests, and pharmacogenetic panels as requiring separate regulatory review. See Letter from Kelly Oliner, Dir., Div. of Immunology & Hematology Devices, Office of *In Vitro* Diagnostics & Radiological Health, Ctr. for Devices & Radiological Health, to Lisa Charter, Dir. Regulatory Affairs & Quality Assurance, 23andMe, Inc. 22–23 (Nov. 2, 2017), https://www.accessdata.fda.gov/cdrh_docs/pdf16/den160026.pdf.

124. Indeed, the FDA's approval of 23andMe's BRCA screening was criticized on similar grounds. See, e.g., Am. Coll. of Med. Genetics & Genomics, *AMCG Responds to FDA's Approval for Direct-to-Consumer Testing for Three BRCA Gene Mutations*, PR NEWSWIRE (Mar. 7, 2018, 6:18 AM), <https://www.prnewswire.com/news-releases/acmg-responds-to-fdas-approval-for-direct-to-consumer-testing-for-three-brca-gene-mutations-300610375.html> (describing the information as "incomplete," requiring "follow-up" and "context," without taking an outright antagonistic stance); Angela Chen, *23andMe's New Genetic Test for Cancer Could Create a False Illusion of Safety*, VERGE (Mar. 6, 2018, 2:41 PM), <https://www.theverge.com/2018/3/6/17086494/23andme-genetic-testing-brca-cancer-health> (quoting the President of the National Society of Genetic Counselors) ("Although this test may help to identify people who have a previously undetected BRCA mutation, there are several limitations and the results may be confusing or misleading without appropriate education."); Turna Ray, *Oncology Community Sees Potential for Patient Harm in FDA OK of 23andMe BRCA Test*, GENOMEWEB (Mar. 7, 2018), <https://www.genomeweb.com/molecular-diagnostics/oncology-community-sees-potential-patient-harm-fda-ok-23andme-brca-test#.XFhtqlxKjcs>.

125. FDA BRCA1/BRCA2 DECISION SUMMARY, *supra* note 47, at 2. See also *id.* at 21 (including as "special control" the inclusion of "[a] warning statement that the test does not diagnose cancer or any other health conditions and should not be used to make medical decisions").

126. *Accord* Spector-Bagdady & Pike, *supra* note 21, at 743.

127. ASRs are one of a handful of devices designated "restricted" by regulation. See Eric Richardson, Presentation at the FDA Small Business Regulatory Education for Industry (REdI), Medical Device Labeling 9 (Sept. 29, 2015), <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM466479.pdf>. Once deemed "restricted devices," the FDA can impose conditions on sale, distribution, and use of all ASRs. Specifically, the rule "restricts ordering the use of in-house developed tests using ASR's to physicians or other health care practitioners . . . [and] also restricts the sale of ASR's to those clinical laboratories regulated under [CLIA]." Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. 62,243, 62,244 (Nov. 21, 1997) (to be codified at 21 C.F.R. pts. 809 and 864).

were classified as Class I medical devices, exempted from premarket notification of 510(k). But the FDA classified a small number of ASRs as Class II or Class III because the FDA determined additional requirements were necessary for their safe and effective use.¹²⁸ The FDA classified a small subset of ASRs as Class III devices whose “use poses unique risks because of the substantial clinical and public health impact of the information generated by using these devices.”¹²⁹ At that time, genetic tests using ASRs were developed exclusively in-house by laboratories; such ASRs were not subject to the regulation given that they were not commercially marketed independent of the laboratory tests. Nonetheless, “FDA considered identifying a subset of ASR’s that are used to develop tests intended for predictive genetic diagnosis as ASR’s that pose unique risks to the public health because of the substantial clinical impact of the information generated using these devices.”¹³⁰ But, at the time, the FDA was not able to “identif[y] criteria that would logically distinguish among genetic tests in order to determine which have the requisite impact to trigger more stringent controls.”¹³¹

The FDA’s actual practice with respect to permitting 23andMe to market various DTC genetic tests could be considered an attempt to do just that. Along with each authorization, the FDA has established “special controls”—namely criteria to assure the test’s accuracy, clinical performance, and labeling. Take, for example, DTC pharmacogenetic tests. The absence of FDA review poses a health and

The FDA also regulates advertising for “restricted” devices. See 21 U.S.C. § 352(q)–(r) (2012). “Most Class III premarket approval devices have been restricted as a condition of approval, but only a few Class I and Class II devices (such as hearing aids) are restricted by regulation.” John Bentivoglio et al., *Up to Their Old Devices? Why Differences in Drug and Device Promotion Standards Matter from an Enforcement Perspective*, FDLI: UPDATE, Sept./Oct. 2013, at 9, <https://www.skadden.com/-/media/files/publications/2013/10/update-article.pdf>; Jeffery K. Shapiro, *What Legal Authority Does FDA Have to Regulate Medical Device Promotion on Internet Social Media Platforms?*, FDA L. BLOG (Sept. 25, 2014), <http://www.fdalawblog.net/2014/09/what-legal-authority-does-fda-have-to-regulate-medical-device-promotion-on-internet-social-media-pla/> (“[N]o Class I or Class II devices are restricted except for hearing aids and ASRs. Additionally, the handful of remaining Class III preamendment devices are not restricted, because they are not subject to a PMA approval order.”).

128. Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. at 62,243–44.

129. *Id.* at 62,245. Examples include ASRs used in tests to diagnose HIV/AIDS or tuberculosis. *Id.*

130. *Id.* “FDA considered designating as class III devices those ASR’s that would be marketed independently for use in tests intended for use in overtly healthy people to identify a genetic predisposition to a dementing disease, or to fatal or potentially fatal medical disorders (e.g., cancers or Alzheimer’s disease), in situations where penetrance is poorly defined or variable and latency is 5 years or longer.” *Id.*

131. *Id.* at 62,246.

safety risk to patients who “may change the dose of their medication for a particular condition or disease based on the results of an unproven genetic test, which may result in inadequate care or worsening illness.”¹³² As part of its authorization for 23andMe’s Pharmacogenetic Reports, the FDA established six special controls, including a labeling requirement that a warning statement must be included noting that the consumer should not use the test results to stop or change any medication. These controls serve as “risk management strategies” central to the FDA’s assessment of benefit-risk of the Pharmacogenetic test.¹³³

The FDA took the further opportunity to issue the following warning:

Today, we are warning the public about the FDA’s concerns with pharmacogenetic tests whose claims have not been reviewed by the FDA. Specifically, we are warning consumers about many such genetic tests being marketed directly to consumers or offered through health care providers that claim to predict how a patient will respond to specific medications.¹³⁴

Indeed, “as the big data industry matures, the companies that traffic in health-related big data will face competitive pressures to make more aggressive claims regarding what their analytics can predict.”¹³⁵

B. *The FDA as Health Information Regulator*

The FDA has traditionally served an information production function (albeit one not as readily appreciated as its safety function). In the era of “big data,” the FDA is poised to play an enhanced role as health information regulator. The FDA can leverage its regulatory authority to coordinate the production, dissemination, and use of genomic information. Given its expertise, the FDA is primed to serve this

132. Shuren & Woodcock FDA Press Release, *supra* note 52. *See also id.* (“[T]he FDA is aware that health care providers have made changes to patients’ medication based on genetic test results that claim to provide information on the personalized dosage or treatment regimens for some antidepressant medications, which could potentially lead to patient harm.”).

133. *See* FDA PHARMACOGENETIC DECISION SUMMARY, *supra* note 53, at 15–16 (“Overall, the likelihood of benefit of pharmacogenetic reports to describe variants associated with the metabolism of some drugs in user reports and inform conversations with healthcare providers that may prompt confirmatory pharmacogenetic testing outweighs the likelihood of erroneous interpretation and incorrect action by the user or healthcare provider, when considering the mitigations provided by the limitations and special controls, beyond general controls.”).

134. Shuren & Woodcock FDA Press Release, *supra* note 52.

135. Cortez, *supra* note 60, at 62 (“Already, patients and practitioners are inundated with claims by thousands of smartphone apps that promise to use data in novel ways to diagnose or manage scores of medical conditions.”).

gatekeeping role. Moreover, the FDA's medical device center has experience regulating software incorporated into medical devices.¹³⁶

136. This potential for an enhanced agency role in regulating data and information is by no means limited to the FDA. While the FDA has jurisdiction to ensure that devices are safe and effective, the FTC has somewhat overlapping jurisdiction to pursue unfair and deceptive trade practices, including spurious health claims. See *Direct-to-Consumer Genetic Tests*, FED. TRADE COMMISSION: CONSUMER INFO. (Feb. 2018), <https://www.consumer.ftc.gov/articles/0166-direct-consumer-genetic-tests> (warning consumers to be skeptical of DTC GT company claims). With the exception of "restricted" medical devices whose advertising is regulated by the FDA, see Richardson, *supra* note 127, at 7, the FTC regulates all medical device advertising. FTC Act Sections 5 and 12 prohibit unfair or deceptive trade practices and false advertising. See 15 U.S.C. §§ 45, 52 (2012). The FTC does not require pre-approval, but it does require substantiation "[f]or health, safety, or efficacy claims" with "competent and reliable scientific evidence." Enforcement Policy Statement on Marketing Claims for OTC Homeopathic Drugs, 81 Fed. Reg. 90,122, 90,122 (Dec. 13, 2016). "'Competent and reliable scientific evidence' [is] defined as 'tests, analyses, research, or studies that have been conducted and evaluated in an objective manner by qualified persons and [that] are generally accepted in the profession to yield accurate and reliable results.'" *Id.* While, as a general matter, this standard may be "more flexible, allowing a broader range of claims" than the FDA's substantial evidence requirement, its laxity may differ by administration or the nature of the claim/product. Press Release, Fed. Trade Comm'n, FTC Staff Provides the FDA with Comments on First Amendment Commercial Speech Doctrine (Sept. 20, 2002), <https://www.ftc.gov/news-events/press-releases/2002/09/ftc-staff-provides-fda-comments-first-amendment-commercial-speech>. For certain health claims (e.g., about specific diseases), the FTC can require randomized, double-blinded, placebo-controlled clinical trials. See, e.g., POM Wonderful, LLC, et al. v. Fed. Trade Comm'n, 777 F.3d 478 (D.C. Cir. 2015) (implicating POM Wonderful's claims that its juice products could help treat or prevent heart disease, cancer, and other conditions).

In 2014, the FTC settled a case against GeneLink, Inc. and foru International Corp., a case in which the FTC charged "that the companies didn't have sound science to support that the[ir] supplements could compensate for genetic disadvantages identified in the [provided] DNA test and reduce that person's risk of illness." Lesley Fair, *When DNA Stands for "Deceptive, Not Authenticated"*, FED. TRADE COMMISSION (Jan. 7, 2014, 11:23 AM), <https://www.ftc.gov/news-events/blogs/business-blog/2014/01/when-dna-stands-deceptive-not-authenticated>. See also, e.g., Gail H. Javitt & Kathy Hudson, *Federal Neglect: Regulation of Genetic Testing*, 22 ISSUES SCI. & TECH., Spring 2006, <http://issues.org/22-3/javitt/> ("The FTC has asserted its jurisdiction to take action against genetic test advertising that is false or misleading, and the agency has announced a joint effort with the FDA and NIH to identify appropriate targets for legal action."). As the Director of FTC's Bureau of Enforcement said,

This case is about the consequences of making false claims It doesn't matter whether the claims deal with the benefits of direct-to-consumer genetic testing or the privacy of personal information. It's against the law to deceive people about your product and to make promises you don't keep.

Press Release, Fed. Trade Comm'n, Companies Pitching Genetically Customized Nutritional Supplements Will Drop Misleading Claims (Jan. 7, 2014), <https://www.ftc.gov/news-events/press-releases/2014/01/companies-pitching-genetically-customized-nutritional-supplements> (internal quotation marks omitted). Cf. *Statement of Commissioner Maureen K. Ohlhausen Dissenting in Part and Concurring in Part*, FED. TRADE COMMISSION (Jan. 7, 2014), <https://www.ftc.gov/sites/default/files/documents/cases/140107genelinkstatementohlhausen.pdf> ("I voted against the consent agreements in the matter of GeneLink, Inc. and foru International Corporation, however, because they impose an unduly high standard of at least two randomized controlled trials (or RCTs) to substantiate *any* disease-related claims, not just weight-loss claims. Adopting a one-size-fits-all approach to substantiation by imposing such rigorous and possibly costly requirements for such a broad category of health- and disease-related claims may, in many instances,

1. *The FDA's Traditional Role in Information Production*

Rebecca Eisenberg pioneered the view that some of the FDA's drug regulation is best understood not only as safety regulation but also as incentivizing the production of data and information as well as incentivizing innovation policy more generally.¹³⁷ Take, for example, the regulation prohibiting drug manufacturers from marketing off-label uses of drugs (although physicians can legally administer off-label drugs). Separate and apart from any safety concern per se is that this incentivizes the drug manufacturer to submit additional clinical trial evidence to the FDA to get the additional indicated use approved. Thus, it is a mechanism whereby the FDA incentivizes the production of medical information that would not otherwise be produced.

The FDA's de novo regulatory framework for authorizing DTC genetic tests performs a critical information production function. The 2016 FDA Guidance details the kinds of data the FDA finds useful and lists the factors the FDA considers in assessing "benefit-risk": (1) the extent of probable benefits, (2) the extent of probable risk and harms, (3) the amount of uncertainty with respect to the device's safety and efficacy, (4) patient-reported assessments and outcomes, (5) the nature of the disease or condition that the device addresses, (6) patient preferences, (7) the availability of alternative treatments or diagnostics, (8) the availability of risk mitigation, (9) the results of post-market studies, and (10) the extent to which the device addresses some unmet medical need.¹³⁸ In its 2017 final guidance on the de novo process, the FDA elaborated on the "[s]upporting . . . [d]ata" a manufacturer should submit: "Provide a summary of all non-clinical and clinical testing (if applicable) *that provide a reasonable assurance of safety and effectiveness for your specific device* and that demonstrate that general controls or general and special controls are sufficient to

prevent useful information from reaching consumers in the marketplace and ultimately make consumers worse off.").

137. Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 107, at 345. Others have further developed the same point. See, e.g., Laakmann, *supra* note 108, at 1035 ("Though conventionally depicted as a drag on technological progress, FDA regulation actually may be a useful tool to ameliorate some of the innovation policy concerns . . ."); Chris Robertson, *Tip of the Iceberg II: How the Intended-Uses Principle Produces Medical Knowledge and Protects Liability*, 11 N.Y.U. J.L. & LIBERTY 770 (2017). See generally Anup Malani & Thomas Philipson, *The Regulation of Medical Products*, in THE OXFORD HANDBOOK OF THE ECONOMICS OF THE BIOPHARMACEUTICAL INDUSTRY 100, 106–15 (Patricia M. Danzon & Sean Nicholson eds., 2012) (describing dual components of FDA regulation of medical products as "minimum quality standard" and "production and dissemination of information and analysis about the quality of drugs and devices").

138. See FDA 2016 DE NOVO GUIDANCE, *supra* note 95.

provide a reasonable assurance of safety and effectiveness.”¹³⁹ Indeed, “the data requirements for *de novo* submissions more closely resemble those for PMAs, in which sponsors are required to demonstrate reasonable assurance that the subject device is safe and effective for its intended use.”¹⁴⁰

The FDA’s authorization decisions to date, moreover, attest to this information production function in terms of the data on analytical validity and clinical studies put forth as part of *de novo* applications.¹⁴¹ As part of its authorization of 23andMe’s pharmacogenetic tests, the FDA imposed special controls with respect to design verification and control, requiring “[d]ata appropriate . . . to demonstrate the analytical accuracy and reliability of the device in intended use specimens, including but not limited to precision, reproducibility, accuracy, limits of detection, and interferences.”¹⁴² And as part of its authorization of the BRCA1/BRCA2 test, the FDA required 23andMe to submit a “summary of the clinical and analytical performance information that must be generated” as well as “details about analytical testing that must be performed and provides criteria for appropriate standards that must be met for performance for many of the components of analytical testing in addition to the standards and evidence required to support clinical performance.”¹⁴³

Without the specter of FDA oversight, DTC genetic testing companies are not forced to provide underlying scientific data and information, which, as a result, may not be produced. Thus, for example, in the realm of pharmacogenetics, “the FDA is aware of genetic tests that claim results can be used by physicians to identify which antidepressant medication would have increased effectiveness or side effects compared to other antidepressant medications.”¹⁴⁴ But, “the relationship between DNA variations and the effectiveness of antidepressant medications has never been established.”¹⁴⁵

139. FDA 2017 DE NOVO GUIDANCE, *supra* note 94.

140. Michele L. Buenafe, *Factors to Consider Before Submitting a De Novo Request*, FDLI: UPDATE, Mar./Apr. 2017, at 11, https://www.morganlewis.com/~media/files/publication/outside%20publication/article/2017/update_april2017buenafe.ashx.

141. See, e.g., Michele Buenafe et al., *The De Novo Pathway to Market*, MORGAN LEWIS 17–18 (Mar. 9, 2017), https://www.morganlewis.com/~media/files/publication/presentation/webinar/2017/fda_de-novo-pathway_9march17.ashx (“Of 26 *de novo* applications granted in [] 2016, approximately: 4 required a prospective clinical study[,] 13 required clinical performance data[,] 3 required a usability study/assessment[, and] . . . [t]wo *de novo* submissions have required or are scheduled for advisory panel review[.]”).

142. FDA PHARMACOGENETIC DECISION SUMMARY, *supra* note 53, at 16.

143. FDA BRCA1/BRCA1 DECISION SUMMARY, *supra* note 47, at 16.

144. Shuren & Woodcock FDA Press Release, *supra* note 52.

145. *Id.*

Given the above, it is perhaps less surprising than it might seem at first blush that the FDA, in its comments pushing back against the Diagnostic Accuracy and Innovation Act (DAIA), voiced concern that the Act would restrict the FDA's ability "to ask for raw data to further evaluate the analytical and clinical validity of these tests," even though the FDA "could require pre- and post-market clinical trial data for high-risk IVCTs."¹⁴⁶

2. *The FDA's Enhanced Role in the Era of "Big Data"*

Information production may play an even more central role for DTC genetic testing than it has for pharmaceutical companies in the FDA drug approval process. Both the FDA and other scholars have noted that the utility of next generation sequencing depends substantially on the "robustness of 'genetic variant data aggregation.'"¹⁴⁷

23andMe (albeit now in the position of the regulated incumbent on the market) stands as a powerful illustration of the force of private market incentives in the development of DTC genetic tests and the accumulation of aggregate datasets. 23andMe encourages its consumers to opt in to research studies in which they volunteer to answer questions about their personal and medical histories.¹⁴⁸ Increasingly, DTC genetic testing companies like 23andMe track their customers' health over time.¹⁴⁹ With that information, the DTC genetic testing company is also either performing additional analyses itself or farming out the data to drug and biomedical companies who are doing the same.¹⁵⁰ 23andMe has a research arm that has secured federal grants¹⁵¹ and publishes articles in peer-reviewed journals.¹⁵²

146. Turna Ray, *FDA Recommends Precertification Program to Legislators as They Consider Dx Regulatory Reform*, GENOMEWEB (May 4, 2018), <https://www.genomeweb.com/molecular-diagnostics/fda-recommends-precertification-program-legislators-they-consider-dx#.WwF2YVMvzaZ>.

147. See Rai, *supra* note 113, at 126 (citations omitted).

148. See, e.g., *Research*, 23ANDME, <https://www.23andme.com/research> [<https://web.archive.org/web/20151015182009/https://www.23andme.com/research/>] (last visited Oct. 15, 2015) ("In order for scientists and researchers to accelerate healthcare, they need large sets of data . . . from all of us. Your research participation could contribute to findings in disease prevention, better drug therapies, disease treatments and ultimately, genetic paths to cures. Once you purchase your kit, you will have the choice to join this research revolution.")

149. See Evans et al., *supra* note 1, at 2260; see also Kelly Servick, *Can 23andMe Have It All?*, 349 SCIENCE 1472, 1474 (2015) ("The 23andMe Cohort . . . [is] highly engaged.")

150. See, e.g., Spector-Bagdady, *supra* note 15, at 516; see also *supra* note 16.

151. See, e.g., *23andMe Receives \$1.7M NIH Grant to Create Sequencing Panel for African Americans*, GENOMEWEB (Oct. 13, 2016), <https://www.genomeweb.com/sequencing/23andme-receives-17m-nih-grant-create-sequencing-panel-african-americans#.XCBaA89KiYU>.

152. See generally *Publications*, 23ANDME, <https://research.23andme.com/publications/#publications> (last visited Dec. 23, 2018).

The FDA faces a peculiar regulatory challenge in the face of the accumulation of immense private datasets by companies such as 23andMe. At the same time, the FDA has distinct advantages as health information regulator given its role as a gatekeeper for insurance coverage. Moreover, the FDA may be uniquely well suited to serve as a model for an experimentalist approach to data regulation, especially in light of some nascent initiatives at the frontier of digital and data science.

a. FDA as Gatekeeper for Insurance Coverage

In March 2018, CMS announced that the federal healthcare program will cover the costs of cancer genetic tests that have been approved by the FDA.¹⁵³ Private insurers often follow the lead of Medicare coverage. Moreover, the testing will generate a huge volume of genomic data on Medicare patients, whose treatments and outcomes can be tracked. This data in turn will assist hospitals and companies to gather evidence to validate their own tests; moreover, it can assist pharmaceutical companies in filling their clinical trials with genetically-matched patients.

b. FDA Poised to Advance an Experimentalist Approach to Data Regulation

i. The Promise of Publicly Accessible Global Databases

According to the FDA, it “currently houses the largest known repository of clinical data.”¹⁵⁴ In 2008, the FDA launched the Sentinel Initiative, a national electronic system for monitoring safety problems with drugs, vaccines, biologics, and medical devices, relying on data from electronic health records, insurance claims, and other sources.¹⁵⁵ As the FDA noted in a 2011 paper entitled “Driving Biomedical Innovation: Initiatives to Improve Products for Patients,” “the ability to share information in a public forum about why products fail, without compromising proprietary information, presents the potential to save

153. Press Release, Ctrs. for Medicare & Medicaid Servs., CMS Finalizes Coverage of Next Generation Sequencing Tests, Ensuring Enhanced Access for Cancer Patients (Mar. 16, 2018), <https://www.cms.gov/newsroom/press-releases/cms-finalizes-coverage-next-generation-sequencing-tests-ensuring-enhanced-access-cancer-patients>.

154. U.S. FOOD & DRUG ADMIN., DRIVING BIOMEDICAL INNOVATION: INITIATIVES TO IMPROVE PRODUCTS FOR PATIENTS 22 (2011) [hereinafter FDA, DRIVING BIOMEDICAL INNOVATION].

155. See FDA’s *Sentinel Initiative*, FDA, <https://www.fda.gov/safety/fdassentinelinitiative/ucm2007250.htm> (last updated Jan. 9, 2019). The Sentinel Initiative was created by the Food and Drug Administration Amendments Act of 2007. *Id.*

companies millions of dollars by preventing duplication of failure.”¹⁵⁶ More ambitiously, the FDA articulated one of its strategic priorities: “[T]o develop a global data information system and network in which regulators worldwide can regularly and proactively share real-time information and resources across markets.”¹⁵⁷

Toward this end, the FDA has taken steps to increase public access to its compliance and enforcement data.¹⁵⁸ In February 2015, the FDA released a paper entitled “Plan to Increase Access to Results of FDA-Funded Scientific Research.”¹⁵⁹

ii. Genetic Testing Initiatives

In 2016, the FDA launched precisionFDA, which is an online database that seeks to gather information from various sources about Next Generation Sequencing (NGS) to enable interested parties to “access and share datasets, analysis pipelines, and bioinformatics tools, in order to benchmark their approaches and advance regulatory science.”¹⁶⁰

On April 13, 2018, the FDA released a final guidance entitled “Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based *In Vitro* Diagnostics.”¹⁶¹ The guidance document describes “how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships in FDA’s regulatory review of both NGS-based tests and genetic and genomic tests based on other technologies.”¹⁶² Further, the gui-

156. See FDA, DRIVING BIOMEDICAL INNOVATION, *supra* note 154, at 22.

157. Dara Katcher Levy, *Pathway to Global Product Safety and Quality—FDA’s Report Regarding Improving the Quality of Imports*, FDA L. BLOG (June 23, 2011), <http://www.fdalawblog.net/2011/06/pathway-to-global-product-safety-and-quality-fdas-report-regarding-improving-the-quality-of-imports/>.

158. See generally U.S. FOOD & DRUG ADMIN., FOOD AND DRUG ADMINISTRATION TRANSPARENCY INITIATIVE: INCREASING PUBLIC ACCESS TO FDA’S COMPLIANCE AND ENFORCEMENT DATA (2014), <https://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM394213.pdf> [<http://wayback.archive-it.org/7993/20171103063123/https://www.fda.gov/downloads/AboutFDA/Transparency/TransparencyInitiative/UCM394213.pdf>].

159. U.S. FOOD & DRUG ADMIN., PLAN TO INCREASE ACCESS TO RESULTS OF FDA-FUNDED SCIENTIFIC RESEARCH (2015), <https://www.fda.gov/downloads/scienceresearch/aboutscienceresearchatfda/ucm435418.pdf>.

160. *About precisionFDA*, PRECISIONFDA, <https://precision.fda.gov/about/what> (last visited Jan. 31, 2019).

161. U.S. FOOD & DRUG ADMIN., FDA-2016-D-1233, USE OF PUBLIC HUMAN GENETIC VARIANT DATABASES TO SUPPORT CLINICAL VALIDITY FOR GENETIC AND GENOMIC-BASED *IN VITRO* DIAGNOSTICS: GUIDANCE FOR STAKEHOLDERS AND FOOD AND DRUG ADMINISTRATION STAFF (2018), <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm509837.pdf>.

162. *Id.* at 4.

dance notes that “[p]ublicly accessible genetic databases may be useful to support the clinical validity of NGS tests as well as single gene or panel tests that use other technology.”¹⁶³

The guidance notes that “[i]n relying on assertions in genetic variant databases that follow the recommendations in this guidance, [the] FDA hopes to encourage the deposition of genetic variant information in such publicly accessible databases, reduce regulatory burden on test developers, and spur advancements in the evaluation and implementation of precision medicine.”¹⁶⁴

The FDA can leverage its regulatory authority to coordinate both the production and dissemination and use of genomic information. Existing law does not provide any regulatory data exclusively for FDA-approved diagnostic tests—or for medical devices more generally. In this way, the policy environment differs sharply from that governing pharmaceutical drug trial data disclosure.¹⁶⁵ In the absence of Congressional action, the FDA should consider stepping in to provide incentives to DTC genetic test companies like those contained in the Hatch-Waxman Act.¹⁶⁶ Scholars have proposed mandatory disclosure of proprietary information coupled with FDA-administered data and market exclusivities like those that are available for innovative drugs.¹⁶⁷ Alternatively,

Licensing requirements for diagnostic tests could be set to drive information production, and the agency could coordinate a sharing regime through structured, staged disclosure of proprietary genomic data. For instance, approval of diagnostic genetic tests might be conditioned on deposit of newly discovered variants into a centralized public database, with manufacturers permitted to keep undisclosed proprietary algorithms and aggregate data sets.¹⁶⁸

163. *Id.*

164. *Id.* at 5 (emphasis added).

165. Specifically, there is no Hatch-Waxman Act-like coverage for data underlying diagnostic tests. For an overview of the impetus behind the Act, the authority it grants the FDA, and the consequences of that authority, see, for example, Eisenberg, *The Role of the FDA in Innovation Policy*, *supra* note 107, at 356–59. For a further elaboration of how the Act might apply in genetic testing space, see Laakmann, *supra* note 108, at 1036–37.

166. Laakmann, *supra* note 108, at 1036 (“Existing regulations governing medical product information provide a template for the FDA to coordinate the generation and use of genomic data.”).

167. See, e.g., Rebecca S. Eisenberg, *Data Secrecy in the Age of Regulatory Exclusivity*, in *THE LAW AND THEORY OF TRADE SECRECY: A HANDBOOK OF CONTEMPORARY RESEARCH* 467, 472–73 (Rochelle C. Dreyfuss & Katherine J. Strandburg eds., 2011); Rai, *supra* note 113, at 1666.

168. Laakmann, *supra* note 108, at 1038.

iii. Innovation Incubator to Harness the Power of “Big Data”

Housed within the FDA’s Oncology Center of Excellence, Information Exchange and Data Transformation (INFORMED) “is a decentralized science and technology incubator designed to harness the power of big data and advanced analytics to improve disease outcomes.”¹⁶⁹ It seeks (1) to standardize and aggregate data that comes from a variety of sources (including, for example, clinical trial data submitted to the FDA)¹⁷⁰; (2) to “develop[], deploy[], and disseminat[e] novel technologies and best practices for big data[;]”¹⁷¹ and (3) to “serv[e] as an incubator focused on driving innovations in agile technology development and advanced analytics,” while “plac[ing] special emphasis on data sharing and the creation of new data assets.”¹⁷² As such, it appears to be a mini information and innovation engine housed within the FDA.

“The objective is to make data analytics an integral part of regulatory decision-making, supported by novel public-private collaborations to engage industry, academia, patients and other FDA stakeholders in a common assault against the silos that limit big data’s potential in fighting disease, particularly for biologically complex conditions like cancer.”¹⁷³ The “emerging active engagement of FDA on digital and data science is . . . critical to the future growth of biopharma, which in many ways is now an information business.”¹⁷⁴ “[B]ig data sets now rule the day at FDA—and will set the agenda for tomorrow.”¹⁷⁵

CONCLUSION

The FDA plays one small but significant part in the wider effort to gather and disseminate data in the health sector. Its emergent hybrid regulatory model for DTC genetic testing has potential implications for ensuring the creation of underlying evidence and substantiation of

169. Sean Khozin, Richard Pazdur, & Anand Shah, *INFORMED: An Incubator at the US FDA for Driving Innovation in Data Science and Agile Technology*, 17 *NATURE REV. DRUG DISCOVERY* 529, 529 (2018).

170. Genetic data would be included as well. *See id.* (“In addition, biomedical sciences in general are largely siloed into specific disciplines rather than multidisciplinary units that can support understanding of disease and the patient’s experience based on the totality of intrinsic (for example, ‘omics’ data) and extrinsic (for example, environmental) variables influencing clinical outcomes.”) (emphasis added).

171. *Id.* at 530.

172. *Id.*

173. William Looney, *Big Data and the FDA: To Mine the Value, First Mind the Gaps*, 36 *IN VIVO*, May 2018, at 24, 24.

174. *Id.*

175. *Id.* at 25.

“big data” medical claims. The FDA has traditionally regulated medical products such as drugs and medical devices as well as the accompanying labeling. With respect to DTC genetic testing, the FDA recognizes the significance of the fact that the product being sold is “medical information” and thus should be subject to regulation on health and safety grounds. But the FDA has also traditionally served an information production function, although it is not as readily appreciated as its safety function. Regulation is needed to ensure accuracy of test results as well as sufficient production of underlying scientific research. In the era of “big data,” the FDA is poised to play an enhanced role as health information regulator. The FDA can leverage its regulatory authority to coordinate the production, dissemination, and use of genomic information.