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Consuming Genomics: Regulating Direct-to-Consumer Genetic and Genomic Information

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TABLE OF CONTENTS

I. Introduction	678
II. Access to One's Own Genetic Information.....	684
A. The Human Genome	684
B. Origins and Evolution of Genetic Testing	686
1. From Discrete Genetic Tests to Large-Scale Testing and Genomic Sequencing	687
2. From Clinician-Provided Testing to Direct-to- Consumer Access	689
C. Concerns Raised by Direct-to-Consumer Genetic Testing	690
1. Investigation by the Government Accountability Office in 2006	692
2. Reports of the Secretary's Advisory Committee on Genetics, Health, and Society	693
3. Investigation by the Government Accountability Office in 2010	696
III. Regulating Direct-to-Consumer Genetic Testing.....	697
A. Food and Drug Administration: Regulation of Medical Devices and Engagement with the Direct- to-Consumer Genetic-Testing Industry	698

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1.	Food and Drug Administration's Regulation of Medical Devices	699
2.	Exemptions for Genetic Tests Under In Vitro Diagnostic Device Regulations	702
3.	FDA Sends Notification Letters to Direct-to-Consumer Genetic-Testing Companies.....	704
a.	Food and Drug Administration Untitled Letters	705
b.	Food and Drug Administration Warning Letter to 23andMe	710
c.	What the Food and Drug Administration Letters Mean for the Industry.....	713
B.	Federal Trade Commission: Regulation of Advertising and Engagement with the Direct-to-Consumer Genetic-Testing Industry.....	717
C.	Centers for Medicare and Medicaid Services and the Clinical Laboratory Improvement Amendments	719
D.	Patent and Trademark Office and the <i>Association for Molecular Pathology v. Myriad Genetics, Inc.</i> ...	722
E.	State Law's Regulation of Direct-to-Consumer Genetic Testing	726
IV.	Regulating Bifurcated Direct-to-Consumer Genetic-Testing Entities.....	728
A.	The Bifurcation of Direct-to-Consumer Genetic-Testing Entities	728
B.	Regulating Entities Producing Genetic Data	730
C.	The Challenges of Regulating Entities That Provide Genetic Information	731
1.	Regulating DTC Web-Based Genetic Interpretation Services: In Search of an Analogy	732
a.	WebMD's Symptom Checker	732
b.	Mobile Medical Devices	734
c.	Software Applications	735
2.	First Amendment Challenges to Regulation	735
V.	Risk-Based Regulation of Entities That Interpret Genetic Information.....	742
VI.	Conclusions and Implications.....	743

I. INTRODUCTION

In 2007, two direct-to-consumer (DTC) genetic-testing companies began offering consumers an interpretation of 0.03% of their genome

for \$1000.¹ In the years since, the popularity of, and scientific know-how behind, genetic testing has exploded.² The healthcare industry has spent an estimated \$5 billion on genetic testing to date, with \$20 billion more expected by 2021.³ President Barack Obama's Presidential Commission for the Study of Bioethical Issues recently released one report focusing on privacy and progress in whole genome (genomic) sequencing⁴ and another considering the ethical issues facing the direct-to-consumer industry;⁵ coverage about the influence of genetic testing on celebrity medical decisions has reverberated throughout the lay media;⁶ the recent Supreme Court decision of *Association for Molecular Pathology v. Myriad Genetics* established the nonpatentability of genetic material;⁷ and a U.S. Food and Drug Administration (FDA) warning sent to 23andMe on November 22, 2013,⁸ and the company's

1. See, e.g., Sancy A. Leachman et al., *Direct-to-Consumer Genetic Testing: Personalized Medicine in Evolution*, AM. SOC'Y CLINICAL ONCOLOGY, 2011, at 34, 35.
2. Timothy Leslie et al., *Market Trends in Genetic Services: Impacting Clinical Care for Better Prediction, Detection, and Care Selection*, BOOZALLEN.COM, http://www.boozallen.com/media/file/GeneticTesting_VP.pdf (last visited Oct. 14, 2013) (noting that the more than 1600 genetic tests available in 2008 nearly doubled by 2012).
3. *New Report Finds Greater Use of Genetic Testing, but Half of Physicians Concerned About Their Lack of Familiarity with Genetic Tests*, UNITEDHEALTH GROUP (Mar. 12, 2012), <http://www.unitedhealthgroup.com/Newsroom/Articles/News/UnitedHealth%20Group/2012/0312GeneticTesting.aspx>.
4. See generally PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, PRIVACY AND PROGRESS IN WHOLE GENOME SEQUENCING (2012), available at http://bioethics.gov/sites/default/files/PrivacyProgress508_1.pdf [hereinafter PRIVACY AND PROGRESS].
5. See generally PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES, ANTICIPATE AND COMMUNICATE: ETHICAL MANAGEMENT OF INCIDENTAL AND SECONDARY FINDINGS IN THE CLINICAL, RESEARCH, AND DIRECT-TO-CONSUMER CONTEXTS (2013), available at http://bioethics.gov/sites/default/files/FINALAnticipateCommunicate_PCSBI_0.pdf [hereinafter ANTICIPATE AND COMMUNICATE].
6. See, e.g., Angelina Jolie, Op-Ed, *My Medical Choice*, N.Y. TIMES, May 14, 2013, at A25; Ed Payne, *Angelina Jolie Undergoes Double Mastectomy*, CNN ENT. (May 16, 2013, 8:09 AM), <http://www.cnn.com/2013/05/14/showbiz/angelina-jolie-double-mastectomy>; Maria Puente et al., *Angelina Jolie's Mastectomy News Shocks, Enlightens*, USA TODAY (May 14, 2013, 10:23 PM), <http://www.usatoday.com/story/life/people/2013/05/14/angelina-jolie-double-mastectomy-shocks-impresses-enlightens-the-world/2158489/>; Scott Hensley, *Angelina Jolie's Mastectomy Decision and Weighing Cancer Risks*, NPR (May 5, 2013, 10:29 AM), <http://www.npr.org/blogs/health/2013/05/15/184166941/angelina-jolies-mastectomy-decision-and-weighing-cancer-risks>.
7. 133 S. Ct. 2017 (2013).
8. See Letter from Alberto Gutierrez, Dir., Office of In Vitro Diagnostics and Radiological Health, Ctr. for Devices & Radiological Health, Food & Drug Admin., U.S. Dep't of Health & Human Services, to Ann[e] Wojcicki, C.E.O., 23andMe, Inc. (Nov. 22, 2013), available at <http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm376296.htm> [hereinafter Warning Letter to Wojcicki].

subsequent hiatus from the health-related information market,⁹ have critically shaped scholarly debate about the science and ethics of, and reinforced the public's interest in access to, health-related genetic information.¹⁰ Despite this increasing visibility, DTC genetic testing has met with controversy and complications throughout its short history.

The medical testing of human genetic material began with discrete genetic tests that looked at a single gene to obtain an answer to a targeted question about a potentially devastating medical condition—such as whether a person was at a high risk to develop Huntington's disease.¹¹ It has since transitioned to large-scale genetic testing or genomic sequencing, returning information about many or all of a person's genes, including those for which the function and significance is still unclear.¹² During this time, both targeted and large-scale testing moved from being within the exclusive province of the clinic—where healthcare professionals were the gatekeepers of this information—to DTC entities that provide genetic data and interpreted information directly to consumers without a clinician intermediary.

Over the past several years, the DTC genetic-testing industry has been the subject of a number of government investigations, including one in 2006 by the U.S. Government Accountability Office (GAO); two reports by the Secretary's Advisory Committee on Genetics, Health, and Society in 2008 and 2010; and a subsequent GAO investigation in 2010. These reports raised serious concerns about the validity and utility of the genetic testing performed by the companies and the medical information that DTC companies were producing and selling to consumers.

Despite these investigations, the DTC genetic-testing industry flourished until 2010, when Pathway Genomics announced that it was going to partner with Walgreens and sell its DTC genetic tests in drug stores across the country.¹³ This garnered the attention of FDA,

9. *23andMe, Inc. Provides Update on FDA Regulatory Review*, 23ANDME (Dec. 5, 2013), <http://mediacenter.23andme.com/press-releases/23andme-inc-provides-update-on-fda-regulatory-review/> [hereinafter *23andMe, Inc. Provides Update*].

10. See, e.g., Adam Liptak, *Justices, 9–0, Bar Patenting Human Genes*, N.Y. TIMES, June 14, 2013, at A1.

11. See *infra* subsection II.B.1.

12. This Article uses the term “genomic testing” to mean large-scale or whole genome testing (i.e., testing most if not all of a person's nuclear DNA). The term “genetic testing” can also include whole genome analysis as well as looking at only one or several discrete genes. Therefore, while all genomic testing is also appropriately described as genetic testing, not all genetic testing includes the analysis of enough genes to be considered genomic testing.

13. See, e.g., Andrew Pollack, *Walgreens Delays Selling Personal Genetic Test Kit*, N.Y. TIMES, May 12, 2010, at B5 [hereinafter Pollack—*Walgreens Delays*]; *Statement Before the H. Subcomm. on Oversight & Investigation of the H. Comm. on Energy & Commerce*, 111th Cong. 11 (2010) (statement of Jeffrey Shuren, M.D.,

which responded by sending twenty-three letters warning companies of potential Food, Drug, and Cosmetic Act violations and stating that DTC genetic tests were medical devices that needed to be cleared or approved by FDA.¹⁴ Soon thereafter, many DTC genetic-testing companies either altered their models by requiring a physician order or intermediary or collapsed entirely. 23andMe also began to work with FDA on clearance filings in 2012,¹⁵ but in 2013 FDA halted 23andMe's health-related offerings indefinitely.¹⁶

Even before 23andMe stopped marketing its health-related product, however, some DTC companies began to bifurcate into entities that offer *genetic data*—a file of As, Ts, Cs, and Gs without any interpretation—and entities that interpret and analyze this genetic data to provide *medical information*—for example the consumer's risk of developing breast cancer.¹⁷

While these bifurcated companies might still be unfamiliar to the public, their influence has played a role, for example, in the well-known case of Henrietta Lacks. The 2010 book *The Immortal Life of Henrietta Lacks* tells the story of a woman who went to the Johns Hopkins Hospital in 1951 for clinical care for her cervical cancer. Unbeknownst to Mrs. Lacks, her clinicians retained specimens of her cancerous tissue for research purposes.¹⁸ The unique and invaluable replicating propensities of her cancer cells enabled the creation of the

Dir., Ctr. for Devices & Radiological Health, Food & Drug Admin., U.S. Dep't of Health & Human Services), available at <http://www.fda.gov/NewsEvents/Testimony/ucm219925.htm> [hereinafter Shuren—Statement].

14. See, e.g., Letter from James Woods, Deputy Dir., Ctr. for Devices and Radiological Health, FDA, to James Plante, Founder and CEO, Pathway Genomics Corp. (May 10, 2010), available at <http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm211866.htm> [hereinafter Letter to Plante].
15. *23andMe Takes First Step Toward FDA Clearance*, 23ANDME BLOG (July 30, 2012), <http://blog.23andme.com/news/23andme-takes-first-step-toward-fda-clearance/>. The 510(k) *de novo* review process is for products that do not rise to the level of Class III regulation. See FDA—DE NOVO CLASSIFICATION, *infra* note 145, at 5 (“If we grant the *de novo* petition, the device is reclassified from class III into class I or class II.”).
16. Warning Letter to Wojcicki, *supra* note 8. Current genetic-testing options, even those that are quasi-DTC, are limited and include Genetic Testing Laboratories (which requires that the DNA sample be taken by “your physician”) and Pathway Genomics (which requires a physician order). See *DNA Predisposition Testing*, GENETIC TESTING LABORATORIES INC., <http://www.gtldna.com/HealthTesting/DNA-Predisposition-Testing.htm> (last visited Jan. 1, 2014); *General Questions*, PATHWAY GENOMICS, <https://www.pathway.com/about-us/faqs> (last visited Jan. 1, 2014).
17. See, e.g., Dan Vorhaus, *DNA DTC: The Return of Direct to Consumer Whole Genome Sequencing*, GENOMICS LAW REP. (Nov. 29, 2012), <http://www.genomicslawreport.com/index.php/2012/11/29/dna-dtc-the-return-of-direct-to-consumer-whole-genome-sequencing/> [hereinafter Vorhaus—DNA DTC].
18. See generally REBECCA SKLOOT, *THE IMMORTAL LIFE OF HENRIETTA LACKS* (Broadway Books 2011) (2010) [hereinafter SKLOOT—THE IMMORTAL LIFE].

first human cell line, and this “HeLa” line was subsequently distributed across the world, enabling countless research protocols and rendering Mrs. Lacks “the godmother of virology and then biotech, benefiting practically anyone who’s ever taken a pill stronger than aspirin.”¹⁹ The HeLa cells did not, however, benefit Mrs. Lacks’s own family any more than any other. The Lacks family did not even know Mrs. Lacks’s cells had been taken in the first place. While this part of the Henrietta Lacks story has become popularized, in 2013 researchers at the European Molecular Biology Laboratory sequenced the HeLa cells and publically posted the genomic sequence of Mrs. Lacks’s cancer cells without consent from the Lacks family. This raw data file of As, Ts, Cs, and Gs did not convey medical information in and of itself; the European Molecular Biology Laboratory stated in a news release that “We cannot infer anything about Henrietta Lacks’s genome, or of her descendants, from the data generated in this study.”²⁰ However, the emergence of new DTC web-based genetic interpretation entities transforms the value of raw genomic data—other scientists were immediately able to upload Mrs. Lacks’s genomic data into *openSNP*, a service that interpreted the data and provided access to her medical information.²¹

With 23andMe’s health-related product currently off the market, bifurcated genetic entities are not only the next frontier, but the only currently viable option for DTC access to genetic health-related information. This Article is one of the first to analyze the effect of the 23andMe Warning Letter on the industry, to focus on the bifurcation of genetic interpretation and information as an independent medical device, and to analyze future regulatory approaches available to FDA. Part II of this Article offers an overview of public access to genetic information: the significance of genetic information, the transition from discrete genetic testing to large-scale genetic testing and genomic sequencing, and the movement of genetic interpretation from the clinic to DTC. This Part will also discuss government scrutiny of the DTC genetic-testing industry.

Part III of this Article will conduct a deeper examination of the agencies poised to regulate DTC genetic testing. This Part analyzes FDA’s Untitled and Warning Letters and highlights four major insights for the industry going forward. But, although FDA is best-positioned to regulate the industry, it is not the only agency with the power to engage. Several other federal agencies—such as the U.S. Federal Trade Commission (FTC) and the U.S. Centers for Medicare and Medicaid Services (CMS)—can also influence access to, and the

19. See Lisa Margonelli, *Eternal Life*, N.Y. TIMES, Feb. 7, 2010, at 20.

20. Rebecca Skloot, *The Immortal Life of Henrietta Lacks, The Sequel*, N.Y. TIMES, Mar. 23, 2013, at SR4.

21. *Id.*

validity and utility of, DTC genetic testing. Finally, the Supreme Court's recent decision in *Myriad*, invalidating patents on human genetic material, eliminates a potential barrier to DTC genetic testing and suggests a way in which the U.S. Patent and Trademark Office (PTO) can help ensure continued access to certain types of genetic interpretation. Part III will clarify the ways these agencies can support access to valid and useful genetic information and will highlight their limitations in this rapidly evolving field. State law provides an additional layer enhancing federal protections.

Part IV considers the particular challenges associated with regulating bifurcated genetic data and interpretation entities. Entities that merely provide genetic data are likely to remain unregulated both because they do not satisfy FDA's definition of a medical device and because FDA officials have explicitly disclaimed interest in their regulation. Entities that *interpret* genetic data and provide associated medical information, even without access to the underlying biological sample, give rise to a different analysis. Here, comparisons to FDA regulatory approaches taken with WebMD and mobile medical devices will likely fall short, whereas the approach taken with regulating software might be helpful—but even then, regulation of DTC interpretation services will face serious First Amendment scrutiny.

Part V offers a risk-based stratification approach to regulate large-scale genetic and genomic information as a medical device—treating interpretation of large-scale genetic data and genomic sequences as a compilation of smaller products as opposed to a single device. This would allow FDA to continue its regulatory focus on genetic interpretation that carries the greatest possible risk to the consumer (such as analyzing genes associated with diagnosing a predisposition to breast cancer for which individuals could seek out risky medical interventions such as mastectomy) without allocating time and energy to genetic interpretation that carries little to no risk (such as analyzing genes associated with earwax type).

FDA has made clear that it will treat DTC genetic tests, including individual components used to produce patient-specific information, as medical devices falling under its regulations—and that labeling these devices as for educational or research use only while marketing them for health-related indications or knowingly selling them to companies will not shield the manufacturer from enforcement. Also, although FDA might consider some genetic tests as falling into lower-risk regulatory categories, a manufacturer's decision not to validate or substantiate individual tests might result in an entire genetic or genomic interpretation device being classified in a higher-risk regulatory category, thereby requiring full FDA premarket approval. However, as companies continue to bifurcate into entities that produce data- or information-only products, including entities that provide Internet-

based, open-source genetic and genomic interpretation, FDA will face increasing difficulty enforcing its medical device regulations as typically done. If FDA and the DTC industry approach large-scale genetic and genomic interpretation as a compilation of discrete genetic tests, they can address the riskiest aspects of the product without allowing the evolving field to overwhelm current quality assurances and without limiting consumer access to accurate and valid genetic information.

II. ACCESS TO ONE'S OWN GENETIC INFORMATION

From time immemorial, humans have asked existential questions about the nature of identity and the origins of disease. The discovery of DNA as heritable genetic material brought with it the potential to delve deeper into these compelling issues. In 1990, a scientific collective sought to unlock some of these answers by sequencing the entire human genome.²² In the years since, knowledge about the human genome has expanded exponentially, as has the ability to interrogate genetic information using discrete genetic tests, large-scale genetic testing, and genomic sequencing.²³ Although once within the exclusive province of medical professionals, genetic testing has increasingly been offered directly to consumers in the absence of any clinician involvement.²⁴ This Part explains the importance of the human genome and describes the evolution of the DTC genetic-testing industry. It also describes government concerns regarding medical information sold DTC.

A. The Human Genome

Deoxyribonucleic acid (DNA) is one of the fundamental building blocks of life.²⁵ Found in nearly every living organism, DNA is made up of four nucleotide bases—adenine (A), thymine (T), cytosine (C), and guanine (G). These nucleotide bases form consistent pairs between the two strands of DNA, forming a sequence that provides instructions for biological functioning.²⁶

In humans, the genomic sequence is approximately three billion nucleotide base pairs long²⁷ and is stored in the nucleus of an individ-

22. *See infra* section II.A.

23. *See infra* section II.B.

24. *See infra* subsection II.B.2.

25. DNA was first identified and isolated by Friedrich Miescher, and the discovery of the double helix is attributed to James Watson, Francis Crick, and Rosalind Franklin. *See, e.g., Ralf Dahm, Friedrich Miescher and the Discovery of DNA*, 278 *DEVELOPMENTAL BIOLOGY* 274, 284 (2005) (displaying a timeline that shows contributions to the discovery of DNA by different individuals).

26. *See, e.g., PRIVACY AND PROGRESS, supra* note 4, at 109.

27. *See, e.g., id.* at 110.

ual's cells in tightly wound super-coils called chromosomes.²⁸ A complete sequence of an individual's nuclear DNA is called an individual's genome.²⁹ All human beings share approximately 99.9% of genetic information.³⁰ The small percentage of genetic variation among individuals, however, gives rise to humanity's wide-ranging diversity and individual biological characteristics.³¹

Sequencing—learning the order of As, Ts, Cs, and Gs— the human genome uncovers any variants encoded in an individual's DNA.³² Genetic variants can take many forms, including changes involving only a single nucleotide base pair, generally referred to as a single nucleotide polymorphism (SNP).³³ Alternatively, variants can be much larger and can involve inserting, deleting, duplicating, translocating, or inverting longer stretches of DNA.³⁴

Genetic variants can have a wide range of meanings and significance for an individual. Some variants signal susceptibility to future disease, including predispositions to breast cancer or diabetes.³⁵ Some variants signal onset of genetic conditions likely to occur later in life, such as Huntington's disease.³⁶ A third category of variants indicates "carrier status"—someone who might pass along a potentially disease-causing variant to offspring but who is unlikely themselves to be affected by the disease.³⁷ Variants might also code for nonmedical physical traits such as eye color.³⁸ Finally, DNA sequencing can uncover variants of unknown significance, the importance of which we do not yet understand.³⁹

Most genetic variants currently fall into this last category of unknown significance. As technologies for sequencing genetic material increasingly allow for rapid sequencing of large amounts of DNA, our technological capacity for discovering variants outpaces scientific understanding regarding their consequences for individuals. Scientific researchers, however, continue to explore the connections between ge-

28. *See, e.g., id.* at 109.

29. *See, e.g., id.* at 110.

30. *See, e.g., id.* at 113.

31. *See, e.g., id.*

32. *See, e.g., id.* at 112. This also includes sequencing the subset of the protein-coding regions of the genome called exons that contain an estimated 85% of known disease-causing mutations, a process known as whole exome sequencing. *See, e.g., id.* at 116–17.

33. *See, e.g., id.* at 113–14.

34. *See, e.g., id.* at 114.

35. *See, e.g., Greer Donley, Sara Chandros Hull & Benjamin E. Berkman, Prenatal Whole Genome Sequencing: Just Because We Can, Should We?, 42 HASTINGS CENTER REPORT 28, 32 (2012).*

36. *See, e.g., id.*

37. *See, e.g., id.*

38. *See, e.g., id.* at 31.

39. *See, e.g., id.*

netic variants and their corresponding physical manifestations,⁴⁰ and new associations are continuously published in the literature.

B. Origins and Evolution of Genetic Testing

At the start of the Human Genome Project in 1990,⁴¹ genetic tests were available for only 100 specific disease-causing genes,⁴² and these tests were generally only accessible by individuals through their clinician.⁴³ Since the completion of the Human Genome Project, the number of tests available has grown exponentially and the means by which the public accesses these tests has evolved. In 2007 (the advent of DTC genetic testing), there were genetic tests for more than 1100 disease-causing variants (some with more supporting data than others);⁴⁴ by 2009, there were 1900;⁴⁵ and as of April 2012, there were discrete genetic tests existing for more than 2600 disease-causing variants.⁴⁶ These 2600 known variants, however, still represent but a small fraction of variants possible in the genome's three billion nucleotide base pairs.⁴⁷

40. See, e.g., PRIVACY AND PROGRESS, *supra* note 4, at 117.

41. The Human Genome Project, which began in 1990 and was coordinated by the U.S. Department of Energy and the National Institutes of Health (NIH), was founded to:

identify all the . . . genes in human DNA, *determine* the sequences of the 3 billion chemical base pairs that make up human DNA, *store* this information in databases, *improve* tools for data analysis, *transfer* related technologies to the private sector, and *address* the ethical, legal, and social issues (ELSI) that may arise from the project.

Human Genome Project, HUMAN GENOME PROJECT INFORMATION, http://web.ornl.gov/sci/techresources/Human_Genome/home.shtml (last visited Oct. 15, 2013). The project states that it achieved “catalyz[ing] the multibillion-dollar U.S. biotechnology industry” and fostered the development of new medical applications. It ended in 2003, but analysis of the data it produced continues. See *id.*

42. See 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); Vicki Brower, *FDA to Regulate Direct-to-Consumer Genetic Tests*, 102 *J. NAT'L CANCER INST.* 1610, 1610 (2010); Felix F. Frueh, et al., *The Future of Direct-to-Consumer Clinical Genetic Tests*, 12 *NATURE REVIEW GENETICS* 511, 513–14 (2011); Arthur L. Beaudet & Gail Javitt, *Which Way For Genetic-Test Regulation?*, 466 *NATURE* 816, 816 (2010).

43. See *infra* subsection II.B.2.

44. See, e.g., Kathy Hudson et al., *ASHG Statement on Direct-to-Consumer Genetic Testing in the United States*, 110 *OBSTETRICS & GYNECOLOGY* 1392, 1392 (2007).

45. See, e.g., Beaudet & Javitt, *supra* note 42, at 816.

46. See, e.g., Palmer, *supra* note 42, at 480.

47. See, e.g., Catherine Gliwa & Benjamin E. Berkman, *Do Researchers Have an Obligation to Actively Look for Genetic Incidental Findings?*, 13 *AM. J. BIOETHICS* 32, 36 (2013) (“Genomic science is still in its infancy, and the amount we know about the relationship between genomic data and human disease is dwarfed by the amount we do not yet know.”).

1. *From Discrete Genetic Tests to Large-Scale Testing and Genomic Sequencing*

Early genetic tests were only capable of identifying mutations within a single gene, such as those associated with Tay-Sachs disease and cystic fibrosis.⁴⁸ They were also only able to recognize genes with high “penetrance”—in which the presence of a mutation gives rise to an extremely high lifetime risk of contracting a disease, such as Huntington’s.⁴⁹ Most currently identified variants, however, are significantly less strongly associated with diseases such that some people with the variant will never develop the associated disease (and those who do develop the disease might experience a range of severity).⁵⁰

Genetic tests are also increasingly helpful in identifying complex, polygenic diseases associated with complicated environmental and gene-gene interactions.⁵¹ Nineteen percent of laboratories responding to a 2013 College of American Pathologists survey stated they were already conducting “next-generation sequencing” (or large-scale sequencing) with more than half of the laboratories stating they planned to begin using this type of testing within the next three years.⁵² Determination of genetic susceptibility to polygenic disease (having many different genetic and environmental causes), however, is more complex.⁵³

Several important and unique attributes further distinguish large-scale genetic testing and genomic sequencing from discrete genetic testing. First, because some large-scale testing and sequencing involves a large portion of an individual’s nuclear DNA, the resulting data are uniquely identifiable to one person. Even if all other identifying information is stripped from the data—preventing them from being “readily identifiable” to the user—the data are still unique to one individual.⁵⁴ In addition, marketers of discrete genetic tests advertise

48. *See, e.g.*, Brower, *supra* note 42, at 1610.

49. *See, e.g.*, Palmer, *supra* note 42, at 479.

50. *See, e.g., id.*

51. Stephanie Bair, *Direct-to-Consumer Genetic Testing: Learning from the Past and Looking Toward the Future*, 67 *FOOD & DRUG L.J.* 413, 416 (2012) (citing MICHAEL WINK, *AN INTRODUCTION TO MOLECULAR BIOTECHNOLOGY* 456 (2006)).

52. Celia Henry Arnaud, *Next Generation DNA Sequencing Finds Use As a Diagnostic*, *CHEMICAL & ENGINEERING NEWS* (July 15, 2013), <http://cen.acs.org/articles/91/i28/Next-Generation-DNA-Sequencing-Finds.html?h=-817242108>.

53. *See, e.g.*, Bair, *supra* note 51, at 416.

54. *See, e.g.*, PRIVACY AND PROGRESS, *supra* note 4, at 83. As preventive measures for keeping genomic data anonymous continue to crumble, it is important for consumers to keep in mind that their genomic sequence, stripped of traditional identifiers and available online, could possibly still be linked back to them, exposing the consumer to increased privacy risk. *See, e.g.*, Melissa Gymrek et al., *Identifying Personal Genomes by Surname Inference*, 339 *SCIENCE* 321, 321–24 (2013) (finding that surnames can be recovered from de-identified personal genomes

them as being able to provide an answer to a specific question.⁵⁵ Large-scale genetic testing and genomic sequencing, by contrast, produce substantially more data, and the medical significance of the majority of them is far more speculative if known at all.⁵⁶

As genetic testing moves from discovering diseases and conditions associated with variations within a single gene toward large-scale genetic testing and genomic sequencing, researchers have also raised serious concerns regarding whether and to what extent determinations about genetic susceptibilities to complex, polygenic diseases are actually at all predictive. One 2008 study found that “variants so far identified by [genome-wide association studies] together explain only a small fraction of the overall inherited risk of each disease”; for example, genetic susceptibility currently explains only five percent of the inherited risk of Type 2 diabetes.⁵⁷ Another study found that of the eighteen genetic variants linked to Type 2 diabetes, none gave a better risk estimate than one simply based on an individual’s body mass index, age, and sex.⁵⁸ It also found that the two most closely associated genetic variants were worse at predicting cholesterol drug response than knowing an individual’s age and sex.⁵⁹ This type of empirical analysis led one researcher recently to conclude that “currently known variants explain too little about the risk of disease occurrence to be of clinically useful predictive value.”⁶⁰

This transition from genetic testing to large-scale testing and genomic sequencing is not just a difference in degree—it is a difference in kind. And this more expansive testing might eventually cost little more than doing discrete tests for single genes. Accordingly, we are moving into an era in which large-scale genetic testing is increasingly likely to be the process through which researchers, clinicians, and DTC companies investigate genetic material.⁶¹

available on free, publicly accessible Internet sites by profiling short tandem repeats from recreational genetic genealogy databases).

55. See, e.g., *Does Breast or Ovarian Cancer Run in Your Family?*, MYRIAD, <http://www.bracnow.com/> (last visited Oct. 29, 2013) (“[K]now your risk for hereditary breast and ovarian cancer . . . by identifying a BRCA gene mutation.”).

56. Donley, Hull & Berkman, *supra* note 35, at 32.

57. David Altshuler et al., *Genetic Mapping in Human Disease*, 322 *SCIENCE* 881, 881 (2008).

58. See Palmer, *supra* note 42, at 482 (citing Clifton Bogardus, *Missing Heritability and GWAS Utility*, 17 *OBESITY* 209, 210 (2009)).

59. See *id.*

60. Teri A. Manolio, *Genomewide Association Studies and Assessment of the Risk of Disease*, 363 *NEW ENG. J. MED.* 166, 173 (2010).

61. See Palmer, *supra* note 42.

2. *From Clinician-Provided Testing to Direct-to-Consumer Access*

When DTC companies 23andMe and deCODEme launched in 2007, genetic testing became available without the use of a clinician intermediary.⁶² In 2008, Knome (pronounced “know-me”) became the first company to offer DTC *genomic* sequencing and interpretation—for the introductory price of \$350,000 a person.⁶³ While the particulars of each DTC genetic-testing service vary, the broad contours are generally the same: DTC companies typically advertise and operate over the Internet; a consumer orders the test and receives a sample collection kit; and the consumer takes a cheek swab or saliva sample, returns it, and then awaits a report of the results by mail or online.⁶⁴ If the company provides genetic counseling, it is usually available to the consumer *after* they have purchased the service⁶⁵ for an additional fee.⁶⁶

Genetic companies offer DTC tests for educational,⁶⁷ paternity, or ancestry purposes, or merely to satisfy the curiosity of the customer.⁶⁸ Tests can predict traits as mundane as excessive earwax; carrier status for severe diseases like cystic fibrosis; the probability of developing disease in the future, such as breast cancer or Alzheimer’s disease; or the ability to metabolize certain drugs, such as Warfarin (a blood thinner).⁶⁹ In 2007, 23andMe began by offering thirteen reports on

62. See, e.g., Hudson et al., *supra* note 44, at 1392.

63. See Amy Harmon, *Gene Map Becomes a Luxury Item*, N.Y. TIMES, Mar. 4, 2008, at F1. Knome no longer offers this service. In 2010 Knome decided to move away from working with the “wealthy healthy” and changed their model to focus on Knome’s technology and technological expertise. It currently markets to medical institutions, researchers, and pharmaceutical companies. As Knome’s chief marketing officer put it: “The model changed as sequencing changed.” Malorye Allison, *Direct-to-Consumer Genomics Reinvents Itself*, 30 NATURE BIOTECHNOLOGY 1027, 1028 (2012). Illumina currently markets genomic sequencing directly to consumers; however, its test requires a physician order. It recommends that potential customers “discuss [their] interest with a physician who can lead [them] through the process, know what genetic information [they] are seeking, and consider what additional information [they] may, or may not, want to learn based on [their] genome sequence.” See *Individual Genome Sequencing (IGS) for Patients/Guardians*, ILLUMINA, http://www.illumina.com/clinical/illumina_clinical_laboratory/figs_for_patients.ilmn#3a (last visited Oct. 15, 2013).

64. See, e.g., Hudson et al., *supra* note 44, at 1393.

65. See, e.g., Bair, *supra* note 51, at 418.

66. *Understanding Your Results: How Do I Find a Medical Genetics Specialist?*, 23ANDME, <https://customer care.23andme.com/entries/21259247-How-do-I-find-a-medical-genetics-specialist-> (last visited Oct. 15, 2013).

67. See, e.g., Brower, *supra* note 42, at 1611.

68. See, e.g., Hudson et al., *supra* note 44, at 1392.

69. See, e.g., Bair, *supra* note 51, at 414–15; Amy L. McGuire et al., *Regulating Direct-to-Consumer Personal Genome Testing*, 330 SCIENCE 181, 181 (2010); Beaudet & Javitt, *supra* note 42, at 817–18.

health-related conditions or traits for \$999.⁷⁰ Through November 2013, 23andMe offered more than 250 reports, including reports on breast and cervical cancer, cystic fibrosis, Tay-Sachs Disease, and ear-wax type, for \$99.⁷¹

A few years ago, nearly thirty DTC companies offered 400 discrete genetic tests.⁷² Over the past several years, due in part to increasing state and federal regulatory scrutiny, a number of formerly DTC companies—including Navigenics, Pathway Genomics, Counsyl, and Illumina—shifted to a prescription-based model,⁷³ and 23andMe has—at least temporarily—discontinued its health-related product.⁷⁴

C. Concerns Raised by Direct-to-Consumer Genetic Testing

DTC genetic testing can offer individuals the possibility of more genetic information than has ever before been available without the involvement of a healthcare professional or “learned intermediary.”⁷⁵ Some see the benefits of granting “unfettered access to genetic information”⁷⁶ as including greater consumer autonomy and empowerment,⁷⁷ enhanced control over (or privacy of) the information

70. JOANNA MOUNTAIN, INCIDENTAL FINDINGS: A 23ANDME PERSPECTIVE, PRESENTATION TO THE PRESIDENTIAL COMMISSION FOR THE STUDY OF BIOETHICAL ISSUES 9 (Apr. 30, 2013), available at <http://bioethics.gov/sites/default/files/Meeting%2013%20Session%206%20TRANSCRIPT.pdf>; Lisa Baertlein, *Google-backed 23andMe Offers \$999 DNA Test*, USA TODAY (Nov. 20, 2007), http://usatoday30.usatoday.com/tech/webguide/internetlife/2007-11-20-23andme-launch_N.htm.

71. See *Living Well Starts with Knowing Your DNA*, 23ANDME, <https://www.23andme.com/health> (last visited Oct. 30, 2013) (this Web page has since been taken down in response to FDA’s November 22, 2013 Warning Letter to 23andMe); *What You Can Expect*, 23ANDME, <https://www.23andme.com/health/all/> (last visited Oct. 30, 2013) (this Web page has since been taken down in response to FDA’s November 22, 2013 Warning Letter to 23andMe) [hereinafter 23ANDME—Health Reports]; *Testing for Common Mutations*, 23ANDME, <https://www.23andme.com/health/risks/> (last visited Oct. 30, 2013) (this Web page has since been taken down in response to FDA’s November 22, 2013 Warning Letter to 23andMe).

72. See, e.g., Beaudet & Javitt, *supra* note 42, at 817–18.

73. See, e.g., Palmer, *supra* note 42, at 484–85.

74. See *Welcome to 23andMe*, 23ANDME, <https://www.23andme.com/ancestry-only-notice/?redirect=bsd1eHc63cDhvlgL8Wrzqwh8stpIXgZXQH0EN6hKzTo=> (last visited Dec. 22, 2013). As FDA does not regulate DTC services that provide only nonhealth information, such as ancestry services, this Article will focus on DTC companies providing medical claims only.

75. Under the “learned intermediary” rule in tort law, a manufacturer is not liable to an injured patient or consumer if a physician prescribed the use of the product or if it was used under the physician’s supervision and the manufacturer adequately warned the physician of any potential harms. Mitchell S. Berger, *A Tale of Six Implants: The Perez v. Wyeth Laboratories Norplant Case and the Applicability of the Learned Intermediary Doctrine to Direct-to-Consumer Drug Promotion*, 55 FOOD & DRUG L.J. 525, 525 (2000).

76. Brower, *supra* note 42, at 1612.

77. See, e.g., Hudson et al., *supra* note 44, at 1392.

obtained,⁷⁸ and the possibility of motivating improved health behaviors.⁷⁹ Others worry about the negative effects this access might have. Several scholars argue that DTC marketing confuses consumers because it “(1) fails to adequately explain complex genetic information; (2) is misleading in its failure to disclose the risks and limitations of testing; (3) allows tests without established clinical validity or utility to be promoted; and (4) does not include the counseling needed to put test results in proper context.”⁸⁰

Some have also expressed concern that “consumers will choose testing without adequate context or counseling, will receive tests from laboratories of dubious quality, and will be misled by unproven claims of benefit.”⁸¹ The risks include “psychological distress and misunderstanding of actual risks, leading to either false reassurance or the possibility of unnecessary medical procedures.”⁸² A consumer falsely reassured by positive information—for example, a decreased risk of heroin addiction (a test that was performed by 23andMe)⁸³—might mistakenly assume that they would not become addicted to the drug.⁸⁴ Consumers also might not understand the limits of particular tests and might expect a service to be more comprehensive than it is—for example, they might not have realized that 23andMe based its breast cancer risk information on the analysis of only three of dozens of variants associated with breast cancer.⁸⁵ Ultimately, many have expressed concern that “consumers may make unwarranted, and even irrevocable, decisions on the basis of test results and associated information, such as the decision to terminate a pregnancy, to forgo needed treatment, or to pursue unproven therapies.”⁸⁶

78. See, e.g., *id.*

79. See Frueh et al., *supra* note 42, at 511.

80. Gail H. Javitt et al., *Direct-to-Consumer Genetic Tests, Government Oversight, and the First Amendment: What the Government Can (and Can't) Do to Protect the Public's Health*, 57 OKLA. L. REV. 251, 253 (2004).

81. Hudson et al., *supra* note 44, at 1392.

82. Frueh et al., *supra* note 42, at 511.

83. *Heroin Addiction*, 23ANDME, <https://www.23andme.com/health/Heroin-Addiction/> (last visited Oct. 17, 2013) (this Web page has since been taken down in response to FDA's November 22, 2013 Warning Letter to 23andMe).

84. See, e.g., Bair, *supra* note 51, at 422.

85. See, e.g., Palmer, *supra* note 42, at 489. The limitations on 23andMe's breast cancer testing, however, are readily available on their website. *BRCA Cancer Mutations (Selected)*, 23ANDME, <https://www.23andme.com/health/BRCA-Cancer/> (last visited Nov. 11, 2013) (this Web page has since been taken down in response to FDA's November 22, 2013 Warning Letter to 23andMe) (“Please remember that the BRCA mutations covered by this report are only three of hundreds in the BRCA1 and BRCA2 genes that can cause cancer. Their absence does not rule out the possibility that you may have another cancer-causing variation in one of those genes.”).

86. Hudson et al., *supra* note 44, at 1393–94. *But see* Palmer, *supra* note 42, at 518 (“But concerns about prophylactic ovary removal or mastectomies seem far-

Taking into account these potential concerns, there is little empirical data supporting either the lauding or condemning of the industry.⁸⁷ In past studies, consumers participating in DTC genetic testing did not score high in signs of stress or distress.⁸⁸ People generally appear to be motivated to make positive health improvements after learning about their DTC genetic information.⁸⁹ But possible benefits and criticisms of DTC genetic testing have been discussed at length in the published literature, and the GAO and high-level advisory committees have weighed in with their concerns and hopes for DTC genetic testing. These reports raise serious concerns about the quality of the results offered by DTC companies—laying the groundwork for other agencies to become more involved in regulating DTC genetic testing, discussed more thoroughly in Part III of this Article.

1. *Investigation by the Government Accountability Office in 2006*

The GAO first investigated the legitimacy of DTC genetic tests and claims made regarding genetically determined health risks in 2006.⁹⁰ In so doing, GAO staff members posed as consumers and submitted twelve samples from one female and another two samples from an un-

fetched: for one thing, women could not unilaterally take those actions without a physician, so a gatekeeper would be involved regardless.”).

87. See, e.g., Frueh et al., *supra* note 42, at 511 (“There is considerable speculation, but little data, about the benefits and harms of DTC testing.”); McGuire et al., *supra* note 69, at 181.
88. See, e.g., Frueh et al., *supra* note 42, at 511 (“Distress appears uncommon”); Bair, *supra* note 51, at 421 (“An empirical study performed by Cinnamon Bloss and colleagues found that consumers undergoing DTC genetic testing did not score significantly higher on stress-related indicators upon learning that they were at increased risk for a particular disease such as heart disease or cancer.”); Palmer, *supra* note 42, at 488 (“[R]ecent studies have found no evidence to support consumer distress resulting from DTC testing.”).
89. See, e.g., Frueh et al., *supra* note 42, at 512 (“The Scripps Genomic Health Initiative, an ongoing 20-year study to assess the behavioural impact of personal genetic testing, has found a positive correlation between disease susceptibility risk as revealed by the tests and consumers’ intent to be screened with medical tests, such as mammograms and colonoscopies.”); *id.* at 511 (“Thus far, there is little evidence that health behaviours or health outcomes are improved. . . . [B]ut there is evidence that genetic risk information may be utilized to guide non-medical decisions.”); McGuire et al., *supra* note 69, at 181 (“In one study, 40% of participants with genetic test results indicating increased risk for Alzheimer’s disease reported increasing their use of medications or vitamins, compared with 20% of those whose results did not indicate increased risk.”); Palmer, *supra* note 42, at 492 (“[S]peculative fears are countered by evidence suggesting that predictive genetic testing motivates individuals to engage in healthy behavior and plan for the future.”).
90. U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-06-977T, NUTRIGENIC TESTING: TESTS PURCHASED FROM FOUR WEB SITES MISLED CONSUMERS, TESTIMONY BEFORE THE S. SPECIAL COMM. ON AGING (July 27, 2006), available at <http://www.gao.gov/new.items/d06977t.pdf> [hereinafter GAO—2006].

related male for analysis.⁹¹ GAO described these samples as coming from adults of various ages, weights, and lifestyles.⁹² It concluded that the four DTC genetic-testing companies it investigated provided results that were so vague as to be virtually useless.⁹³

The recommendations produced by the DTC companies also appeared to be more responsive to the results provided in a lifestyle survey rather than to the genetic analysis itself. For example, if a lifestyle description indicated that a person was a smoker, he or she received advice to stop smoking.⁹⁴ Test results from the same genetic sample should have resulted in similar recommendations—instead, the recommendations were inconsistent and varied in accordance with the different information that was included in the lifestyle description.⁹⁵

The investigation also raised concerns about quality control. For example, one DTC company's laboratory was not approved under the Clinical Laboratory Improvement Amendments (CLIA) (discussed in more detail in section III.C).⁹⁶ Another DTC company recommended expensive dietary supplements, estimated to cost \$1,200 per year, that were found to be “substantially the same as typical multivitamins that can be found in any grocery store for about \$35 per year.”⁹⁷ In response to this investigation, FDA, the U.S. Centers for Disease Control and Prevention (CDC), and FTC warned consumers to be wary of claims made by DTC genetic-testing companies in a public consumer alert.⁹⁸

2. *Reports of the Secretary's Advisory Committee on Genetics, Health, and Society*

The Secretary's Advisory Committee on Genetics, Health, and Society (Advisory Committee) was chartered in 2002 by then-Secretary of Health and Human Services (HHS) Tommy Thompson “as a public

91. *Id.* at 2–3.

92. *Id.*

93. For example, one company informed consumers that they “may” be “at increased risk” for developing heart disease. *Id.* at 8.

94. *Id.* at 6 (“Even if the predictions could be medically proven, the way the results are presented renders them meaningless.”).

95. *Id.*

96. CLIA was passed in 1988 to establish quality standards for laboratory testing “to ensure the accuracy, reliability and timeliness” of test results. *Id.* at 1. See also *Clinical Laboratory Improvement Amendments*, FDA, <http://www.fda.gov/medicaldevices/deviceregulationandguidance/ivdregulatoryassistance/ucm124105.htm> (last visited Oct. 17, 2013) (“Congress passed [CLIA] . . . to ensure the accuracy, reliability and timeliness of patient test results.”).

97. GAO—2006, *supra* note 90, at 5–6.

98. *Consumer Information: At Home Genetic Tests*, U.S. FED. TRADE COMM'N, <http://www.consumer.ftc.gov/articles/0166-home-genetic-tests> (last visited Oct. 17, 2013) [hereinafter FTC—*Consumer Alert*].

forum for deliberation on the broad range of policy issues raised by the development and use of genetic tests.”⁹⁹ The Advisory Committee expressed concerns about genetic testing generally, and DTC testing in particular, in a series of reports.

In the first of these reports, *U.S. System of Oversight of Genetic Testing: A Response to the Charge of the Secretary of Health and Human Services* issued in April 2008, the Advisory Committee was tasked with “investigating specific questions related to the adequacy and transparency of the current oversight system for genetic testing.”¹⁰⁰ It recognized that the “responsibilities for the oversight of genetic testing are shared by multiple governmental and nongovernmental bodies,” including, at the federal level, FDA and CMS (discussed further in Part III of this Article).¹⁰¹

In its analysis, the Advisory Committee identified gaps related to the oversight of genetic testing in five main areas: (1) the regulations governing clinical laboratory quality; (2) oversight of the clinical validity of genetic tests; (3) the transparency of genetic testing; (4) the level of current knowledge about the clinical usefulness of genetic tests; and (5) the educational needs of “health professionals, the public health community, patients, and consumers.”¹⁰² In response, the Advisory Committee proposed several action-guiding recommendations, including that:

- CMS require proficiency testing under CLIA (a process by which a laboratory’s genetic tests are compared to and measured against an established, external standard);
- FDA address concerns about clinical validity in all laboratory tests “regardless of how they are produced” (discussed further in Part III of this Article);¹⁰³
- HHS appoint and fund a lead agency to develop a “mandatory, publicly available, Web-based registry for laboratory tests;”¹⁰⁴ and
- Public health surveillance and other mechanisms be used in assessing the clinical utility of genetic tests.¹⁰⁵

99. SEC’Y’S ADVISORY COMM. ON GENETICS, HEALTH, & SOC’Y, U.S. DEP’T OF HEALTH & HUMAN SERVS., U.S. SYSTEM OF OVERSIGHT OF GENETIC TESTING: A RESPONSE TO THE CHARGE OF THE SECRETARY OF HEALTH AND HUMAN SERVICES (Apr. 2008), available at http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_oversight_report.pdf [hereinafter SACGHS—2008].

100. Letter from Steven Teutsch, M.D., Current Chair, SACGHS, & Reed V. Tuckson, M.D., Former Chair, SACGHS, to The Hon. Michael O. Leavitt, Sec’y, Dep’t of Health and Human Servs. (Apr. 30, 2018), in SACGHS—2008, *supra* note 99.

101. SACGHS—2008, *supra* note 99, at 2.

102. *Id.*

103. *Id.*

104. *Id.*

105. *See id.*

In a subsequent report focused specifically on DTC genetic testing released in April 2010,¹⁰⁶ the Advisory Committee identified gaps in four areas that limit “the ability of consumers to make informed decisions about DTC genetic testing services”¹⁰⁷ The gaps that the Advisory Committee identified included: (1) federal oversight of DTC testing, specifically the lack of review by FDA and FTC of genetic-testing claims and promotional materials made by DTC genetic-testing companies; (2) the evidence of clinical validity and utility for most DTC genetic tests; (3) privacy and research protections for consumers using DTC genetic services given the potentially limited applicability of federal laws and inadequacy of state law protections; and (4) inadequate knowledge of DTC testing by healthcare providers who are asked about it by their patients.¹⁰⁸ Although the Advisory Committee recognized that deficiencies exist in the delivery and oversight of clinical genetic testing, it nevertheless wanted “to ensure that standards for DTC genetic tests harmonize with standards for provider-based genetic tests.”¹⁰⁹

As in its previous report, the Advisory Committee provided a number of action-guiding recommendations, including that:

- FDA and CMS “should develop the necessary guidance and/or regulations that close gaps in the oversight” of DTC genetic testing;
- HHS and FTC should establish a task force to provide the necessary expertise to “develop guidelines to use as a basis to evaluate claims made by companies providing DTC genetic services;” and
- Various HHS agencies should identify the specific gaps in state and federal research and privacy protections for information generated through DTC genetic testing and develop strategies to address those gaps.¹¹⁰

106. SEC’Y’S ADVISORY COMM. ON GENETICS, HEALTH, & SOC’Y, U.S. DEP’T OF HEALTH & HUMAN SERVS., DIRECT-TO-CONSUMER GENETIC TESTING (Apr. 2010), *available at* http://oba.od.nih.gov/oba/sacghs/reports/SACGHS_DTC_Report_2010.pdf [hereinafter SACGHS—2010].

107. Letter from Steven Teutsch, M.D., Current Chair, SACGHS, to The Hon. Kathleen Sebelius, Sec’y, Dep’t of Health and Human Servs. (Apr. 28, 2010), in SACGHS—2010, *supra* note 106.

108. SACGHS—2008, *supra* note 99.

109. *Id.* at 3.

110. The Advisory Committee also recognized several areas concerning DTC testing that were ripe for future study including: the extent to which DTC services are being used for surreptitious genetic testing, the implications of DTC genetic testing for children, the psychosocial impact of DTC genetic testing, research use of specimens and data obtained through DTC genetic testing, the impact of DTC genetic testing on the health care system, and the potential for DTC services to exacerbate health disparities. SACGHS—2010, *supra* note 106. A third topical SACGHS report, *Gene Patents and Licensing Practices and Their Impact on Pa-*

3. *Investigation by the Government Accountability Office in 2010*

Despite GAO's 2006 investigation and the concerns voiced by the Advisory Committee, DTC genetic-testing companies continued to build public trust and attention. For example, the "retail DNA test" with a profile of 23andMe won *Time* magazine's "invention of the year" in 2008.¹¹¹ GAO, however, noted that "experts remain concerned that the test results mislead consumers" and in 2010 once again launched an investigation of the legitimacy of DTC genetic testing.¹¹² It found the new results of DTC companies to be just as troubling as the results from the previous investigation.¹¹³ GAO purchased ten DTC genetic tests each from four companies, selected five donors, and sent two samples from each: one with accurate lifestyle information and one with fictionalized information, including age, race, and/or ethnicity data.¹¹⁴ The same donors ended up receiving "disease risk predictions that varied across the four companies, indicating that identical DNA samples yield contradictory results," and "DNA-based disease predictions that conflicted with their actual medical conditions."¹¹⁵ The DTC companies also provided only incomplete results to these fictionalized African- or Asian-American donors due to the companies' limited data sets on participants with similar heritages, but they did not disclose this limitation to consumers prior to purchase.¹¹⁶

Two of the companies also sold consumers supplements marketed to "repair damaged DNA," a claim experts dismissed as having no scientific basis.¹¹⁷ Some told consumers that they could predict at which sports the consumers' children would excel—a claim one expert dismissed as "complete garbage."¹¹⁸ Despite the fact that surreptitious genetic testing is restricted in thirty-three states, one company spokesperson told a consumer that she could surprise her fiancé with

tient Access to Genetic Tests, also released in April 2010, is discussed in more detail in Part III of this Article. See SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, U.S. DEP'T OF HEALTH & HUMAN SERVS., GENE PATENTS AND LICENSING PRACTICES AND THEIR IMPACT ON PATIENT ACCESS TO GENETIC TESTS (Apr. 2010), available at http://oba.od.nih.gov/oba/sacghs/reports/sacghs_patents_report_2010.pdf [hereinafter SACGHS—GENE PATENTS].

111. Anita Hamilton, *Best Inventions of 2008*, TIME, Oct. 29, 2008, http://content.time.com/time/specials/packages/article/0,28804,1852747_1854493_1854113,00.html.
112. U.S. GOV'T ACCOUNTABILITY OFFICE, GAO-10-847T, DIRECT-TO-CONSUMER GENETIC TESTS: MISLEADING RESULTS ARE FURTHER COMPLICATED BY DECEPTIVE MARKETING AND OTHER QUESTIONABLE PRACTICES (July 22, 2010) (statement of Gregory Kutz, Managing Dir., Forensic Audits & Special Investigations), available at <http://www.gao.gov/assets/130/125079.pdf> [hereinafter GAO TESTIMONY].
113. GAO TESTIMONY, *supra* note 112.
114. *Id.*
115. *Id.*
116. *Id.*
117. *Id.*
118. *Id.*

a genetic test conducted secretly.¹¹⁹ Last, one company spokesperson informed a consumer “that an above average risk prediction for breast cancer meant she was ‘in the high risk of pretty much getting’ the disease.”¹²⁰

Once again, GAO concluded that there was much work to be done before DTC genetic tests could be considered as valid and clinically useful as consumers expected them to be.¹²¹

While genetic testing holds out tremendous promise in understanding the causes—and potential cures—of disease, there is still much to be learned regarding the interpretation of this information. Genetic testing has progressed rapidly from targeted tests of single genes highly associated with diseases to more complicated genome-wide analyses and large-scale testing, allowing consumers to explore their genetic data and interpreted medical information more broadly.¹²² But this movement toward large-scale genetic testing and genomic sequencing brings with it attendant concerns about the interpretation of complex information by non-expert consumers, as well as the actual validity and utility of the information. As discussed in Part III of this Article, this evolution presents many unique challenges for agencies tasked with regulating DTC testing.

III. REGULATING DIRECT-TO-CONSUMER GENETIC TESTING

Many federal agencies are involved in regulating DTC genetic testing, attempting to ensure valid and useful genetic data and information for the public. Part III of this Article examines the various agencies that have jurisdiction over DTC testing and concludes that although several agencies have the capacity to regulate the DTC genetic-testing industry, parameters and limitations might stymie their ability to fully ensure the accuracy and reliability of DTC genetic testing.

119. *Id.*

120. *Id.*

121. See GAO TESTIMONY, *supra* note 112, at 1–2. Of note, a much more recent article appearing in the *New York Times* purported to conduct the same type of inquiry—comparing the medical results of 23andMe, Genetic Testing Laboratories, and Pathway Genomics for the same single consumer—and alleging that the “discrepancies were striking.” See Kira Peikoff, *I Had My DNA Picture Taken, with Varying Results*, N.Y. TIMES, Dec. 30, 2013, at D1.

122. See, e.g., *How It Works*, 23ANDME, <https://www.23andme.com/howitworks/> (last visited Nov. 3, 2013).

A. Food and Drug Administration: Regulation of Medical Devices and Engagement with the Direct-to-Consumer Genetic-Testing Industry

FDA has the jurisdiction to regulate DTC genetic tests as medical devices and plays the largest role in their oversight.¹²³ Although FDA considers genetic tests to be in vitro diagnostic devices (medical devices intended to perform diagnoses in a controlled environment outside a living organism),¹²⁴ it does not consider them to fall under the laboratory developed test exemption (an exemption for a subset of in vitro diagnostic devices that FDA allows to enter the market without prior approval).¹²⁵ Although FDA traditionally exercised enforcement discretion over DTC genetic testing,¹²⁶ it recently strengthened its supervision of devices labeled for research or investigational use only, which had been another unregulated aspect of genetic tests.¹²⁷ After a respite of enforcement discretion, FDA began direct engagement with the DTC industry in 2010 with potential violation notifications,¹²⁸ culminating with an official warning to the final major player standing (23andMe) in November 2013.¹²⁹ The sections that follow

123. 21 U.S.C § 321(h) (2006).

124. 21 C.F.R. § 809.3 (2013).

125. See, e.g., Letter from Alberto Gutierrez, Ph.D., Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Device & Radiological Health, to Jorge Conde, Co-Founder & CEO, Knome, Inc. (June 10, 2010), available at <http://www.fda.gov/downloads/medicaldevices/resourcesforyou/industry/ucm215239.pdf> [hereinafter Letter from Gutierrez to Conde]; Peter Barton Hutt, *A Brief History of the Regulation of In Vitro Diagnostic Products*, in *IN VITRO DIAGNOSTICS: THE COMPLETE REGULATORY GUIDE*, 1, 6 (Scott D. Danzis & Ellen J. Flannery eds., 2010).

126. See Medical Devices; Classification/Reclassification; Restricted Devices; Analyte Specific Reagents, 62 Fed. Reg. 62,243, 62,243 (Nov. 21, 1997) [hereinafter Classification/Reclassification] (“The Food and Drug Administration (FDA) is issuing a final rule to classify/reclassify analyte specific reagents (ASR’s) presenting a low risk to public health into class I (general controls), and to exempt these class I devices from the premarket notification (510(k) requirements.”). FDA had originally planned to regulate laboratory developed tests, however, after pressure from industry, it instead decided to regulate the “analyte specific reagents” used in the laboratory developed tests. Palmer, *supra* note 42, at 499.

127. FDA expressed concern that the “[u]se of such tests for clinical diagnostic purposes may mislead healthcare providers and cause serious adverse health consequences to patients, who are not aware that they are being diagnosed with research or investigational products.” FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF, COMMERCIALY DISTRIBUTED IN VITRO DIAGNOSTIC PRODUCTS LABELED FOR RESEARCH USE ONLY OR INVESTIGATIONAL USE ONLY: FREQUENTLY ASKED QUESTIONS 5–6 (June 1, 2011), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM257460.pdf> [hereinafter FDA—RESEARCH USE ONLY]; see 21 C.F.R. § 809.10(c) (2013).

128. Letter to Plante, *supra* note 14.

129. See Warning Letter to Wojcicki, *supra* note 8.

further expand upon this regulatory analysis and set forth four important insights for the industry.

1. *Food and Drug Administration's Regulation of Medical Devices*

FDA is tasked with protecting the public's health by assuring the "safety, effectiveness, and security" of myriad medical interventions.¹³⁰ The Food and Drugs Act of 1906 provided the original grant of FDA authority.¹³¹ The act was amended in 1938, expanding FDA jurisdiction to include medical devices,¹³² currently defined as any "instrument, apparatus, implement, machine, in vitro reagent, or 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."¹³³ FDA regulates companies who "manufacture, repackage, relabel, and/or import" medical devices sold in the United States.¹³⁴

FDA classifies medical devices into three categories—Class I, II, or III—on the basis of risk to the consumer.¹³⁵ The greater the risk to the consumer, the more control perceived necessary to ensure the safety and effectiveness of the device, and the higher the classification it receives.¹³⁶ Devices that are not intended to help support or sustain life or that are not substantially important in preventing impairment to human health (and that do not present an unreasonable risk of illness or injury) are classified as Class I. Class I devices include exam gloves, adhesive bandages, and toothbrushes. Class II devices are designed to perform as indicated without causing injury or harm to the user and include mercury thermometers, powered wheelchairs, and surgical drapes. Class III devices are those that support or sustain

130. *FDA Fundamentals*, FDA, <http://www.fda.gov/AboutFDA/Transparency/Basics/ucm192695.htm> (last updated May 6, 2013).

131. Hutt, *supra* note 125, at 1.

132. FDA immediately noticed the limitations of the 1906 legislation regarding lack of control over "fraudulent medical devices." *Id.* (citing C.L. Alsberg, *Report of the Chemist*, in ANNUAL REPORTS OF THE DEPARTMENT OF AGRICULTURE FOR THE YEAR ENDED JUNE 30, 1917 at 199, 214 (1918)). In fact, this was one of the major goals of the 1933 revision. When the Food, Drug and Cosmetic Act was amended again later in the wake of the thalidomide disaster of 1963, the medical device portions were not substantively updated. Hutt, *supra* note 125, at 1.

133. 21 U.S.C § 321(h) (2006).

134. *Overview of Device Regulation*, FDA, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/overview/default.htm> (last updated Mar. 5, 2013). Specifically, the Center for Devices and Radiological Health regulates the device industry. *Id.*

135. *Classify your medical device*, FDA, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm> (last updated Dec. 3, 2012) [hereinafter FDA—*Classify Your Device*].

136. *See id.*

human life; are of substantial importance in preventing impairment of human health; or present a potential, unreasonable risk of illness or injury (or for which there is insufficient information to make such a determination).¹³⁷ Class III devices include items such as defibrillator machines, replacement heart valves, and silicone breast implants.¹³⁸

Classification dictates the level of engagement companies must have with FDA before being able to legally market and sell their devices in the United States. As FDA presumes Class I devices pose minimal potential for harm, they are only subject to “General Controls” including:

- Registration of manufacturers, distributors, repackages, and re-labelers;
- Listing products and activities with FDA;
- Manufacturing according to Good Manufacturing Practices (defining, for example, design controls, identification and traceability requirements, and handling instructions);¹³⁹ and
- Labeling requirements (such as intended use, adequate directions, and a prohibition against false or misleading statements).¹⁴⁰

Class II devices are subject to the above General Controls, as well as Special Controls adding stricter labeling requirements, performance standards, and/or postmarket surveillance.¹⁴¹ Most Class II devices must submit a premarket notification (510(k)) before marketing.¹⁴² In that notification, the manufacturer must demonstrate that the device is at least as safe and effective, i.e. “substantially equivalent,” to another device already being legally marketed. FDA will accept the new device as substantially equivalent if it has the same intended use and technological characteristics of a device already on the market or has the same intended use, does not raise new questions of safety and effectiveness, and is at least as safe and

137. FOOD & DRUG ADMIN., INFORMATION SHEET GUIDANCE FOR IRBs, CLINICAL INVESTIGATORS, AND SPONSORS: FREQUENTLY ASKED QUESTIONS ABOUT MEDICAL DEVICES 2 (Jan. 2006), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127067.pdf>; *Regulatory Controls*, FDA, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/default.htm> (last updated Apr. 11, 2013) [hereinafter FDA—Controls].

138. *Id.*

139. 21 C.F.R. § 820 (2013).

140. 21 C.F.R. § 801 (2013). Technically, submission of a premarket notification (510(k)) before marketing the device is a general control as well; however, most Class I devices are exempt from this requirement. *Class I/II Exemptions*, FDA, <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/ucm051549.htm> (last updated Dec. 5, 2012).

141. See FDA—Controls, *supra* note 137.

142. 21 C.F.R. § 807 (2013).

effective.¹⁴³ In 2003, when FDA began clearing discrete genetic tests, it generally did so through its Class II 510(k) notification process.¹⁴⁴

FDA created the *de novo* 510(k) review process to alleviate an imbalance in the classification system just described. Before the *de novo* process, novel and unique devices could not be cleared by the “substantially equivalent” test even if they gave rise to less risk than a traditional Class III device. FDA therefore released guidance in 2011 to establish a *de novo* program designed to allow low- to moderate-risk devices on the market even without substantially equivalent predicate devices,¹⁴⁵ which is the process it used in several cases to consider genetic tests.¹⁴⁶

143. *Premarket Notification (510K)*, FDA, <http://www.fda.gov/medicaldevices/device-regulationandguidance/howtomarketyourdevice/premarketnotifications/premarketnotification510k/default.htm> (last updated Sept. 3, 2010).

144. Gail H. Javitt, *In Search of a Coherent Framework: Options for FDA Oversight of Genetic Tests*, 62 *FOOD & DRUG L.J.* 617, 628 (2007). There are several limitations to the premarket clearance process pertinent to the genetic-testing industry. For example, premarket clearance applications typically require data supporting analytical validity but do not require data about clinical validity. The Advisory Committee argued that, for the genetic-testing industry, the production of genetic data is more straightforward than the interpretation and analysis required to generate patient-specific medical information, and FDA’s lack of focus on clinical validity gives rise to a potential gap needed to ensure the accuracy and validity of genetic interpretation services. Regulating clinical validity, however, faces several critical challenges in part because data associating genetic sequences with disease “are often unavailable or incomplete for years after a test is developed, especially for predictive or presymptomatic tests.” SACGHS—2008, *supra* note 99, at 4.

145. *See* FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY AND FDA STAFF, DE NOVO CLASSIFICATION PROCESS (EVALUATION OF AUTOMATIC CLASS III DESIGNATION) 3 (Oct. 3, 2011), *available at* <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM273903.pdf> [hereinafter FDA—DE NOVO CLASSIFICATION] (“FDA believes that the process could be improved and greater clarity could be provided regarding suitability and data needed so that the *de novo* process may be a more viable pathway for novel low to moderate risk devices.”). In addition to the devices themselves, FDA regulates the labeling of all devices and the advertising of prescription devices. Under the Food, Drug, and Cosmetic Act, a label is defined as a “display of written, printed, or graphic matter upon the immediate container of any article” and labeling as “all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article.” 21 U.S.C. §§ 321(k), (m) (2006). The term “accompanying” has been broadly interpreted by the Supreme Court not to require an actual physical association with the device at issue but to include things such as brochures, letters, films, or recordings disseminated by the manufacturer. *Kordel v. United States*, 335 U.S. 345, 349–50 (1948); 21 C.F.R. § 202.1(a)–(b) (2013). “Advertising” is defined in regulations as publications in journals, magazines, newspapers, and broadcasts; most advertising is, however, considered to be a subset of labeling. 21 C.F.R. § 202.1(a)(1) (2013); *United States v. Research Laboratories, Inc.*, 126 F.2d 42, 45 (7th Cir. 1942).

146. *See, e.g.*, 23andMe, @23andMe, TWITTER (July 30, 2012, 4:07 PM), <https://twitter.com/23andMe/status/230077137040842754> [hereinafter 23andMe—TWITTER].

Most Class III devices require “premarket approval,” a rigorous premarket review during which manufacturers must demonstrate that their device is safe and clinically valid. The Secretary of HHS may restrict that device to only be sold, distributed, or used “upon the [written or oral] authorization of a practitioner licensed by law to administer or use such device” if FDA determines that there cannot otherwise be reasonable assurance of the device’s safety and effectiveness.¹⁴⁷

2. *Exemptions for Genetic Tests Under In Vitro Diagnostic Device Regulations*

The definition of a medical device was expanded in 1976 to include in vitro diagnostic devices,¹⁴⁸ which generally are diagnostic test kits used by a clinical laboratory.¹⁴⁹ FDA considers genetic tests to be in vitro diagnostic devices because they fall within the FDA’s definition of in vitro devices as they are “reagents, instruments, and systems intended for use in 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” and “intended for use in the collection, preparation, and examination of specimens taken from the human body.”¹⁵⁰

When FDA originally promulgated regulations for in vitro diagnostic products, it exempted those intended and labeled for research or investigational use only.¹⁵¹ FDA’s stated goal was to encourage and protect products “intended for use in discovering and developing novel and fundamental medical knowledge.”¹⁵² However, scholars argue, FDA soon became concerned about the overwhelming use of this exemption.¹⁵³

A “laboratory developed test” is another type of in vitro diagnostic device that a *single* laboratory manufactures and offers—as opposed to diagnostic tests that require the expertise of several laboratories working together. It is sometimes also known as a “home brew

147. *Marketing or Medicine: Are Direct-to-Consumer Medical Device Ads Playing Doctor?: Hearing Before the S. Special Comm. on Aging*, 110th Cong. 62 (Sept. 17, 2008) (statement of Daniel Schultz, Director, Center for Devices & Radiological Health, Food & Drug Administration), available at <http://www.gpo.gov/fdsys/pkg/CHRG-110shrg49768/pdf/CHRG-110shrg49768.pdf>.

148. Hutt, *supra* note 125, at 5–6.

149. The Office of In Vitro Diagnostic Device Evaluation and Safety, Under the Center for Devices and Radiological Health within the FDA, is responsible for their regulation. *Id.* at 6.

150. 21 C.F.R. § 809.3 (2009).

151. 21 C.F.R. § 809.10(c) (2009).

152. FDA—RESEARCH USE ONLY, *supra* note 127, at 8.

153. *See, e.g.*, Hutt, *supra* note 125, at 8.

test.”¹⁵⁴ Although laboratory developed tests are considered medical devices, FDA has stated in the past that it would exercise enforcement discretion over them,¹⁵⁵ as they were generally “either well-characterized, low-risk diagnostics or for rare diseases for which adequate validation would not be feasible and the tests were being used to serve the needs of the local patient population.”¹⁵⁶

Genetic-testing companies that produce their own genetic data and conduct their own analyses have, in the past, fallen under the laboratory developed test “home brew” exemption.¹⁵⁷ However (as discussed in subsection II.C.2 of this Article), the Advisory Committee recommended that FDA address concerns about clinical validity in *all* laboratory tests regardless of whether they were a commercial test kit or a laboratory developed test.¹⁵⁸

In 2010, FDA stated that it had reconsidered its position regarding non-enforcement of laboratory developed tests, reasoning that the industry was shifting toward using component parts that were not individually regulated and were being used to assess high-risk diseases and direct treatments. In addition, an increasing number of laboratory developed test manufacturers were corporations—as opposed to the hospitals or public laboratories for which FDA originally carved out the exemption. Recently, FDA expressed concern that laboratory developed tests that have not been appropriately validated put patients at risk for “missed diagnosis, wrong diagnosis, and failure to

154. *See id.* at 6.

155. *See* Classification/Reclassification, *supra* note 126 (“[FDA] is issuing a final rule to classify/reclassify analyte specific reagents presenting a low risk to public health into class I (general controls), and to exempt these class I devices from the premarket notification (510(k)) requirements.”).

156. *FDA/CDRH Public Meeting: Oversight of Laboratory Developed Tests (LDTs)*, FDA, <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm#> (last updated Sept. 17, 2010).

157. Hutt, *supra* note 125, at 10. FDA began to narrow this home-brew exemption in the late 2000s, beginning with exempting in vitro diagnostic multivariate assays (which typically involve complex software analysis). *See generally* FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY, CLINICAL LABORATORIES, AND FDA STAFF, IN VITRO DIAGNOSTIC MULTIVARIATE INDEX ASSAYS (July 26, 2007), *available at* <http://www.fda.gov/downloads/MedicalDevices/. . . /ucm071455.pdf> (“[In vitro diagnostic multivariate assays] . . . do not fall within the scope of [laboratory diagnostic test] over which FDA has generally exercised enforcement discretion” as they “raise significant issues of safety and effectiveness.”). FDA never issued finalized guidance. Turna Ray, *FDA Shelves IVDmia Final Guidelines in Order to Focus on Overall LDT Regulation*, PHARMACOGENOMICS REP. (June 23, 2010), <http://www.genomeweb.com/dxpgx/fda-shelves-ivdmia-final-guidelines-order-focus-overall-ldt-regulation> (“It’s possible that we will issue [an in vitro diagnostic multivariate assay] guidance in the future but with this public meeting [scheduled for July], we are addressing [laboratory developed tests] at once in a public dialogue, instead of dealing with subset by subset.”).

158. *See generally*, SACGHS—2008, *supra* note 99.

receive appropriate treatment.”¹⁵⁹ To date, however, FDA has not released additional guidance.¹⁶⁰

3. *FDA Sends Notification Letters to Direct-to-Consumer Genetic-Testing Companies*

Marketing or distributing a medical device not cleared or approved by FDA is a violation of the Food, Drug, and Cosmetic Act.¹⁶¹ FDA, however, generally operates under the assumption that companies *intend* to comply with the law, such that notice of a violation is a standard, but not obligatory, part of FDA enforcement.¹⁶² Two types of FDA notice are Warning Letters and Untitled Letters. Warning Letters highlight violations that may lead to enforcement action, such as a recall or seizure of products, if not “promptly and adequately corrected.”¹⁶³ Untitled Letters are for less significant violations, such as minimization of risk in product advertising.¹⁶⁴ In 2010, FDA sent twenty-three Untitled Letters to the DTC genetic-testing industry,¹⁶⁵ which resulted in almost all companies dropping out of the DTC market; 23andMe, however, began the premarket clearance regulatory process. However, in November 2013, FDA sent 23andMe a Warning Letter requiring that it cease marketing its personal genome service without FDA clearance or approval.¹⁶⁶ 23andMe stopped selling its health-related testing package to consumers,¹⁶⁷ and as of May 2014,

159. Oversight of Laboratory Developed Tests: Public Meeting: Request for Comments, 75 Fed. Reg. 34,463, 34,463–64. (June 17, 2010).

160. *See, e.g., Bill Malone, Straight Talk on Lab-Developed Tests From FDA*, 39(10) CLINICAL LABORATORY NEWS (Oct. 2013), <http://www.aacc.org/publications/cln/2013/october/Pages/AM-LDTs.aspx#>.

161. 21 U.S.C. § 331(a).

162. *See Regulatory Procedures Manual*, GRIMES & REESE, P.L.L.C., ch. 10, http://www.mlmlaw.com/library/guides/fda/reg_proc/rchap10.html (last visited Nov. 3, 2013).

163. FOOD & DRUG ADMIN., WARNING AND UNTITLED LETTERS (Dec. 20, 2011), *available at* <http://www.fda.gov/downloads/AboutFDA/Transparency/PublicDisclosure/GlossaryofAcronymsandAbbreviations/UCM212064.pdf> [hereinafter FDA—LETTERS].

164. *See, e.g.,* Letter from Zarna Patel, Pharm.D., Regulatory Review Officer, Office of Prescription Drug Promotion & Amy Toscano, Pharm.D., RAC, CPA, Team Leader, Office of Prescription Drug Promotion, to Roxanne McGregor-Beck, Dir., Johnson & Johnson Int’l, Inc. (June 6, 2013), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM357833.pdf>. FDA generally posts both types of letters online, making both types available to the public. *See* FDA—LETTERS, *supra* note 163.

165. *See, e.g.,* Letter to Plante, *supra* note 12.

166. *See* Warning Letter to Wojcicki, *supra* note 8.

167. *Changes to Our Health-Related Product*, 23ANDME, <https://www.23andme.com/health/> (last visited Dec. 27, 2013) (“Customers who purchase or have purchased 23andMe’s Personal Genome Service (PGS) on or after November 22, 2013, the date of the Warning Letter from the FDA, will receive ancestry information, as

there was no major player on the DTC health-related genetic-testing market.

a. Food and Drug Administration Untitled Letters

FDA first entered the DTC genetic-testing enforcement arena in May 2010 when Pathway Genomics announced that it was going to sell its “home-use saliva collection kit” at more than 6000 Walgreens stores across the United States.¹⁶⁸ Although Pathway had sold this product online for the preceding two years, FDA stated it became concerned that a partnership with Walgreens would make the DTC genetic-testing kit more readily accessible to the public.¹⁶⁹

As discussed above, FDA conducts its oversight of devices on the basis of risk that a test will potentially give rise to an inaccurate test result.¹⁷⁰ An FDA representative stated that the DTC distribution of genetic tests can *increase* the risk of a device because “a patient may make a decision that adversely affects [his or her] health, such as stopping or changing the dose of a medication or continuing an unhealthy lifestyle, without the intervention of a learned intermediary.”¹⁷¹ He noted FDA’s belief that this increased risk raised the importance of “ensuring that consumers are also provided accurate, complete, and understandable information about the limitations of test results they are obtaining.”¹⁷²

FDA took immediate note of Pathway Genomics’ increase in public access to genetic testing and sent an Untitled Letter on May 10, 2010, informing the DTC genetic-testing company that its kit—“intended to report customary and personal genetic health disposition results for more than 70 health conditions, including pharmacogenetics, . . . propensity for complex disease, and carrier status” for the purpose of health regime modification to “live a healthier, longer life”—

well as their raw genetic data without interpretation. These new customers may receive additional health-related results in the future, dependent upon FDA marketing authorization.”) [hereinafter 23ANDME—Changes].

168. See, e.g., Pollack—*Walgreens Delays*, *supra* note 13; Shuren—*Statement*, *supra* note 13.

169. See, e.g., Pollack—*Walgreens Delays*, *supra* note 13. The following month, 23andMe had a lab error that resulted in ninety-six customers receiving and viewing the wrong genetic data. See Shari Roan, *Personal Genetic Test Results Were Mixed Up, Company Admits*, L.A. TIMES (June 8, 2010, 10:22 AM), http://latimesblogs.latimes.com/booster_shots/2010/06/genetic-testing-23andme.html; see also Michelle D. Irick, *Comment, Age of an Information Revolution: The Direct-to-Consumer Genetic Testing Industry and the Need for a Holistic Regulatory Approach*, 49 SAN DIEGO L. REV. 279, 317 (2012) (stating that “a false advertisement is misleading in a material respect whether it inaccurately represents the product or fails to disclose material facts”).

170. Shuren—*Statement*, *supra* note 13.

171. *Id.*

172. *Id.*

“appeared” to meet the definition of a device.¹⁷³ FDA pointed out that Pathway Genomics did not have clearance or approval for the kit and requested that it respond within fifteen days.¹⁷⁴

Walgreens, one of the largest pharmacy chains in the country and a proposed distributor for Pathway’s test, decided to delay selling the kit until the issue was resolved.¹⁷⁵ Alberto Gutierrez, Director of the Office of In Vitro Diagnostic Device Evaluation and Safety (and signatory of subsequent Untitled Letters), pointed out that many DTC genetic companies had different business models, so it was hard to pinpoint exactly which companies needed FDA oversight; however, “[o]nce you take a collection device and you are marketing through a drugstore, it is very easy for me to say whether something would fall under our policy.”¹⁷⁶ Walgreens eventually dropped the plan entirely. Pathway currently markets its genetic test online but only provides results to physicians.¹⁷⁷

The following month, FDA sent five additional Untitled Letters to five different DTC companies. As opposed to suggesting that these genetic tests “appeared” to meet the definition of a device, FDA asserted that the tests *were* indeed devices based on the manufacturers’ claims regarding the test results.¹⁷⁸ The tests at issue claimed to:

- “[D]escribe the genetic basis of specific disease traits or conditions on which consumers may base medical decisions;
- [P]rovide personalized information on which medications are more likely to work given a person’s genetic makeup; and
- [P]rovide genetic predispositions for important health conditions and medication sensitivities.”¹⁷⁹

The letters described FDA’s concerns that consumers might make medical decisions in reliance on this potentially inaccurate genetic interpretation and stated that devices must be “analytically and clinically accurate so that individuals are not misled by incorrect test results or unsupported clinical interpretations.”¹⁸⁰ FDA also confirmed that it did not consider these devices to be laboratory developed

173. Letter to Plante, *supra* note 12.

174. *Id.*

175. *See, e.g.,* Pollack—Walgreens Delays, *supra* note 13.

176. *Id.*

177. *See General Questions*, PATHWAY GENOMICS, <https://www.pathway.com/medical-professionals/physicians> (last visited Nov. 3, 2013) (“A physician will need to register with Pathway and order the report for you.”).

178. Shuren—*Statement*, *supra* note 13, at 7.

179. *Id.*

180. Letter from Gutierrez to Conde, *supra* note 125. FDA pointed out in these letters that “premarket review allows for an independent and unbiased assessment of a diagnostic test’s ability to generate tests results that can reliably be used to support good healthcare decisions.” *Id.*

tests, as they were not developed or used in a single laboratory.¹⁸¹ The FDA Untitled Letters did not require that companies pull their tests from the market; rather, companies were requested to begin discussions with the FDA.¹⁸²

The five companies that FDA targeted in this round included:

- Two companies (Knome and 23andMe) that used software programs that interpreted genetic data created by an external laboratory in order to generate patient-specific medical information;¹⁸³
- A company (Navigenics) that claimed to provide personalized medical information on which medications were more likely to work best for a consumer given their “genetic makeup,” which included providing consumers with genetic predispositions for health conditions and medication sensitivities;¹⁸⁴
- A company (deCODE Genetics) that provided genetic medical information but obtained its components from other manufacturers;¹⁸⁵ and
- A company (Illumina) that produced the genetic-analysis system used by deCODE and 23andMe to do scans and interpretation to provide genetic information to their customers.¹⁸⁶

181. *See, e.g., id.*

182. Dr. Gutierrez said in an interview with the New York Times that that it would be “unfair” to remove the tests from the market when FDA had not yet clearly said that they needed agency approval in the first place. However, he stated FDA was concerned because “[i]t is not unknown for women to take out their ovaries if they are at high risk of ovarian cancer [FDA] really [doesn’t] have any issues with denying people information [,] we just want to make sure the information they are given is correct.” Andrew Pollack, *F.D.A. Faults Companies on Unapproved Genetic Tests*, N. Y. TIMES, June 11, 2010, at B2 [hereinafter Pollack—*FDA Faults*].

183. Letter from Gutierrez to Conde, *supra* note 125; *see* Letter from Alberto Gutierrez, Ph.D., Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Device & Radiological Health, to Anne Wojcicki, CEO and Co-Founder, 23andMe (June 10, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM215240.pdf> [hereinafter Untitled Letter to Wojcicki].

184. Letter from Alberto Gutierrez, Ph.D., Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Device & Radiological Health, to Vance Vanier, M.D., President & CEO, Navigenics (June 10, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM215243.pdf>.

185. Letter from Alberto Gutierrez, Ph.D., Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Device & Radiological Health, to Earl M. Collier, CEO, deCODE Genetics (June 20, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ResourcesforYou/Industry/UCM215241.pdf> [hereinafter Letter to Collier].

186. Letter from Alberto Gutierrez, Ph.D., Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Device & Radiological Health, to Jay T. Flatley, President & CEO, Illumina, Inc. (June 10, 2010), *available at* <http://www.fda.gov/downloads/medicaldevices/resourcesforyou/industry/ucm215242.pdf> [hereinafter

When queried by *Newsweek* as to why FDA waited three years before engaging with the industry, Dr. Gutierrez pointed to the changing claims of the companies. Three years ago, he argued, the claims “were very, very vague”; now, companies were making claims about metabolizing specific drugs and risk of specific chronic diseases.¹⁸⁷ When questioned directly as to why FDA sent letters regarding software programs that only *interpreted* corresponding medical information from genetic data that consumers could have had generated anywhere, Dr. Gutierrez responded that “[s]oftware is a medical device, and they’re making medical claims. They’re taking results and making medical claims that come out of those results.”¹⁸⁸

The following month, FDA sent out fourteen additional letters. FDA again used language indicating that the tests at issue “appeared” to meet the definition of a device, but FDA pointed out that it was “unable to identify any [FDA] clearance or approval number” for any of the products at issue¹⁸⁹—the implication being that none of the companies had engaged in premarket clearance or approval through the Class II or III process, respectively. Out of the fourteen companies receiving Untitled Letters, half provided general genetic health predisposition information—including information regarding cardiac health, diabetes, obesity, immune efficiency, cancers, and “information from which one can modify [his or her] health regime to live a healthier, longer life.”¹⁹⁰ The other half offered targeted genetic tests

Letter to Flatly]. Illumina had labeled its product for “Research Use Only.” However, FDA found that because Illumina knowingly provided the chip to the companies for clinical diagnostic use, no matter how it was labeled or marketed, the company was obligated to seek clearance or approval. *See id.*

187. Mary Carmichael, *Why the FDA Is Cracking Down on Do-It-Yourself Genetic Tests: An Exclusive Q&A*, NEWSWEEK (June 11, 2010), <http://www.thedailybeast.com/newsweek/blogs/the-human-condition/2010/06/11/why-the-fda-is-cracking-down-on-do-it-yourself-genetic-tests-an-exclusive-q-a.html> [hereinafter Carmichael—*FDA Cracking Down*].

188. *Id.*

189. Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Kenneth W. Friedenberg, Owner, Graceful Earth Inc. (July 19, 2010), available at <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219585.pdf> [hereinafter Letter to Friedenbergl].

190. Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Fei Lu, CEO, SeqWright DNA Technology Services, Inc. (July 19, 2010), available at <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219586.pdf>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Lewis H. Bender, CEO, Interleukin Genetics, Inc. (July 19, 2010), available at <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219587.pdf>; Letter from James Woods, Deputy Dir., Patient

marketed to provide medical information regarding Alzheimer's disease, carrier status for genetic diseases of interest to persons of Ashkenazi Jewish descent, individualized response to asthma medications, breast cancer, celiac disease, or fetal gene and chromosomal abnormalities.¹⁹¹

Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Marin Munzer, President & CEO, CyGene Direct™ (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219590.pdf>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Bill White, President, The Genetic Testing Laboratories, Inc. (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219593.pdf>.

191. See Letter to Friedenber, *supra* note 189; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Bennett Greenspan, President & CEO, Family Tree DNA (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219589.pdf>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Chinh Bach, CEO, Consumer Genetics, LLC (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219591.pdf>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Larry S. Corder, Ph.D., President & CEO, Matrix Genomics, Inc. (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219592.pdf>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Harry F. Hixson Jr., Ph.D., Chairman & CEO, Sequenom®, Inc. (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219595.pdf>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Kenneth Fine, M.D., Medical Dir. & Dir. of Operations, EnteroLab Reference Lab. (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219596.pdf>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Holt Vaughan, President, HealthCheckUSA (July 19, 2010), *available at* <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM219600.pdf>. Dr. Gutierrez, speaking with the Washington Post in 2010, stated that:

It's come to the point where really there's a need for some oversight . . . We know of reports of people who have found a test, found a doctor that is willing to order the test since they are so afraid of the disease, and even removed ovaries based on questionable results.

Rob Stein, *Genetic Test Mix-Up Reignites Regulation Debate*, WASH. POST, July 17, 2010, at A7. During a later interview, however, Dr. Gutierrez stated that the *Washington Post* took this quote out of context and that the cases that he was referring to were of invalid laboratory tests, as opposed to DTC genetic tests.

In May 2011, FDA sent out its final three Untitled Letters. The recipient companies claimed to provide athletes and parents of sports competitors information regarding potential health conditions, along with information about other diseases and conditions such as breast cancer.¹⁹²

b. *Food and Drug Administration Warning Letter to 23andMe*

In July 2012, 23andMe became the first DTC genetic company to file *de novo* premarketing clearance for some of their health-related genetic tests with FDA.¹⁹³ At the time, 23andMe stated that it disagreed that its services should even be considered a device and that “we believe that people have the right to know as much about their genes and their bodies as they choose.”¹⁹⁴ 23andMe nevertheless planned to submit another 100 tests for review by the end of 2012.¹⁹⁵ However, according to FDA, despite “more than 14 face-to-face and teleconference meetings, hundreds of email exchanges, and dozens of written communications”¹⁹⁶ between FDA and 23andMe, FDA sent a Warning Letter on November 22, 2013, cautioning the CEO of 23andMe that “[t]o date, 23andMe has failed to provide adequate information to support a determination that the [personal genome ser-

Mary Carmichael, *DNA Dilemma: The Full Interview with the FDA on DTC Genetic Tests*, NEWSWEEK, June 11, 2010 [hereinafter Carmichael—*DNA Dilemma*].

192. Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Romain Bonjean, CEO, Lumigenix Inc. (May 11, 2011), *available at* <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm255347.htm>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Bill Miller, CEO, American International Biotechnology Services (May 11, 2011), *available at* <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm255348.htm>; Letter from James Woods, Deputy Dir., Patient Safety & Product Quality, Office of In Vitro Diagnostic Device Evaluation & Safety, Ctr. for Devices & Radiological Health, to Andre Gous, CEO, Precision Quality DNA (May 11, 2011), *available at* <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm255349.htm>.
193. See 23andMe—TWITTER, *supra* note 146; & 23andMe Takes First Step Toward FDA Clearance, *supra* note 15. The 510(k) *de novo* review process is for products that do not rise to the level of Class III regulation. See FDA—DE NOVO CLASSIFICATION, *supra* note 145, at 5 (“If we grant the *de novo* petition, the device is reclassified from class III into class I or class II.”); Warning Letter to Wojcicki, *supra* note 8.
194. Pollack—*FDA Faults*, *supra* note 182. One director there, however, described FDA’s actions as “appallingly paternalistic.” *Id.*
195. Matthew Perrone, *23andMe Seeks FDA Approval for Personal DNA Test*, BLOOMBERG BUSINESSWEEK NEWS, July 30, 2012 [hereinafter Perrone—*23andMe*].
196. Warning Letter to Wojcicki, *supra* note 8.

vice] is substantially equivalent to a legally marketed predicate for any of the uses for which you are marketing it”¹⁹⁷

The letter stated that FDA was primarily concerned about the “public health consequences of inaccurate results from the [personal genome service] device” given that “the main purpose of compliance with FDA’s regulatory requirements is to ensure that the tests work.”¹⁹⁸ FDA cited to two 23andMe health-related tests as being particularly worrisome, including assessments for BRCA-related genetic risks (associated with breast and ovarian cancer) and drug responses (e.g., blood anticoagulant sensitivity), “because of the potential health consequences that could result from false positive or false negative assessments for high-risk indications such as these,” including that consumers could potentially undergo unwarranted prophylactic surgeries or might inaccurately self-manage their drug dosages.¹⁹⁹

Despite the lack of pre-marketing clearance or approval, 23andMe had recently hired a new president to grow their product marketing, launch a television and Internet advertising campaign, and reach its goal of one million members by the end of 2013.²⁰⁰ But much like when Pathway Genomics announced its potential rapid expansion of clientele via Walgreens in 2010²⁰¹—a move that instigated the initial twenty-three Untitled Letters to the industry (including 23andMe)²⁰²—this potentially increased consumer base factored into FDA’s decision to act.²⁰³ In its Warning Letter, FDA cautioned 23andMe it was marketing its personal genome service without clear-

197. *Id.*

198. *Id.*

199. *Id.* On November 27, 2013, a class action lawsuit was also filed claiming that 23andMe “falsely and misleadingly advertises their Saliva Collection Kit/Personal Genome Service . . . as providing ‘health reports on 240+ conditions or traits,’ ‘drug response,’ [and] ‘carrier status,’ among other things, when there is no analytical or clinical validation for the [personal genome service] for its advertised uses.” Class Action Complaint at 1–2, *Casey v. 23andMe*, No. 13CV2847 H JMA (S.D. Cal. Nov. 27, 2013).

200. See Kara Swisher, *23andMe Names Former Gilt Exec Andy Page as President*, ALL THINGS DIGITAL (June 11, 2013), <http://allthingsd.com/20130611/23andme-names-former-gilt-exec-andy-page-as-president/>; Christina Farr, *Why the FDA is Targeting Google-Backed 23andMe: Unnecessary MRIs, Mastectomies*, VENTUREBEAT (Nov. 26, 2013), <http://venturebeat.com/2013/11/26/warning-letter-to-23andme-could-be-a-landmark-case-for-health-care/> (“In this particular case, the FDA may have taken issue with 23andMe’s aggressive marketing tactics.”).

201. See, e.g., Pollack—*Walgreens Delays*, *supra* note 13; Shuren—*Statement*, *supra* note 13.

202. See Untitled Letter to Wojcicki, *supra* note 183.

203. Warning Letter to Wojcicki, *supra* note 8. (“[W]e have become aware that you have initiated new marketing campaigns, including television commercials that, together with an increasing list of indications, show that you plan to expand the PGS’s uses and consumer base without obtaining marketing authorization from FDA.”).

ance or approval and the device was therefore both “adulterated” and “misbranded.”²⁰⁴ Thus, “months after [23andMe] submitted [its] 510(k)s and more than 5 years after [it] began marketing,” FDA requested 23andMe to “immediately discontinue marketing the [personal genome service] until such time as it receives FDA marketing authorization for the device”²⁰⁵ or face seizure, injunction, or civil money penalties.²⁰⁶ FDA also stated that 23andMe’s previous premarket clearance submissions were considered withdrawn.²⁰⁷

23andMe immediately penned a press release stating that “[w]e recognize that we have not met the FDA’s expectations regarding timeline and communication regarding our submission. Our relationship with the FDA is extremely important to us and we are committed to fully engaging with them to address their concerns.”²⁰⁸ On December 5, 2013, 23andMe disassembled its health-related offerings on its Web site and stopped providing new customers with health-related genetic information (retroactive to the November 22 date of the Warning Letter), reaffirming its continued commitment to clearing its health-related genetic tests through appropriate FDA processes.²⁰⁹ 23andMe continues to offer ancestry testing and still returns consumers’ raw genetic data without interpretation.²¹⁰

204. *Id.* The Food, Drug, and Cosmetic Act prohibits introduction or delivery for introduction into interstate commerce any device that is adulterated or misbranded. 21 U.S.C. § 331(a). Despite some apparent confusion regarding what FDA meant by requesting that 23andMe cease “marketing” their product (see Michael del Castillo, *Calm Down About 23andMe, the Media Is Getting It Wrong*, UPSTART BUS. J. (Dec. 3, 2013), <http://upstart.bizjournals.com/news/technology/2013/12/03/23andme-website-after-fda-warning.html?page=all> (last visited Dec. 31, 2013) (“Not being able to market is certainly bad for business, but as of now there’s no reason to believe the company has stopped selling it’s [sic] product.”)). “Marketing” in this regulatory context is broader than advertising.

205. See Warning Letter to Wojcicki, *supra* note 8.

206. *Id.*

207. *Id.*

208. *23andMe Statement Regarding FDA Warning Letter*, 23ANDME, <http://media.center.23andme.com/press-releases/fda-letter-2013> (last visited Dec. 31, 2013).

209. See, e.g., *23andMe, Inc. Provides Update*, *supra* note 9 (“We remain firmly committed to fulfilling our long-term mission to help people everywhere have access to their own genetic data and have the ability to use that information to improve their lives Our goal is to work cooperatively with the FDA to provide that opportunity in a way that clearly demonstrates the benefit to people and the validity of the science that underlies the test.”).

210. 23ANDME—*Changes*, *supra* note 167. (“Customers who purchase or have purchased 23andMe’s Personal Genome Service (PGS) on or after November 22, 2013, the date of the Warning Letter from the FDA, will receive ancestry information, as well as their raw genetic data without interpretation.”).

c. *What the Food and Drug Administration Letters Mean for the Industry*

Twenty-four letters into FDA's engagement with DTC genetic testing, several things of import to the industry have become clear. First, in contrast to its tentative first letter to Pathway Genomics stating that their product *appeared* to meet the definition of a medical device,²¹¹ FDA has stated confidently that products such as 23andMe's DTC genetic test *are* devices because their saliva collection kit is an "article"²¹² that is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease . . ." ²¹³ For example, the 23andMe personal genome service was marketed as "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."²¹⁴ In fact, FDA concluded that most of the intended uses for when 23andMe was marketing were medical device uses.²¹⁵

Second, FDA is not going to consider DTC genetic tests marketed to consumers for health-related indications to fall under either the laboratory developed tests/home brew or the research/investigational use only exemptions. Although DTC genetic tests are *in vitro* diagnostic devices,²¹⁶ the original Untitled Letters clearly stated that FDA did not consider the genetic tests to fall under the laboratory developed tests/home brew exemption to regulation.²¹⁷ Scholars have argued that FDA concluded that the genetic tests did not qualify because the genetic data (the As, Ts, Cs, and Gs that make up human DNA) were generated at an outside laboratory, while the corresponding medical information resulting from the interpretation of the genetic material (e.g., that a particular genetic variant was associated with increased consumer risk for diabetes) was done in-house—

211. Letter to Plante, *supra* note 12.

212. Hank Greely, *The FDA Drops an Anvil on 23andMe—Now What?*, CENTER FOR L. & BIOSCIENCES BLOG (Nov. 25, 2013), <http://blogs.law.stanford.edu/lawandbiosciences/2013/11/25/the-fda-drops-an-anvil-on-23andme-%E2%80%93-now-what/> ("A plastic tube for collecting spit doesn't look much like an MRI machine or an implantable left ventricular assist device, but it is an "article" that, from its marketing information, 23andMe "intend[s] for [medical] use."").

213. 21 U.S.C. § 321(h) (2006); Warning Letter to Wojcicki, *supra* note 8.

214. Warning Letter to Wojcicki, *supra* note 8.

215. *Id.*

216. 21 C.F.R. § 809.3 (2009).

217. *See, e.g.*, Letter from Gutierrez to Conde, *supra* note 125 ("You should be aware that FDA does not consider your device to be a laboratory developed test because the KnomeCOMPLETE™ is not developed by and used in a single laboratory.").

thereby constituting a two-step process.²¹⁸ Also, these genetic tests were far from the “relatively simple, well-understood” tests used by physicians and pathologists in their clinical laboratory that inspired the original exemption.²¹⁹ Finding DTC genetic tests to be laboratory developed tests seemingly undermined the policy goals behind the original exemption.²²⁰

Likewise, labeling devices for research or investigational use only, but marketing them to consumers for health-related purposes, is not going to exempt device manufacturers from FDA clearance or approval. Indeed, a year after the Untitled Letters, FDA released guidance confirming that any research or investigational use only product must be labeled “For Research Use Only. Not for use in diagnostic procedures” and has to be noninvasive and low-risk.²²¹ In addition, any research or investigational use only device must “not be used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.”²²² FDA

218. See Palmer, *supra* note 42, at 501–02 (“This distinction seems to emphasize the two-step process used by these services: after the third-party laboratory genotypes a consumer’s sample, the information is then transmitted to the DTC company for interpretation.”).

219. FDA to Host Public Meeting on Oversight of Laboratory-Developed Tests, FDA (June 16, 2010), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm215766.htm>.

220. See Bair, *supra* note 51, at 432 (“To exempt a subset of DTC genetic tests from more comprehensive regulation under the [laboratory developed test] enforcement exception because these tests happen to be developed and performed in the same lab—a feature that has little relation to the broader concerns surrounding DTC genetic testing—while other DTC genetic tests are subject to full regulatory review would constitute both an uneven application of the law and unwise policy.”).

221. FDA—RESEARCH USE ONLY, *supra* note 127, at 6.

222. *Id.* FDA expressed concern that the “use of such tests for clinical diagnostic purposes may mislead healthcare providers and cause serious adverse health consequences to patients, who are not aware that they are being diagnosed with research or investigational products.” *Id.* at 5. In August 2013, the Medical Testing Availability Act was introduced in the House of Representatives as a response to this new draft guidance. This Act would amend the Food, Drug, and Cosmetic Act to state that a product with research use only labeling:

may not be deemed to be misbranded under this Act on the basis that the manufacturer or distributor of the product: (A) sells the product to an end user who uses the product in a manner inconsistent with such statement; or (B) engages in business communications regarding the product with an end user of the product.

Medical Testing Availability Act of 2013, H.R. 3005, 113th Cong. (2013). It was supported strongly by the President and CEO of the Biotechnology Industry Organization (BIO), who issued a press release stating that “Guidance recently released by FDA would make manufacturers responsible for downstream use of a product outside of a manufacturer’s control. FDA’s approach in the [Draft Guidance] is impractical for manufacturers to implement, and threatens patient access to important clinical and research tools that have been used in pathology laboratories for decades . . . to expand the definition of intended use to include

warned that any in vitro diagnostic device *not* intended for research or investigational use only, but labeled as such, would be deemed “misbranded” under the Food, Drug, and Cosmetic Act, potentially triggering heavy penalties.²²³ For example, in its Terms of Service, 23andMe stated that its services “are for research, informational, and educational use only. We do not provide medical advice.”²²⁴ But FDA looked to 23andMe’s marketing, which claimed to provide health reports for “a first step in prevention” enabling users to “take steps toward mitigating serious diseases” to support its conclusion that 23andMe’s genetic test was, in fact, being marketed as a medical device.²²⁵

Also in this research use only guidance, and in turning away from typical drug-marketing policy, FDA clarified that assessing the intent of research or investigational use only in vitro diagnostic device manufacturers would include looking to “the manufacturer’s *knowledge* that its product is offered and used for a purpose for which it is neither labeled nor advertised,” as opposed to only requiring the manufacturer to use appropriate labeling or advertising.²²⁶ This reinforces the position FDA took in 2010, treating Illumina’s Infinium HumanHap550 array (a system of genetic analysis used by deCODE and 23andMe to provide genetic information to their customers) as an independent medical device.²²⁷ In fact, just three days before 23andMe was sent its Warning Letter, FDA announced the clearance of four Illumina next generation sequencing diagnostic devices—including two assays analyzing the *CFTR* gene (detecting mutations and variants associated with cystic fibrosis) and granting *de novo* petitions for Illumina’s sequencer and universal kit that allows laboratories to develop their own diagnostic tests.²²⁸

downstream use of the product outside of a manufacturer’s control ignores legal precedent, and establishes a significant shift in the regulation of product promotion under the Agency’s jurisdiction.” *BIO Praises House for Introducing the Medical Testing Availability Act of 2013*, BIO (Aug. 21, 2013), <http://www.bio.org/media/press-release/bio-praises-house-introducing-medical-testing-availability-act-2013>.

223. FDA—RESEARCH USE ONLY, *supra* note 127, at 6.

224. *Terms of Service*, 23ANDME, <https://www.23andme.com/about/tos/> (last visited Jan. 28, 2013) [hereinafter 23ANDME—*Terms of Service*].

225. Warning Letter to Wojcicki, *supra* note 8.

226. FDA—RESEARCH USE ONLY, *supra* note 127, at 6.

227. *See* Letter to Flatley, *supra* note 186.

228. *FDA Allows Marketing of Four “Next Generation” Gene Sequencing Devices*, FDA (Nov. 19, 2013), <http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm375742.htm> [hereinafter FDA—*FDA Allows Marketing*]. It is worth noting, however, that FDA in its press release did not mention DTC use of the devices and rather focused on giving “physicians the ability to take a broader look at their patients’ genetic makeup and [helping] in diagnosing disease or identifying the cause of symptoms.” *Id.*; Jennifer K. Wagner, *What Does the FDA Approval of*

The third major conclusion from the FDA letters is a related one: that FDA can consider components used together to generate patient-specific medical information to be independent devices.²²⁹ This is true even when components are used to analyze genetic data produced by another company. Thus Illumina, which was marketing products to produce genetic *data*, received an Untitled Letter just as did deCODE, which was producing genetic *information* for consumers.²³⁰

Last, the letters and Illumina clearance offer insight regarding the possible regulatory classification of DTC genetic tests. As discussed above, Illumina recently received FDA “premarket clearance” for two of their cystic-fibrosis-related products and was granted *de novo* petitions for its sequencer and universal kit reagents.²³¹ Pre-marketing clearance is for Class II devices, which require stricter labeling requirements, performance standards, and/or postmarket surveillance than Class I, but which are perceived to be less risky than Class III devices.²³² The fact that two of Illumina’s devices were granted *de novo* petitions also means that Illumina successfully established that its devices, despite being novel and unique with no substantially equivalent predicate, were still low- to moderate-risk and should not have to go through the regulatory burdens of the Class III premarket approval process.

As FDA pointed out in its Warning Letter to 23andMe, however, most of 23andMe’s advertised uses for its personal genome service were not currently classified, and therefore required “premarket approval or *de novo* classification”²³³ This was the process that 23andMe had begun in 2012.²³⁴ FDA stated that, since then, it had spent “significant time” evaluating 23andMe’s intended uses to determine whether its personal genome service should be classified as a Class II or Class III device and even “proposed modifications to the device’s labeling that could mitigate risks and render certain intended uses appropriate for *de novo* classification.”²³⁵ However, FDA stated that 23andMe failed to provide information to support a determina-

the MiSeqDx Platform Mean for DTC?, GENOMICS L. REP. (Dec. 31, 2013), <http://www.genomicslawreport.com/index.php/author/wagjen/>.

229. See Letter to Flatley, *supra* note 186.

230. See *id.*; Letter to Collier, *supra* note 185.

231. See *Illumina’s MiSeqDx™ Receives FDA Premarket Clearance with Two Cystic Fibrosis Assays and Universal Kit for Open Use: Premarket Clearance is an Industry First for Next-Generation Sequencing System*, ILLUMINA (Nov. 19, 2013), <http://investor.illumina.com/phoenix.zhtml?c=121127&p=irol-newsArticle&ID=1878430&highlight=>; FDA—*FDA Allows Marketing*, *supra* note 228.

232. See FDA—*Controls*, *supra* note 137; 21 C.F.R. § 807 (2013).

233. Warning Letter to Wojcicki, *supra* note 8 (italics added).

234. *23andMe Takes First Step Toward FDA Clearance*, *supra* note 15.

235. Warning Letter to Wojcicki, *supra* note 8 (emphasis added). This implies that FDA was considering treating the personal genome service as made up of individual devices that could be regulated accordingly.

tion that its product was substantially equivalent to a legally marketed predicate (i.e., a traditional 510(k) application) or information to support a *de novo* petition (i.e., that there was no predicate device, but it was still low to moderate risk).²³⁶ Thus, FDA informed 23andMe that it was going to consider the entire personal genome service to be a Class III device.²³⁷

B. Federal Trade Commission: Regulation of Advertising and Engagement with the Direct-to-Consumer Genetic-Testing Industry

Although FDA retains authority over the labeling of medical devices, FTC has the power to regulate DTC advertising to ensure that it is not false or misleading.²³⁸ Generally, FTC works to reduce “fraud, deception, and unfair business practices in the marketplace.”²³⁹ While FDA regulates medical device labeling, such as packaging display panels and warnings, FTC retains responsibility for the regulation of nonprescription device advertising.²⁴⁰ FTC will consider an advertisement false if it fails to reveal material facts relevant to its use and consequences.²⁴¹ If a claim relates to public health, it will presumptively be considered material. For example, when POM Wonderful advertising claimed that its product “prevents or reduces the risk of” or “treats” heart disease, prostate cancer, or erectile dysfunction, FTC intervened and barred POM marketers from making claims that their product was “effective in the diagnosis, cure, mitigation, treatment, or prevention of any disease.”²⁴²

DTC genetic tests, by definition, are available to the public without a prescription—thus their advertising falls under the FTC’s jurisdiction. In 2006, in conjunction with FDA and CDC, FTC released a cautionary consumer pamphlet regarding “At Home Genetic Tests.”²⁴³ In this release, FTC educated consumers about the complicated basis for genetic medical claims, pointing out that diseases typically are caused by interactions between genes and environmental factors, and that consumers should be cautious in assuming that the tests are clinically

236. *Id.*

237. *Id.*

238. *Who We Are*, FTC, <http://www.ftc.gov/bcp/> (last visited Nov. 3, 2013) [hereinafter FTC—*Who We Are*]; 15 U.S.C. § 52 (2006).

239. *Id.*

240. Memorandum of Understanding Between the Fed. Trade Commission and the Food and Drug Admin., FDA (Apr. 27, 1971), *available at* <http://www.fda.gov/AboutFDA/PartnershipsCollaborations/MemorandaofUnderstandingMOUs/DomesticMOUs/ucm115791.htm>.

241. 15 U.S.C. § 55(a)(1) (2006).

242. In the matter of Pom Wonderful LLC, F.T.C. Docket No. 9344, 2012 WL 2340406 (F.T.C.) (May 17, 2012); Irick, *supra* note 169, at 317.

243. FTC—*Consumer Alert*, *supra* note 98.

valid.²⁴⁴ In addition, FTC recommended that consumers discuss any DTC results with a healthcare professional, as genetic test results are “complex and serious,” and medical decisions should not be based on “incomplete, inaccurate, or misunderstood information.”²⁴⁵ Finally, FTC warned consumers that while FDA generally confirms the safety and effectiveness of home-use medical tests, FDA had not reviewed any DTC *genetic* test or evaluated the accuracy of any claims.²⁴⁶

In January 2014, FTC also filed a complaint against GeneLink, Inc. and Foru International Corporation, which both sold nutritional supplements and skincare products allegedly tailored to consumers’ DNA.²⁴⁷ FTC alleged that these companies represented that their custom-blended nutritional supplements “1) effectively compensate for genetic disadvantages identified by [their] DNA assessments, thereby reducing an individual’s risk of impaired health or illness, and 2) treat or mitigate diabetes, heart disease, arthritis, and insomnia”²⁴⁸ (both of which are nutrigenetic claims similar to the ones that GAO investigated in 2006).²⁴⁹ For example, in a monthly news letter, Foru (formerly GeneWize) highlighted a “top leader” who claimed that six months after he began taking the product “[his] blood sugar [had] stabilized . . . and [his] diabetic problem [was] over, while a recent medical report [had] revealed the reduction of [his] heart to normal size.”²⁵⁰ Supplements and skin repair serum through these companies cost more than \$100 per month.²⁵¹ The FTC found GeneLink, Inc. and Foru International Corporation’s claims to be false and misleading and published consent agreements for final approval that prohibited the companies from making any such health benefit, performance, or health efficacy claims in the future unless they are substantiated by reliable scientific evidence.²⁵²

FTC’s power to regulate DTC marketing compliments FDA’s oversight over DTC labeling and clinical validity. Coming on the heels of

244. *See id.*

245. *Id.*

246. *See id.*

247. Complaint at 1–2, *In re GeneLink, Inc. & Foru Int’l Corp.*, No. 112-3095 (F.T.C. Jan. 7, 2014).

248. GeneLink, Inc.; Foru™ International Corporation; Analysis of Proposed Consent Orders to Aid Public Comment, 79 Fed. Reg. 2,662, 2,663 (Jan. 15, 2014).

249. GAO—2006, *supra* note 90.

250. Complaint at 8, *In re GeneLink, Inc. & Foru Int’l Corp.*, No. 112-3095 (F.T.C. Jan. 7, 2014).

251. *Companies Pitching Genetically Customized Nutritional Supplements Will Drop Misleading Disease Claims; GeneLink, Inc. and Former Subsidiary Also Agree to Improved Safeguards of Consumers’ Sensitive Medical Information*, FTC (Jan. 7, 2014), <http://www.ftc.gov/news-events/press-releases/2014/01/companies-pitching-genetically-customized-nutritional-supplements>.

252. GeneLink, Inc.; Foru™ International Corporation; Analysis of Proposed Consent Orders to Aid Public Comment, 79 Fed. Reg. 2,662, 2,664 (Jan. 15, 2014).

FDA's Warning Letter to 23andMe, FTC's foray into prosecuting companies for violating its regulations creates a potentially powerful governmental partnership.

C. Centers for Medicare and Medicaid Services and the Clinical Laboratory Improvement Amendments

In addition to FDA and FTC, CMS has jurisdiction to protect consumers who obtain DTC genetic testing through enforcement of CLIA, a law that requires certification of laboratories that analyze human specimens to "report patient specific results"²⁵³ regarding "information for the diagnosis, prevention, or treatment of any disease."²⁵⁴ CLIA focuses on the quality control and assurance of laboratory testing and assurance of analytic validity (how well a test recognizes a genetic variant). CLIA does not, however, address clinical validity (the association of a variant with a disease or medical condition) or clinical utility (whether the information regarding a disease or medical condition can be of clinical use to a consumer)²⁵⁵ or review laboratory marketing or communications.²⁵⁶

CLIA divides tests into three levels: tests that are so straightforward they receive a waiver, tests of moderate complexity, and tests of high complexity.²⁵⁷ Tests of moderate and high complexity must establish "performance specifications" for tests that ensure precision, analytical sensitivity and specificity, and other characteristics "required for test performance."²⁵⁸ Through CLIA, CMS requires laboratories to "ensure that their test results are accurate, reliable, timely, and confidential and do not present the risk of harm to patients."²⁵⁹

253. 42 C.F.R. § 493.3(b)(2) (2003).

254. 42 C.F.R. § 493.2 (2003). CLIA was first passed in 1967 in response to the variability of clinical testing upon which healthcare professionals based medical treatment decisions. They were updated in 1988 after an exposé in the Wall Street Journal covering inadequate oversight of test results such as Papanicolaou tests (i.e., "pap smears"). See, e.g., Walt Bogdanich, *Lax Laboratories: The Pap Test Misses Much Cervical Cancer Through Labs' Errors*, WALL ST. J., Nov. 2, 1987. For further discussion, see Hutt, *supra* note 125, at 6–7.

255. U.S. Nat'l Library of Med., *How Can Consumers Be Sure a Genetic Test Is Valid and Useful?*, GENETICS HOME REFERENCE, <http://ghr.nlm.nih.gov/handbook/testing/validtest> (last visited Jan. 6, 2013); see also Matthew Piehl, *Regulating Hype and Hope: A Business Ethics Model Approach to Potential Oversight of Direct-to-Consumer Genetic Tests*, 16 MICH. ST. U. J. MED. & LAW 59, 75, 76 (2011) ("CLIA, then, only governs the conduct of the laboratory, not the accuracy of the results obtained by the test. CLIA merely ensures that the laboratory conducts the genetic test in a scientifically valid and reliable manner.").

256. See Piehl, *supra* note 255, at 75.

257. 42 C.F.R. § 493.5 (2003).

258. 42 C.F.R. § 493.1253 (2003).

259. *Id.* § 493.1253(b)(2)(vii). While CMS, with the help of CDC, provides compliance guidance to laboratories, they do not provide specific protocols. See, e.g., SACGHS—2008, *supra* note 99, at 3.

Generally, moderate or high complexity tests must adhere to a proficiency-testing program—a process by which a laboratory’s genetic tests are compared to, and measured against, an established external standard—“considered to be the most rigorous form of performance assessment currently available.”²⁶⁰ CLIA lays out detailed proficiency testing requirements for these specialties and subspecialties in its regulations.²⁶¹

Genetic testing generally falls under CLIA’s purview as it analyzes human specimens to report patient specific results regarding diagnosis of disease. 23andMe, for example, performs its genotyping in LabCorp’s CLIA-certified laboratory. 23andMe still labeled its health reports, however, as “intended for research and educational purposes only, and . . . not for diagnostic use.”²⁶² Its “health reports” Web site, before being pulled down, included the warning that “tests have not been cleared or approved by the FDA but have been analytically validated according to CLIA standards.”²⁶³

While CLIA requires a testing request from an “authorized person” (who is also the only person allowed to receive the test results),²⁶⁴ this authorized person needs only be “authorized under State law to order tests or receive test results.” It need not be a healthcare professional²⁶⁵ and could be a DTC company or an individual. Therefore, CLIA certified laboratories may, state law permitting, run testing and return results directly to consumers.²⁶⁶

Scholars have voiced several concerns about CLIA’s capacity to ensure valid DTC genetic testing. First, much like the focus of FDA’s premarket clearance 510(k) process, CLIA’s main goal is to ensure analytic validity. However, a significant concern about genetic testing is not whether the test itself is performed correctly, but whether the test

260. SACGHS—2008, at 4.

261. 42 C.F.R. § 493.801(b) (1992).

262. 23ANDME—Health Reports, *supra* note 71.

263. *Id.* (“The information on this page is intended for research and educational purposes only, and is not for diagnostic use.”).

264. 42 C.F.R. §§ 493.1241, 493.1291 (2003).

265. 42 C.F.R. § 493.2 (2003); *see also* Palmer, *supra* note 42, at 503 (stating that the authorized person need not be a physician).

266. Palmer, *supra* note 42, at 504. CDC also plays a role regarding genetic testing. In 2004, it created the Evaluation of Genomic Applications in Practice and Prevention to act as an independent advisory working group to “establish and assess a ‘systematic, evidence-based process for evaluating genetic tests and other applications of genomic technology that are in transition from research to clinical and public health practice’” with a goal of providing “objective, timely, and credible information that is clearly linked to available scientific evidence” to “distinguish genetic tests that are safe and useful.” Jessica D. Gabel, *Redeeming the Genetic Groupon: Efficacy, Ethics, and Exploitation in Marketing DNA to the Masses*, 81 Miss. L.J. 363, 422 (2012). Following the Evaluation of Genomic Applications in Practice and Prevention recommendations, however, is not mandatory for CLIA-certified laboratories. *Id.*

is *clinically* valid and the results are *clinically* useful.²⁶⁷ For example, the recognition of a genetic variant on the *BRCA1* or *BRCA2* gene is not the same as establishing its relationship to a heightened risk of breast cancer. Analytic validity is therefore a necessary, but not sufficient, step toward ensuring clinical validity—a test that satisfies the highest analytic standards might nevertheless produce genetic information that is inaccurate if the association between the genetic variant and clinical manifestation of disease is not strong.²⁶⁸ CLIA, however, does nothing to ensure the clinical validity or utility of particular concern for genetic medical information.²⁶⁹

Another limitation of CLIA is that while genetic testing is generally considered to be highly complex, there is no proficiency genetic-testing subspecialty recognized.²⁷⁰ Thus, while a laboratory that performs genetic testing is required to “establish and maintain the accuracy of its testing procedures,”²⁷¹ any detailed proficiency requirements are absent.²⁷² Agencies and specialty committees have been calling for the establishment of a genetic-testing specialty since 1997, but in 2006 CMS publically stated it was no longer pursuing that option.²⁷³

267. Palmer, *supra* note 42, at 511.

268. Bair, *supra* note 51, at 428 (CLIA “does not address situations, often encountered in DTC genetic health tests, where a test may be performed correctly, but the results themselves are misleading. This could occur, for example, if a test is based on weak association data or is valid only for a specific ethnic group”).

269. Palmer, *supra* note 42, at 511.

270. See Am. Soc’y of Human Genetics Bd. of Dirs., ASHG Statement on Direct-to-Consumer Genetic Testing in the United States, 81 AM. J. HUMAN GENETICS 635, 636 (2007).

271. 42 C.F.R. § 493.801(a)(2)(ii) (1992).

272. A Laboratory might therefore meet the accuracy requirements in a number of ways, including “conducting its own statistical tests of patient results or comparing its test results with another lab.” Bair, *supra* note 51, at 427.

273. In 1997, an NIH and Department of Energy joint Task Force on Genetic Testing began the call, later taken up by both CDC and the Advisory Committee. See Neil A. Holtzman, *Promoting Safe and Effective Genetic Tests in the United States: Work of the Task Force on Genetic Testing*, 45 *Clinical Chemistry* 732, 736 (1999); SACGHS—2008, *supra* note 99, at 13. Of particular relevance to the DTC testing industry is a 2011 CMS-proposed rulemaking with the goal of amending CLIA to specify that laboratories must provide access to identifiable completed test reports at a patient’s (or consumer’s) request. While the Health Insurance Portability and Accountability Act’s [HIPAA] Privacy Rule currently exempts CLIA laboratories from the requirement that test reports must be returned to individuals upon request, this proposed rule would revoke that exemption—giving individuals “the right to receive their test reports directly from laboratories.” CLIA Program and HIPAA Privacy Rule; Patients’ Access to Test Reports, 76 *Fed. Reg.* 56,712, 56,712 (Sept. 14, 2011).

D. Patent and Trademark Office and the Association for Molecular Pathology v. Myriad Genetics, Inc.

A recent decision by the Supreme Court, *Association for Molecular Pathology v. Myriad Genetics*,²⁷⁴ limited the ability of PTO to grant patents on human genetic material. Patents held on genetic material threatened the business models of DTC companies, many of which claimed to provide interpretation of variants that were subject to patent. The Supreme Court's decision removed a potential barrier to DTC large-scale genetic testing and genomic sequencing.

Section 101 of the Patent Act defines patentable subject matter as “any new and useful *process*, machine, manufacture, or *composition of matter*, or any new and useful improvement thereof . . .”²⁷⁵ Genetic patents generally fall into two main categories: (1) composition of matter claims and (2) process, or “method,” claims.²⁷⁶ Composition of matter patents for genetic material generally claim physically isolated DNA molecules.²⁷⁷ Molecules that were not isolated using human intervention, however, already exist in nature and therefore fall outside the scope of patent-eligible material. Although genetic patents cover the physically isolated DNA molecule, they do not permit exclusive use of the meaning of the information contained therein.²⁷⁸

A method patent, by contrast, covers a specific way of doing something.²⁷⁹ For example, a method patent could cover the particular steps required to analyze whether a particular genetic variant gives rise to physical symptoms of disease. Method patents are considered less protective than composition of matter patents because they are infringed only if another party replicates *every step* of the method described—even one alteration is enough to avoid infringement.²⁸⁰ Composition claims are considered more protective as they are harder for others to innovate around.²⁸¹ Myriad Genetics held both method and composition of matter claims related to the *BRCA* genes (variants of which are associated with breast and cervical cancer); although others were able to test particular cancer drugs in ways that avoided Myriad's method claims, Myriad claimed that any tests or procedures

274. *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2017 (2013).

275. 35 U.S.C. § 101 (2006) (emphasis added).

276. See W. Nicholson Price II, *Does Whole Genome Sequencing Circumvent Gene Patents?*, BIO IT WORLD (Dec. 10, 2012), <http://www.bio-itworld.com/2012/12/10/does-whole-genome-sequencing-circumvent-gene-patents.html> [hereinafter Price—*Gene Patents*].

277. *See id.*

278. *See id.*

279. John Conley, *Some Thoughts on Myriad After the Supreme Court Argument*, GENOMICS L. REP. (May 1, 2013), <http://www.genomicslawreport.com/wp-content/plugins/as-pdf/generate.php?post=12729>.

280. *See id.*

281. *See id.*

that involved isolating *BRCA* genes infringed on its composition of matter patent.²⁸²

Although Myriad Genetics holds one of the most widely recognized genetic patents, it is by no means alone in patenting genetic material. One estimate claimed that twenty to thirty percent of the human genome was patented before *Myriad* was decided.²⁸³ 23andMe itself holds a patent on “Polymorphisms associated with Parkinson’s disease,”²⁸⁴ which claims a method of screening individuals for susceptibility to Parkinson’s disease.²⁸⁵

Scholars and practitioners have expressed concern about the advisability of granting patents on genetic material from a public policy perspective. In its report entitled *Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests*, the Advisory Committee (discussed in subsection II.C.2 of this Article) found that “patents on genetic discoveries do not appear to be necessary for either basic genetic research or the development of available genetic tests” and that “patents have been used to narrow or clear the market of existing tests, thereby limiting, rather than promoting availability of testing.”²⁸⁶ In addition, “when there is a patent-enforcing sole provider, patients cannot obtain independent second-opinion testing, and sample sharing as a means of ensuring the quality of testing is not possible.”²⁸⁷ Moreover, because the federal government is a major funder of basic genetic research, it found that “the prospect of patent protection of a genetic research discovery does not play a significant role in motivating scientists to conduct genetic research.”²⁸⁸

The Advisory Committee also pointed out ways that patents can restrict consumer access to genetic tests. It noted that more than fifty private and public entities offer testing for cystic fibrosis under a non-exclusive license,²⁸⁹ and more than fifty academic and commercial

282. *See id.*

283. *See* Tia Ghose, *6 Ways Gene Patent Case Could Impact Biotechnology*, LIVE SCI. (Apr. 15, 2013), <http://www.livescience.com/28731-gene-patent-supreme-court-implications.html>.

284. *See* Dan Vorhaus, *Patenting and Personal Genomics: 23andMe Receives Its First Patent, and Plenty of Questions*, GENOMICS L. REP. (June 1, 2012), <http://www.genomicslawreport.com/index.php/2012/06/01/patenting-and-personal-genomics-23andme-receives-its-first-patent-and-plenty-of-questions/>.

285. It is based on variants in eight particular regions of the genome and generates a prognosis based on analyzing those genetic variants in consideration with an individual’s family history, diet, exercise, and medical history. *See id.*

286. Letter from Steven Teutsch, M.D., Current Chair, SACGHS, to The Hon. Kathleen Sebelius, Sec’y, Dep’t of Health and Human Servs. (Mar. 31, 2010), in SACGHS—GENE PATENTS, *supra* note 110 [hereinafter Letter from Teutsch to Sebelius—March, 2010].

287. *Id.*

288. SACGHS—GENE PATENTS, *supra* note 110, at 1.

289. *Id.* at 2.

laboratories offer genetic testing for Huntington's disease under a non-exclusive license.²⁹⁰ When companies successfully enforce their exclusive rights over a genetic variant, as had been the case with genetic tests for breast cancer, there is often only one company providing the genetic test to the public.²⁹¹ The Advisory Committee therefore concluded that "the presence of multiple laboratories offering competing genetic testing for the same condition can also lead to improvements in the overall quality of testing through innovation in developing novel and more thorough techniques of testing."²⁹²

Beyond the particular policy considerations about patent claims are concerns about whether and to what extent patents on genetic material could discourage companies from offering large-scale testing and genomic sequencing and correspondingly hamper advances expected to arise from continued analysis of the relationship between genetic data and medical information.²⁹³ Because genomic sequencing involves determining the sequence of the whole genome, many were concerned that such sequencing violated the many thousands of patents on isolated DNA molecules.²⁹⁴ Some noted that if "gene patents are broadly upheld, a company that wants to sequence someone's entire genome, rather than just a few genes, could in theory have to pay a fee, or 'toll,' to the patent holders for each of those patented genes"²⁹⁵—an outcome that could severely limit the ability of DTC companies to stay in business or keep genomic testing affordable. The Advisory Committee also expressed concern that the "substantial number of existing patents on genes and methods of diagnosis also pose a threat to the development of . . . whole-genome sequencing . . ."²⁹⁶

Attorneys in the *Myriad* case, however, "disagreed vigorously about whether [genomic sequencing] would infringe Myriad's patents."²⁹⁷ Some argue that because composition of matter claims patent "isolated" genetic material (which they must do to be patentable in the first place), and because most genomic sequencing does not actually isolate particular DNA sequences, genomic sequencing does not actually infringe on the "composition of matter" patent claims.²⁹⁸ Be-

290. *Id.*

291. *Id.*

292. *Id.* at 4.

293. See Price—*Gene Patents*, *supra* note 276.

294. See *id.*; see also W. Nicholson Price II, *Unblocked Future: Why Gene Patents Won't Hinder Whole-Genome Sequencing and Personalized Medicine*, 33 CARDOZO L. REV. 1601 (2012) [hereinafter Price—*Unblocked Future*] (noting that the violation of many patents was a major concern surrounding genomic sequencing).

295. Ghose, *supra* note 283.

296. Letter from Teutsch to Sebelius—March, 2010, *supra* note 286.

297. Price—*Unblocked Future*, *supra* note 294, at 1605.

298. See Price—*Gene Patents*, *supra* note 276.

cause next-generation sequencing techniques do not locate “isolated” DNA molecules,²⁹⁹ and because previous techniques generally read strands of DNA too short to be covered by most genetic patents,³⁰⁰ genomic sequencing was not thought to infringe on patents covering isolated portions of genetic material.

The Supreme Court evaluated the patenting of genetic material in 2013 with the *Myriad* case.³⁰¹ The Court was faced with the question of “whether a naturally occurring segment of DNA is patent eligible under 35 U.S.C. §101 by virtue of its isolation from the rest of the human genome.”³⁰² Myriad Genetics, the company holding the patents at issue, had identified the exact location of the *BRCA1* and *BRCA2* genes on chromosomes 17 and 13. Three mutations on these genes in particular are associated with an increased risk of cervical and breast cancer. Knowing how to identify the *BRCA1* and *BRCA2* genes allowed Myriad Genetics to establish what an *unaffected* genetic sequence would look like—which enabled them to create a test to recognize a sequence *affected* by the any of the three mutations.³⁰³ Myriad Genetics then applied for and received a number of patents giving rise to several different composition claims.³⁰⁴ The practical effect of Myriad Genetics’ patents and claims was to “give it the exclusive right to isolate an individual’s *BRCA1* and *BRCA2* genes”³⁰⁵ and hold a virtual monopoly over genetic tests intended to recognize mutations associated with breast and cervical cancer.

To determine whether these patents were legitimate, the Court had to answer the question of whether Myriad Genetics had patented any “new and useful . . . composition of matter”³⁰⁶ or whether PTO had incorrectly allowed the patenting of a naturally occurring substance. The Court noted that it “is undisputed that Myriad [Genetics] did not create or alter any of the genetic information encoded in the *BRCA1* and *BRCA2* genes.”³⁰⁷ The Court recognized that Myriad Genetics had “found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention. Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry.”³⁰⁸ The Court recognized the “considerable danger that the grant of patents would ‘tie up’ the use of such

299. *See id.*

300. *See id.*

301. *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2017 (2013).

302. *Id.* at 2111.

303. *Id.* at 2112.

304. *Id.* at 2113.

305. *Id.* “[P]atents would also give Myriad the exclusive right to synthetically create BRCA cDNA.” *Id.*

306. 35 U.S.C. § 101 (2006).

307. *Myriad*, 133 S. Ct. at 2116.

308. *Id.* at 2117.

[genetic-testing] tools and thereby ‘inhibit future innovation premised upon them’³⁰⁹ and held that “a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.”³¹⁰

Within hours of the Supreme Court’s decision, a number of companies and academic laboratories announced that they would offer breast and cervical cancer genetic testing at a lower price than the \$4000 charged by Myriad Genetics.³¹¹ Several weeks later, however, Myriad Genetics sued two of these competitors—Ambry Genetics and Gene By Gene³¹²—claiming that the genetic testing nevertheless infringed on Myriad Genetics remaining patents not invalidated by the Supreme Court.³¹³ In February 2014, Myriad Genetics and Gene By Gene settled, with Gene by Gene agreeing to cease selling or marketing *BRCA* testing alone or in gene panels in North America. Under the agreement, Gene by Gene can continue to sell and market its genome, exome, and custom array products—which all include variants for *BRCA 1* and *BRCA 2*.³¹⁴

E. State Law’s Regulation of Direct-to-Consumer Genetic Testing

In addition to federal agencies and case law, state laws could also add a diversity of protections to DTC genetic testing. Twenty-five states either prohibit or limit DTC testing in CLIA laboratories, ad-

309. *Id.* at 2116.

310. *Id.* at 2111. The Court also held, however, “that cDNA is patent eligible because it is not naturally occurring.” *Id.* This is so because “the natural creation of mRNA involves splicing that removes introns, the synthetic DNA created from mRNA also contains only the exon sequences. This synthetic DNA created in the laboratory from mRNA is known as complementary DNA (cDNA).” *Id.* at 2112. Because cDNA is not a “product of nature,” it is patent eligible. *Id.* at 2119. The Court did explicitly note however that it had not deliberated or decided upon “the patentability of DNA in which the order of the naturally occurring nucleotides has been altered,” as “[s]cientific alteration of the genetic code presents a different inquiry,” and expressed no opinion about its patentability. *Id.* at 2120. *Myriad* therefore leaves open the possibility of patenting highly engineered strands of DNA and raises questions about the patentability of DNA that has been trivially altered in nonnatural ways. See Claire Laporte et al., *So Now What? Implications of the Supreme Court’s Myriad Ruling*, FOLEY HOAG LLC (June 17, 2013), <http://www.foleyhoag.com/publications/alerts-and-updates/2013/june/implications-of-the-supreme-court-myriad-ruling>.

311. Andrew Pollack, *2 Competitors Sued by Genetics Company for Patent Infringement*, N.Y. TIMES, July 10, 2013, at B3.

312. *Id.*

313. *Id.* Going forward, Myriad has announced that it will expand operations in Europe relying not on its patents, “but on its proprietary database of associations between gene variants and clinical outcomes.” Conley, *supra* note 279.

314. *BRCA Patent Owners and Gene by Gene, Ltd. Resolve Suit*, MYRIAD (Feb. 7, 2014), investor.myriad.com/releasedetail.cfm?ReleaseID=824154.

ding an additional layer of constraint.³¹⁵ For example, some states have their own laboratory analytic validity assurances, requiring that laboratories follow both the federal CLIA standards as well as additional state requirements. Washington and New York state are at least partially exempt from federal standards as their own regulations either meet or exceed protections provided by CLIA.³¹⁶

In addition to enhanced CLIA protections, thirteen states completely prohibit DTC genetic testing.³¹⁷ Another twelve states limit consumer access to DTC testing in some respect,³¹⁸ such as by prohibiting DTC testing of all but a few exempted tests (e.g., cholesterol or pregnancy tests)³¹⁹ or limiting the ordering of testing and return of results to licensed healthcare professionals or persons performing official duties.³²⁰ 23andMe, for example, has responded to these state restrictions by stating on its Web site that, while it is “authorized to ship sample collection kits” to the state of New York, it cannot process saliva collected in or mailed from the state. It suggests that consumers “collect [their] sample[s] and mail [them] from outside the state of New York” and “affirm under penalty of law that the sample[s] for the saliva kit ha[ve] not been collected in or mailed from the state of New York.”³²¹

Several federal agencies, including FDA, FTC, and CMS, in conjunction with case and state law, can help ensure that DTC genetic testing is valid, reliable, and of clinical use to consumers. FDA, how-

315. See GENETICS & PUB. POLICY CTR., JOHNS HOPKINS UNIV., SURVEY OF DIRECT-TO-CONSUMER TESTING STATUTES AND REGULATIONS 1–14 (2007), available at <http://www.dnapolicy.org/resources/DTCStateLawChart.pdf>.

316. *CLIA Certificate of Waiver Fact Sheet*, CDC, <http://www.cdc.gov/hiv/testing/lab/clia/> (last visited Jan. 6, 2014).

317. These states include Alabama, Connecticut, Georgia, Hawaii, Idaho, Kentucky, Michigan, New Hampshire, Pennsylvania, Rhode Island, South Carolina, Tennessee, and Wyoming. GENETICS & PUB. POLICY CTR., JOHNS HOPKINS UNIV., *supra* note 315.

318. These states include Arizona, California, Colorado, Florida, Illinois, Maine, Maryland, Massachusetts, Nevada, New Jersey, New York, and Oregon. See *id.*

319. See, e.g., CAL. BUS. & PROF. CODE § 1246.5 (Parker 2013) (“The tests that may be conducted pursuant to this section are: pregnancy, glucose level, cholesterol, occult blood, and any other test for which there is a test for a particular analyte approved by the federal Food and Drug Administration for sale to the public without a prescription in the form of an over-the-counter test kit.”).

320. See, e.g., N.Y. COMP. CODES R. & REGS. tit. 10, § 58-1.7 (2000) (“[A] clinical laboratory shall examine specimens only at the request of licensed physicians or other persons authorized by law to use the findings of laboratory examinations in their practice or the performance of their official duties.”).

321. *Is the 23andMe Service Available in the State of New York?*, 23ANDME, <https://customer.care.23andme.com/entries/23150752-Is-the-23andMe-service-available-in-the-state-of-New-York-> (last visited Nov. 3, 2013).

ever, is currently the agency that has engaged most extensively with the industry and also appears to be the best-positioned in terms of regulatory oversight and administrative structure to exert influence over it going forward. The remainder of this Article will therefore focus on FDA's options and challenges in regulating DTC genetic testing.

IV. REGULATING BIFURCATED DIRECT-TO-CONSUMER GENETIC-TESTING ENTITIES

With the clearance of the Illumina sequencing devices, the 23andMe Warning Letter, and 23andMe's current hiatus from the DTC genetic health-related information market, the state of DTC genetic testing changed dramatically at the end of 2013. But there was already a new genetic interpretation platform waiting in the wings. Even before November 2013, two distinct new types of entities had begun to emerge—those that provide genetic data (the As, Ts, Cs, and Gs in an individual's genome) and those that interpret the genetic material to produce medical information (informing consumers of disease-related risks, personalized responses to medicine and ancestry, and other biomedical information). Both of these types of entities pose serious challenges to FDA's current regulatory structure. While FDA has stated that producing genetic data alone (presumably without the intent that that data will be used to create medical information—such as when Illumina was providing genetic data for 23andMe to interpret in 2010)³²² will not be considered a device under the Food, Drug, and Cosmetic Act, the medical claims resulting from genetic interpretation most likely will, thereby posing unique hurdles for regulators.

A. The Bifurcation of Direct-to-Consumer Genetic-Testing Entities

Following FDA's initial round of DTC genetic-testing Untitled Letters, a number of entities that had previously provided DTC data and interpretation services modified their business models. Many DTC genetic-testing companies, such as the DTC branch of deCODE, went out of business.³²³ Other companies, like Pathway, transitioned to a model that required a physician-intermediary.³²⁴ Some newer companies, however, began selling bifurcated products—offering either genetic data or interpretation-only services.³²⁵

322. See Letter to Flately, *supra* note 186.

323. DECODEME, <http://www.decodeme.com/> (last visited Nov. 3, 2013) (“Sales of Genetic Scans direct to consumer through deCODEme have been discontinued!”).

324. FAQs, PATHWAY GENOMICS, <https://www.pathway.com/about-us/faqs> (last visited Nov. 3, 2013).

325. DNA DTC, GENE BY GENE LTD., GENE BY GENE LAUNCHES DNA DTC (Nov. 29, 2012), available at <http://www.genebygene.com/pdf/gbglaunchesdttc.pdf>.

In November 2012, Gene By Gene, Ltd. announced its new DNA DTC branch offering “highly reliable and competitively priced genomic testing solutions to institutional customers as well as to the Direct-to-Consumer market.”³²⁶ DNA DTC notes, however, that “data analysis” is not included in the package—that it is selling “raw data” or only the genomic sequence.³²⁷ While other companies, such as 23andMe, had allowed consumers to download their genetic data *in addition* to offering analysis services,³²⁸ DNA DTC’s emergence in the market is the first time that a leading DTC company has offered a product without any related medical interpretation.³²⁹ In addition, after its Warning Letter, 23andMe has scaled back to just offering raw genetic data without health-related interpretation (and ancestry information).³³⁰ For the majority of consumers, however, a file of As, Ts, Cs, and Gs does not provide helpful information—data services require a parallel offering of interpretation-only services to provide a marketable product.³³¹

One example of this type of interpretation-only service is *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.”³³² *openSNP* is an open-source project and is compatible with genetic data from 23andMe, deCODEme, or FamilyTreeDNA.³³³ Con-

326. *Id.* DNA DTC priced its genomic sequencing at \$6995. A minimum order of three samples is required. Products, DNA DTC, <http://www.dnadt.com/products.aspx> (last visited Nov. 3, 2013) [hereinafter DNA DTC—Products].

327. *Id.*

328. *How Do I Find My Raw Data?*, 23ANDME, <https://customercare.23andme.com/entries/21729836-How-do-I-find-my-raw-data-> (last visited Nov. 3, 2013). 23andMe performs “genotyping” as opposed to sequencing services and thus does not offer “genomic” data. *See, e.g., What’s the Difference Between Genotyping and Sequencing?*, 23ANDME CUSTOMER CARE, <https://customercare.23andme.com/entries/21262606-What-is-the-difference-between-genotyping-and-sequencing-> (last visited Jan. 3, 2013).

329. *See* Vorhaus—DNA DTC, *supra* note 17.

330. 23ANDME—Changes, *supra* note 167 (“Customers who purchase or have purchased 23andMe’s Personal Genome Service (PGS) on or after November 22, 2013, the date of the Warning Letter from the FDA, will receive ancestry information, as well as their raw genetic data without interpretation.”).

331. *See* Vorhaus—DNA DTC, *supra* note 17.

332. OPENSNP, <http://opensnp.org/> (last visited Nov. 3, 2013). In addition, Promethease offers a report of medical information derived from genomic data. It offers a free report or a five-dollar report with several enhancements. *Promethease/Features*, SNPEDIA, <http://www.snpedia.com/index.php/Promethease/Features> (last visited Nov. 3, 2013).

333. OPENSNP, *supra* note 332. There are other available programs that allow a user to upload data derived from a source requiring a physician order, e.g., Illumina’s 99-cent MyGenome app for the iPad. Illumina, Inc., *MyGenome*, iTUNES, <https://itunes.apple.com/us/app/mygenome/id516405838?mt=8> (last visited Nov. 3,

sumers can upload their genetic data into *openSNP*, even if generated by a DTC company that only provides ancestry analysis (like the current 23andMe offering), for interpretation free of charge.³³⁴ Promethease, a tool used to build a personalized genetic medical information report “based on *SNPedia* and a file of genotypes,”³³⁵ offers another free basic report and an enhanced report for five dollars.³³⁶ These interpretation services do not require access to the biological specimen from which the original data was generated.³³⁷

B. Regulating Entities Producing Genetic Data

As discussed in Part III of this Article, FDA has jurisdictional authority to regulate products “intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease”³³⁸ Genetic data in the hands of a layperson cannot diagnose, cure, mitigate, treat, or prevent disease in and of itself.³³⁹ Expertise required to convert such data into medical information can require “molecular and computational biologists, geneticists, pathologists and physicians with exquisite knowledge of the disease and of treatment modalities, research nurses, genetic counselors, and IT and systems support specialists, among others.”³⁴⁰ Also, it is possible that the *intended* use of providing genetic data might be for strictly ancestral purposes or for no specific stated purpose at all, depending on how a company marketed and sold the instrument, which

2013). MyGenome only allows consumers to explore a genome sequenced by the Illumina Clinical Services Laboratory (which requires a physician order). *Individual Genome Sequencing (IGS) for Patients/Guardians*, ILLUMINA, http://www.illumina.com/clinical/illumina_clinical_laboratory/igs_for_patients.ilmn (last visited Nov. 3, 2013). See, e.g., *Ancestry*, 23ANDME, <https://www.23andme.com/ancestry/> (last visited Nov. 3, 2013); *Take a More Active Role in Managing Your Health*, 23ANDME <https://www.23andme.com/health/> (last visited Nov. 3, 2013) (this portion of the Web page has since been taken down in response to FDA’s November 22, 2013 Warning Letter to 23andMe). FamilyTreeDNA markets its data for ancestry use but produces identical genetic data to those used for medical purposes. FAMILYTREEDNA, <http://www.familytreedna.com/> (last visited Nov. 3, 2013).

334. *Frequently Asked Questions*, OPENSNP, <http://opensnp.org/faq> (last visited Nov. 3, 2013).

335. *Promethease*, SNPEDIA, <http://snpedia.com/index.php/Promethease> (last visited Nov. 3, 2013).

336. *Promethease/Features*, *supra* note 332.

337. Palmer, *supra* note 42, at 510.

338. *Is the Product a Medical Device?*, FDA, http://www.fda.gov/medicaldevices/device_regulationandguidance/overview/classifyyourdevice/ucm051512.htm (last visited Feb. 18, 2013).

339. As discussed in Part III of this Article, devices are “intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease.” *Id.*

340. Elaine R Mardis, *The \$1,000 Genome, the \$100,000 Analysis?*, 2 GENOME MED. 84, 84 (2010).

likely would fall outside of the current understanding of the definition of a medical device.

In the press release announcing DNA DTC, Gene By Gene President Bennett Greenspan described its new branch as for “investigators exploring the cutting edge of research to pioneer and enhance treatment of disease, enhance quality of life, break new ground in genealogical inquiry and otherwise advance the science of genomics.”³⁴¹ This description could be construed to sound as if DNA DTC data is being marketed for researchers to interpret and use in the diagnosis, treatment, or prevention of disease; however, DNA DTC’s understated Web site makes no such claims.³⁴² The Web site also states that the genomic data it provides is for “research use only,”³⁴³ although, as discussed above, if DNA DTC has *knowledge* that its product is being used for diagnostic purposes, it will be considered “misleading” under the Food, Drug, and Cosmetic Act.³⁴⁴

If DNA DTC’s research use only labeling holds up to scrutiny, however, it appears that FDA will remain uninvolved. FDA representatives have stated that if companies that just provide raw genetic data “don’t make any medical claims about that data, then they’re free to provide information as far as we’re concerned.”³⁴⁵

C. The Challenges of Regulating Entities That Provide Genetic Information

Unlike DTC genetic data services, which are unlikely to fall under FDA regulations both because they do not meet FDA’s definition of a device and because FDA representatives have disclaimed an interest in regulating them, FDA *has* regulated companies’ interpretations of medical claims based on genetic data generated by a different laboratory.³⁴⁶ Regulation of this type requires locating the source of jurisdictional authority, which, in this new type of case, must be done by reasoning analogically to other areas in which FDA has already regulated. Any attempts at FDA regulation will also have to contend with the formidable First Amendment challenges associated with limiting the free speech of Internet-based genetic interpretation services that do not charge the consumer.

341. DNA DTC, GENE BY GENE LTD., *supra* note 325.

342. DNA DTC, <http://www.dnadt.com/> (last visited Nov. 3, 2013).

343. *Id.*

344. See FDA—RESEARCH USE ONLY, *supra* note 127, at 10.

345. Carmichael—DNA Dilemma, *supra* note 191.

346. Letter from Gutierrez to Conde, *supra* note 125.

1. *Regulating DTC Web-Based Genetic Interpretation Services:
In Search of an Analogy*

As discussed in section IV.B of this Article, FDA has considered medical information from companies that only interpret genetic data from an outside laboratory to be a medical device.³⁴⁷ DTC Web-based genetic interpretation services, however, pose new challenges to FDA's regulatory position. In seeking to regulate these new interpretation services, FDA will likely look to analogous areas where it has chosen either to regulate products as medical devices or to exercise regulatory discretion (by not enforcing its regulations against violators). Areas that raise similar concerns as DTC Web-based genetic interpretation—and which therefore might serve as a locus of jurisdictional authority—include WebMD, mobile medical devices, and software applications.

a. *WebMD's Symptom Checker*

Entities that interpret genetic data, providing an information-only product without testing biological samples, might—at first glance—appear analogous to medical Web-based information generated by, for example, WebMD's "Symptom Checker." Both are online portals that allow users to input specific pieces of information and receive health-related medical information in return. Both are widely accessible (a consideration taken into account when FDA considers classification risk): Sixty million unique users visit WebMD-related sites every month, and DTC genetic-testing services were similarly widely available online until recently.³⁴⁸ And both give rise to the possibility that individuals will make medical decisions on the basis of medical information generated without clinician involvement (WebMD users report user-generated content on sites has a "strong impact on their health or . . . treatment decisions,"³⁴⁹ and FDA cited the concern that the public might make medical decisions on the basis of DTC genetic test results as a motivation for enforcement of their regulations³⁵⁰). But while FDA sent DTC genetic-testing entities Untitled and Warning Letters requiring clearance or approval as a medical device, the seemingly analogous WebMD has been unregulated as a device and, in fact,

347. *Id.*

348. Wayne Gattinella, President & CEO, WebMD Health Corp., *Testimony on the Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools* 1 (Nov. 12, 2009), available at <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM193440.pdf>.

349. *Id.*

350. Letter from Gutierrez to Conde, *supra* note 125.

has partnered with FDA on its Web site to assist the FDA in its mission to “protect and promote your health.”³⁵¹

Some scholars have argued that there is a distinction under the Food, Drug, and Cosmetic Act between products for the diagnosis of disease and products for general “wellness.”³⁵² Indeed there are many different kinds of software applications available online, some through the federal government, that are not considered devices but calculate patient-specific risks based on standard epidemiological analysis.³⁵³ As discussed above, FDA regulates medical devices on the basis of the intent of the manufacturer. If health information is presented with the intent to *educate*, rather than diagnose or treat, it will not be regulated as a device—even if consumers use the information to self diagnose.³⁵⁴ WebMD’s Symptom Checker states (in grey font that a user must scroll down to see): “This tool does not provide medical advice. It is intended for informational purposes only. It is not a substitute for professional medical advice, diagnosis or treatment. Never ignore professional medical advice in seeking treatment because of something you have read on the WebMD Site”³⁵⁵ Recall, however, that 23andMe in its terms of service (in black font that was bolded) stated that its products were “for research, informational, and educational use only. We do not provide medical advice.”³⁵⁶ But FDA based its

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351. *Protect Your Health: Food, Medical Product & Cosmetic Safety*, WEBMD, <http://www.webmd.com/fda/default.htm> (last visited Nov. 3, 2013).
352. BRADLEY MERRILL THOMPSON ET AL., MHEALTH REGULATORY COALITION, A CALL FOR CLARITY: OPEN QUESTIONS ON THE SCOPE OF FDA REGULATION OF MHEALTH 9 (2010), available at <http://mhealthregulatorycoalition.org/wp-content/uploads/2013/07/mrcwhitefinal122210.pdf>.
353. See, e.g., *Risk Assessment Tool for Estimating Your 10-year Risk of Having a Heart Attack*, NAT’L HEART, LUNG, & BLOOD INST., NAT’L INST. HEALTH, <http://cvdrisk.nhlbi.nih.gov/> (last visited Jan. 1, 2014); Joe Pickrell, *Should the FDA Regulate the Interpretation of Traditional Epidemiology?*, GENOMES UNZIPPED: PUB. PERS. GENOMICS (Feb. 12, 2013), <http://www.genomesunzipped.org/2013/12/should-the-fda-regulate-the-interpretation-of-traditional-epidemiology.php> (last visited Jan. 1, 2013) (“[A]ll of the scientific points made about risk prediction from 23andMe (the models are not very predictive, they’re missing a lot of important variables, there are likely errors in measurements, etc.) of course apply to traditional epidemiology as well. Ultimately, I think a lot rides on the question: what is the aspect of 23andMe that sets them apart from these websites and makes them more suspect? Is it because they focus on genetic risk factors rather than ‘traditional’ risk factors (though note several of these sites ask about family history, which of course implicitly includes genetic information)? Is it the fact that they’re a for-profit company selling a product? . . . Is it because some genetic risk factors (like BRCA1) have strong effects, while standard epidemiological risk factors are usually of small effect? Or is it something else?”).
354. Alex Krouse, *Note, iPads, iPhones, Androids, and Smartphones: FDA Regulation of Mobile Phone Applications As Medical Devices*, 9 IND. HEALTH L. REV. 731, 756 (2012).
355. *WebMD Symptom Checker*, WEBMD, <http://symptoms.webmd.com/#introView> (last visited Nov. 3, 2013).
356. 23ANDME—*Terms of Service*, *supra* note 224.

jurisdictional analysis on 23andMe's marketing and intent for the information, which, it concluded, was to enable users to "take steps toward mitigating serious diseases."³⁵⁷ It appears, therefore, that FDA has interpreted WebMD to fall under this general wellness exemption, but it is unlikely to be the model for regulation of DTC genetic-interpretation services.

b. Mobile Medical Devices

FDA has recently focused on regulating the mobile medical application market, releasing draft guidance for products that meet the definition of a medical device but are also either "used as an accessory to a regulated medical device, or transform[] a mobile platform into a regulated medical device."³⁵⁸ This definition includes software applications that "can be executed . . . on a mobile platform, or a web-based software application that is tailored to a mobile platform but is executed on a server."³⁵⁹ Similar to the reasoning discussed in the WebMD context, FDA has carved out an exemption from regulation for information provided by a mobile medical application for "general health and wellness" not intended for diagnosing or treating a specific disease.³⁶⁰ But, FDA has expressed specific interest in regulating mobile applications that allow users to "input patient-specific information [such as 'patient-specific lab results'] and—using formulae or a processing algorithm—output a patient-specific result, diagnosis, or treatment recommendation that is used in clinical practice or to assist in making clinical decisions."³⁶¹

DTC Web-based genetic interpretation platforms such as *openSNP* and *Promethease* most likely will not fit the narrow definition of a mobile medical device presented in the draft guidance. Neither program transforms a mobile platform itself into a medical device (such as an application that turns an iPhone into a cardiac event monitor that the consumer can press to his or her chest),³⁶² and neither is tailored to a mobile platform (although they can be accessed on a mobile device).³⁶³ Despite the fact that they do not appear to fall under the mobile medical application draft guidance, however, DTC Web-based

357. Warning Letter to Wojcicki, *supra* note 8.

358. FDA, DRAFT GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF: MOBILE MEDICAL APPLICATIONS 7 (2011), available at <http://www.fda.gov/downloads/MedicalDevices/. . ./UCM263366.pdf>.

359. *Id.*

360. *Id.* at 11.

361. *Id.* at 19.

362. Nathan Cortez, *The Mobile Health Revolution?* (SMU Dedman Sch. of L., Legal Studies Research Paper No. 128, 2013), available at http://papers.ssrn.com/sol3/papers.cfm?abstract_id=2284448##.

363. Both Web sites can be retrieved on a mobile platform but are only available as full Web sites as opposed to tailored mobile platforms.

genetic-interpretation entities provide services that raise many of the same concerns as mobile medical applications—including the input of patient-specific laboratory results that lead to patient-specific results using formulae.

c. Software Applications

Although DTC Web-based genetic interpretation entities are unlikely to be regulated as mobile medical applications specifically, FDA also regulates software generally. FDA first expressed an interest in regulating software beginning in 1987, in the wake of several software-related radiation deaths. At the time, FDA promulgated draft guidance entitled *FDA Draft Policy for the Regulation of Computer Products*.³⁶⁴ FDA subsequently withdrew this guidance in 2005.³⁶⁵

In its 2010 Untitled Letters to Knome and 23andMe, FDA informed these entities that they were diagnostic devices given that they were software programs analyzing genetic data “generated by an external laboratory in order to generate a patient specific test report.”³⁶⁶ Based upon existing genetic data, *openSNP* and Promethease conduct interpretation and produce patient-specific medical information. Like Knome and 23andMe, because these new DTC Web-based genetic interpretation platforms perform the same function as companies previously receiving Untitled and Warning Letters and produce patient-specific results rather than provide mere general health and wellness information, FDA would most likely consider them to be diagnostic medical devices.³⁶⁷

2. First Amendment Challenges to Regulation

A serious attempt by FDA to regulate DTC genetic interpretation services is likely to come under First Amendment scrutiny. Recently, in *Washington Legal Foundation v. Friedman* in D.C., FDA challenged the applicability of the First Amendment to its regulation of “off-label”

364. Draft Policy for the Regulation of Computer Products, 52 Fed. Reg. 36,104 (Sept. 25, 1987).

365. In 2005, FDA released new guidance on 510(k) submissions for software “contained in” medical devices, although it appears that this guidance will not apply to genomic interpretation entities because the software they use is not “contained in” a medical device—it is the medical device. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY AND FDA STAFF: GUIDANCE FOR THE CONTENT OF PREMARKET SUBMISSIONS FOR SOFTWARE CONTAINED IN MEDICAL DEVICES 2 (2005), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf>.

366. Letter from Gutierrez to Conde, *supra* note 125.

367. Likewise, as they use data generated from an outside laboratory, they would also not fall under the laboratory developed test exemption. For more discussion, see Palmer, *supra* note 42, at 513.

speech (speech that promotes the use of drugs or devices in ways that have not been specifically approved by FDA) on two grounds that could both apply to the regulation of DTC Web-based genetic interpretation services. In *Friedman*, FDA attempted to characterize its guidance on off-label speech as a restriction on *conduct* rather than speech.³⁶⁸ The D.C. Circuit was “highly skeptical” of the agency’s position,³⁶⁹ noting that off-label *speech* is “only ‘conduct’ to the extent that moving one’s lips is ‘conduct.’”³⁷⁰ FDA also argued that the First Amendment does not apply when speech “occurs in an area of extensive government regulation.”³⁷¹ The Court also rejected this argument.

The scope of FDA’s ability to regulate speech in these cases often turns on whether or not the speech at issue is considered “commercial.”³⁷² If a regulated entity’s speech *is* considered commercial, FDA has greater power to ensure that the speech is not false or misleading. FDA can also compel particular speech, impose prior restraints, and limit even accurate speech.³⁷³ If the speech is *not* considered commercial, FDA is subject to much stricter limitations as to what extent speech can be limited.³⁷⁴

In recent years, FDA has faced considerable difficulty when confronted by First Amendment challenges to its attempts at regulating commercial speech.³⁷⁵ In *Thompson v. Western States Medical Center*,³⁷⁶ the Supreme Court struck down a provision of the Food and Drug Modernization Act that exempted compounding pharmacies from certain provisions of the Food, Drug, and Cosmetic Act *provided* that pharmacies did not advertise or promote their products. The provision was found to place an unconstitutional restriction on commercial speech.³⁷⁷ In *Pearson v. Shalala*,³⁷⁸ the D.C. Circuit held that FDA’s outright ban on proposed health claims made by dietary supple-

368. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 59 (D.D.C. 1998).

369. Krista Hessler Carver, A *Global View of the First Amendment Constraints on FDA*, 63 FOOD & DRUG L.J. 151, 182 (2008).

370. *Friedman*, 13 F. Supp. 2d at 59.

371. *Id.* at 60.

372. For a discussion of this issue, see Nathan Cortez, *Can Speech by FDA-Regulated Firms Ever Be Noncommercial?*, 37 AM. J. L. & MED. 388 (2011) [hereinafter Cortez—*Noncommercial*].

373. *See id.* at 388.

374. *Id.*

375. For a more extensive look at the First Amendment challenges that FDA has faced and for an argument that “many of the agency’s speech-related policies violate the First Amendment,” see Gerald Masoudi & Christopher Pruitt, *Food and Drug Administration v. The First Amendment: A Survey of Recent FDA Enforcement*, 21 HEALTH MATRIX 111 (2011).

376. 535 U.S. 357 (2002).

377. *Id.* at 371–77.

378. 164 F.3d 650 (D.C. Cir. (1999)).

ment manufacturers failed constitutional commercial speech scrutiny.³⁷⁹ And in the recent decision *United States v. Caronia*,³⁸⁰ the Second Circuit held that the First Amendment protects the truthful promotion of a drug, even for medical indications not specifically approved by FDA and included on the labeling, and that the government cannot prosecute speech about an FDA-approved product—even if the product is being promoted for something FDA did not specifically clear (e.g., a sales representative is allowed to promote an FDA-approved drug for the treatment of insomnia as a treatment for narcolepsy).³⁸¹

The test for determining whether speech should be considered “commercial” and receive less robust constitutional protections was first established in *Bolger v. Youngs Drug Products*.³⁸² *Bolger* defines commercial speech as speech that either proposes a commercial transaction or speech that satisfies a three-prong test.³⁸³ Speech proposes a commercial transaction when it states, for example, “I will sell you the X . . . at the Y price.”³⁸⁴ The three-prong test asks:

1. Whether speech is an “advertisement?”³⁸⁵
2. Whether the speech at issue refers to a “specific product?”³⁸⁶ and
3. Whether the speaker has an “economic motivation” for engaging in the speech?³⁸⁷

Speech satisfying all three factors will be considered commercial. It is not clear, however, whether speech satisfying only one or two of those factors would be.³⁸⁸

The case of *Washington Legal Foundation v. Friedman*—considering FDA’s regulation of off-label speech—provides an instructive comparison for any analysis of how a court might assess whether DTC genetic interpretation services should be considered commercial. In its analysis, the D.C. Federal District Court found that the off-label

379. *Id.* at 651–52, 658.

380. 703 F.3d 149 (2d Cir. 2012).

381. *Id.*

382. 463 U.S. 60, 66–67 (1983).

383. *Id.* at 66–67; *see also* Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 761 (1976) (serving as a precursor to *Bolger*). *Bolger v. Youngs Drug Prods.*, 463 U.S. 60, 66–67 (1983).

384. *Va. State Bd. of Pharmacy*, 425 U.S. at 761.

385. *Bolger*, 463 U.S. at 66–67.

386. *Id.*

387. *Id.*

388. *See, e.g., id.* at 60, 67 (1983) (noting that none of the factors by themselves would “compel the conclusion that they are commercial speech”); *see also* Masoudi & Pruitt, *supra* note 375, at 121 (“Speech fulfilling all three of these factors will almost surely be considered commercial, but it is unsettled whether speech meeting only one or two of these factors will be considered commercial in nature.”). At least one scholar has noted that economic motivation alone is insufficient to consider speech commercial. *See* Carver, *supra* note 369, at 170.

speech at issue proposed a commercial transaction because the speech “suggest[s] that a physician should prescribe—and a consumer will therefore purchase—the subject drug.”³⁸⁹ The Court also concluded that each of the *Bolger* factors was satisfied. First, the off-label speech was found to fall under a broad definition of “advertisement”—a definition that included materials that “call[] public attention to [the product] . . . so as to arouse a desire to buy.”³⁹⁰ Second, the off-label speech at issue was found to refer to a specific product because the manufacturers only distributed reprints of articles that specifically discussed their products.³⁹¹ Third, the off-label speech was found to have an “economic motivation” because the materials were distributed in hopes of increasing sales.³⁹² Accordingly, because each of the factors was satisfied, the Court found that the off-label speech at issue should be considered commercial.

It is unlikely that some DTC genetic-interpretation services would similarly be considered commercial speech. FDA would have difficulty arguing that services like *openSNP*, which allows users to access Web-based genetic interpretation services *free of charge*, are commercial. *openSNP* likely does not propose a commercial transaction;³⁹³ it interprets data that has been uploaded by the user. *openSNP*'s Web site also most likely would not be considered an “advertisement,” as there is nothing available for purchase. In addition, *openSNP* is not economically motivated as a “speaker” (recognizing the inherent ambiguity of that term as applied to an open-source online platform), as it provides a free service. Lastly, although the speech at issue refers to a specific product, it is unlikely that satisfying this factor alone would be sufficient to render *openSNP*'s DTC Web-based genetic-interpretation service “commercial.”³⁹⁴

In 1976, the Supreme Court, in *Virginia State Board of Pharmacy v. VA Citizens Consumer Council*, recognized that even commercial speech warrants some First Amendment protection and found that the public's interest in commercial speech might be “as keen, if not keener by far” than its interest in political debate.³⁹⁵ The Court expressed a strong preference for disclosure as opposed to suppression of informa-

389. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 64 (D.D.C. 1998).

390. *Id.*

391. *Id.*

392. *Id.*

393. *Frequently Asked Questions*, *supra* note 334 (“We take the ‘open’ in openSNP serious, so everything is free of charge.”).

394. Such services propose a commercial transaction: the speech could be considered an advertisement under the broader *Friedman* definition, the speech at issue refers to a specific product, and the speaker has an economic motivation. For-profit interpretation services that charge a fee for the interpretation of large-scale genetic sequences are more likely to be considered commercial.

395. Va. State Bd. of Pharmacy v. Va. Citizens Consumer Council, Inc., 425 U.S. 748, 763 (1976).

tion³⁹⁶ and expressed “disdain for arguments that audiences cannot comprehend truthful information.”³⁹⁷ Accordingly, the Court struck down a state law ban against the advertising of prescription drug prices.³⁹⁸

Thus, to the extent the speech of DTC Web-based genetic interpretation services is—however unlikely—considered commercial, regulations on such speech would be evaluated in accordance with a case decided later that same year. In *Central Hudson Gas Electric Corp. v. Public Service Central Hudson*, the Supreme Court again considered the First Amendment’s protections for commercial speech.³⁹⁹ *Central Hudson* articulates a four-part test for determining whether and how commercial speech can be regulated constitutionally.⁴⁰⁰

The first prong of *Central Hudson* requires determining whether the commercial speech at issue is inherently false or misleading.⁴⁰¹ Commercial speech that is inherently misleading—that cannot be made nonmisleading by disclaimers or qualifying language or that “experience has proved [to be] subject to abuse”⁴⁰²—can be banned outright.⁴⁰³ Commercial speech that is only potentially misleading should be regulated using less restrictive means, such as disclaimers.⁴⁰⁴ The first prong also allows the government to regulate commercial speech if the underlying subject matter concerns an activity that is, itself, illegal.⁴⁰⁵ For example, the Supreme Court upheld a ban on commercial sex-based employment listings in a newspaper.⁴⁰⁶

The second prong asks whether the government can assert a substantial interest in regulating the speech in question,⁴⁰⁷ meaning that the speech at issue poses a real, rather than hypothetical, harm.⁴⁰⁸ The government can generally satisfy this requirement with ease, as courts have found a wide range of interests sufficiently “substantial.”⁴⁰⁹ In the context of FDA regulation of commercial speech, the

396. *Id.* at 769–70.

397. Carver, *supra* note 369, at 171.

398. *Va. State Bd. of Pharmacy*, 425 U.S. at 748.

399. See Cortez—*Noncommercial*, *supra* note 372, at 389.

400. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 566 (1980).

401. *Id.*

402. See Carver, *supra* note 372, at 172 (citing *In re R.M.J.*, 455 U.S. 191, 203, 206–07 (1982)).

403. *In re R.M.J.*, 455 U.S. at 203.

404. *Va. State Bd. of Pharmacy*, 425 U.S. 748.

405. *Pittsburgh Press Co. v. Human Relations Comm’n*, 413 U.S. 376, 388–89 (1973).

406. *Id.* at 389.

407. *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm’n*, 447 U.S. 557, 566 (1980).

408. Courts have found that the government has not satisfied this requirement in only a handful of cases. *Friedman v. Rogers*, 440 U.S. 1, 12–17 (1979).

409. For a description of government interests that the Supreme Court has classified as “substantial” and for the handful of instances in which the Court has not found this prong to be satisfied, see Carver, *supra* note 369, at 173.

government's interest in preserving the new *drug* application approval process—analogue to the Class III *device* approval process—was considered substantial by the Supreme Court,⁴¹⁰ as was the government's interest in protecting the public health and guarding against deceptive market practices.⁴¹¹

The third *Central Hudson* prong asks whether the government's regulation directly advances this substantial interest.⁴¹² The government must show that its regulation directly and consistently advances its goals,⁴¹³ that the regulation alleviates harm to a material degree, and that the connection between the two does not consist of "mere speculation or conjecture."⁴¹⁴ The regulation of speech must also be both consistent and rational.⁴¹⁵ The Supreme Court has generally upheld limitations on speech where the government presented such justificatory evidence.⁴¹⁶

The fourth and final prong of the test asks whether the regulation is both narrowly tailored and restricts no more speech than is necessary.⁴¹⁷ In other words, "regulating speech must be a last, not first, resort."⁴¹⁸ The fourth prong is not satisfied if "numerous and obvious less-burdensome alternatives" exist.⁴¹⁹ In the several instances in which FDA has sought to ban speech outright, rather than requiring a disclaimer or pursuing other means of regulating speech, courts have generally found that FDA's restrictions fail this prong. This failure renders the FDA restrictions unconstitutional and unenforceable.⁴²⁰

Again, the *Friedman* case is instructive as to how a court would apply the *Central Hudson* test in the context of DTC genetic interpretation services. With regard to FDA's restriction on off-label speech, FDA argued that the speech at issue failed the inherently-false or misleading prong of *Central Hudson* both because the speech itself was illegal and because the safety and efficacy claims lacked FDA ap-

410. *See* *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 362–65 (2002).

411. *Pearson v. Shalala*, 164 F.3d 650, 655–56 (D.C. Cir. 1999).

412. *Cent. Hudson Gas*, 447 U.S. at 566.

413. *See* *Carver*, *supra* note 369, at 174.

414. *Edenfield v. Fane*, 507 U.S. 761, 770–71 (1993).

415. *See* *Carver*, *supra* note 369, at 174.

416. *See id.*

417. *Cent. Hudson Gas*, 447 U.S. at 566.

418. *Thompson v. W. States Med. Ctr.*, 535 U.S. 357, 373 (2002).

419. *City of Cincinnati v. Discovery Network, Inc.*, 507 U.S. 410, 418 n.13 (1993).

420. *See, e.g., Thompson*, 535 U.S. at 373 (noting that FDA's guidance exempting compounding drugs from certain regulations provided that they do not advertise failed the fourth prong of the *Central Hudson* test because the government did not justify its failure to seek alternative means of regulation); *Pearson v. Shalala*, 164 F.3d 650, 657–58 (D.C. Cir. 1999) (holding that the government's refusal to adopt a disclaimer policy caused it to fail prong four and that the fourth prong could not be satisfied "when the government chooses a policy of suppression over disclosure—at least where there is no showing that disclosure would not suffice to cure the misleadingness").

proval, which rendered the claims inherently misleading. The D.C. Federal District Court rejected both of these claims, noting that the underlying activity to which the speech pertained—physician prescription of an off-label use—was decidedly legal⁴²¹ and found that the speech was not otherwise inherently misleading.⁴²² As is generally the case, the Court found the government satisfied the second prong, concluding that the government's interest in providing incentives for obtaining new drug approval was "substantial." The Court did, however, reject FDA's claimed interest in ensuring that physicians receive accurate information as a paternalistic notion that physicians, "a sophisticated audience, cannot evaluate the validity of promotional materials."⁴²³ The Court found prong three—the requirement that the restriction directly advance the government's asserted interest—satisfied because mandating that manufacturers promote their products "on label" encouraged them to pursue additional FDA approval for any other indications for which they wished to promote their products.⁴²⁴ But the Court found the policy to fail prong four (requiring that regulations restrict no more speech than is necessary)⁴²⁵ because FDA completely banned off-label speech—rather than considering less-restrictive measures, such as disclaimers—and thus the Court held FDA's enforcement unconstitutional.

Applying the *Central Hudson* test to DTC Web-based genetic interpretation, it appears that any attempts by FDA to regulate or restrict genetic interpretation would likely fail if FDA attempted to ban the speech entirely—but could succeed if FDA merely required a disclaimer stating that the medical information presented is not evaluated or approved by FDA. Although FDA could likely establish a substantial interest in the speech, satisfying prong two (either by asserting an interest in preserving its medical device approval process or in protecting the public health), FDA might have difficulty satisfying prong one. Certainly, FDA would be unable to prove that the speech pertained to an illegal activity—interpreting genetic data is currently legal; FDA might, however, succeed in showing that the interpretive services are misleading if provided directly to a consumer who has limited ability to understand the complex medical information being conveyed. Satisfaction of the third and fourth prong would depend on the specific type of regulation that FDA proposed. Any proposed ban on the speech of entities that interpret genetic data would likely fail prong four; more narrowly tailored approaches, however, could survive constitutional scrutiny.

421. *Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 66 (D.D.C. 1998).

422. *Id.* at 67.

423. *See Carver, supra* note 369, at 183–84 (citing *Friedman*, 13 F. Supp. 2d at 69–71).

424. *Friedman*, 13 F. Supp. 2d at 71–72.

425. *Id.* at 73–74.

Thus, if DTC Web-based genetic interpretation platforms are not considered commercial speech, any regulation would be subject to strict scrutiny, the most stringent standard of judicial review. Oft described as “strict in theory, fatal in fact,”⁴²⁶ strict scrutiny could pose a barrier to speech regulation that FDA would have difficulty overcoming. When laws target noncommercial speech, the government must demonstrate: (1) a compelling interest and (2) that the restriction advances that interest using the least-restrictive means available.⁴²⁷ Although the second factor under strict scrutiny addresses the same concerns as prong four under *Central Hudson*’s test for commercial speech, courts are generally more tolerant of restrictions on commercial speech.⁴²⁸ Accordingly, if the speech of DTC Web-based genetic-interpretation entities was not considered commercial (a distinct possibility for entities that provide such services at no cost), FDA would face serious difficulties in regulating it.

V. RISK-BASED REGULATION OF ENTITIES THAT INTERPRET GENETIC INFORMATION

As discussed in subsection III.A.1 of this Article, FDA’s device regulation structure imposes a classification system based on perceived risk. The higher the anticipated risk, the more involved FDA clearance or approval of the device becomes. In 2008, the Advisory Committee recommended that FDA use a risk-based approach for assessing genetic testing,⁴²⁹ and other scholars have supported a “risk stratification” approach to DTC genetic testing where FDA would classify and regulate lower-risk tests differently than higher-risk tests.⁴³⁰ The classification status of DTC genetic testing is currently unclear—FDA representatives have noted that a genetic test for a benign trait such as baldness, for example, would be considered a Class I device, if considered a device at all;⁴³¹ 23andMe had been working with FDA on Class II premarket clearance filings for its personal genome service;⁴³² and most recently, FDA informed 23andMe in its Warning Letter that its personal genome service was going to be considered to fall under Class III.⁴³³

426. See, e.g., *Wittmer v. Peters*, 87 F.3d 916, 918 (7th Cir. 1996).

427. See, e.g., *Reno v. ACLU*, 521 U.S. 844, 868–70 (1997).

428. See *Cortez—Noncommercial*, *supra* note 372, at 391 (citing Nat Stern, *In Defense of the Imprecise Definition of Commercial Speech*, 58 MD. L. REV. 55, 65 (1999)).

429. SACGHS—2008, *supra* note 99, at 174.

430. McGuire et al., *supra* note 69, at 182.

431. Rita Rubin, *FDA Groups Genetic Tests with Medical Devices, Requiring Approval*, USA TODAY (June 14, 2010), http://usatoday30.usatoday.com/news/health/2010-06-15-genetic-testing15_ST_N.htm.

432. See, e.g., Warning Letter to Wojcicki, *supra* note 8.

433. *Id.*

But, as the DTC genetics industry moves from discrete genetic tests to large-scale genetic and genomic interpretation, a test-by-test assessment of the clinical validity of every association with every gene becomes untenable. First, assessing the medical implications of every genetic variant for safety and effectiveness through either the premarket clearance or approval process would be impossible. Even if FDA began such a byzantine task, by the time it finished its review, scientific knowledge would have evolved and would require FDA to evaluate related medical claims anew.⁴³⁴ Second, if FDA treats large-scale genetic and genomic interpretation as a single device (as FDA was possibly implying by informing 23andMe that its personal genome service “is in Class III”), each piece of medical information might be required to follow the controls required of the riskiest piece of medical information produced. This would require treating findings of a predisposition to baldness the same as genetic mutations correlated with Huntington’s disease.

Instead of treating the interpretation of much of or all of one’s genome as a single device, FDA could pursue regulation of the interpretation of large-scale genetic testing or genomic sequencing as a compilation of smaller devices—an approach it was possibly working toward with 23andMe before FDA issued its Warning Letter. FDA could classify each variant associated with a medical condition (or group of variants associated with a medical condition) on the basis of its individual risk and register, clear, and/or approve the test for each variant on its own merits. This would allow FDA to target the medical interpretations that it feels carry the highest risk (e.g., those associated with breast cancer) for oversight, while allowing lower-risk interpretations (e.g., those associated with the soapy taste of cilantro) to be accessible to consumers with less regulatory involvement.

VI. CONCLUSIONS AND IMPLICATIONS

Since its advent in 2007, DTC genetic testing has raised increasingly complex regulatory and policy issues for the industry and regulators alike. For years, FDA exercised discretion and did not enforce its device regulations against DTC genetic-testing entities. FDA only intervened when one DTC genetic-testing company considered selling its product directly to customers in brick-and-mortar stores. FDA then sent Untitled Letters to a number of DTC companies. Subsequently, many DTC genetic-testing companies stopped testing altogether or required physician involvement. In November 2013, FDA sent its first DTC genetic-testing Warning Letter to 23andMe, one of the few remaining providers of DTC genetic data and interpretation, prompting the company to cease its health-related marketing indefi-

434. See Beaudet & Javitt, *supra* note 42.

nately. While some companies had developed bifurcated services previously and had begun offering either genetic data *or* interpretation, the fact that a leader in the DTC genetic-testing industry currently provides only raw genetic data (and ancestry-related information) might steer more consumers to open-source genetic-interpretation platforms—exacerbating potential regulatory challenges.⁴³⁵

Entities that provide genetic data for research use only likely do not fit within FDA's definition of a device and will probably remain unregulated by FDA. The consequences of not regulating entities that provide genetic data are not particularly significant in terms of risk to consumers alone, as the data are unlikely to harm consumers who do not also receive corresponding medical information. Moreover, concerns about the analytic validity of genetic data fall within the jurisdiction of CMS and CLIA and so can be regulated accordingly.

However, entities that provide genetic interpretation and corresponding information to consumers can reveal more sensitive medical information about an individual's propensity to develop disease and pharmacogenomic information about the efficacy of particular drugs given a particular genetic makeup—which places these services within FDA's definition of a device. Recently, many of these interpretation services have developed as open-source, Web-based platforms that interpret genetic data free of charge. First Amendment challenges might thwart FDA's attempts to regulate these entities.

The need for federal involvement continues to be publically recognized. From the Advisory Commission of 2008⁴³⁶ to the Presidential Commission for the Study of Bioethical Issues in 2013,⁴³⁷ federal advi-

435. In fact, some scholars in the arena have called for researchers to provide research participants access to their raw genetic data to, among other things, give participants the option of independent analysis. Jeantine E. Lunshof, George M. Church & Barbara Prainsack, *Raw Personal Data: Providing Access*, 343 *SCIENCE* 373, 373–74 (2014). While discussing this article in a “Live Chat,” John Wilbanks, the Vice President of Science at Science Commons, pointed out that following this recommendation is another potential avenue for raw data entering the hands of potential consumers directly: “Part of why I believe in [providing genetic research participants with their raw data] is that I think that it’s going to . . . accelerate the transition from data, to information, to knowledge, to wisdom When the data are really clustered in the hands of a small group of people . . . there’s no pressure to create better tools . . . to make that transition more accurate, more user-friendly, more pleasant, and more distributive [I]f a lot of people have raw data, that creates a market—that creates a market for startups, that creates a market for publishers, and that creates a market for healthcare providers.” John Wilbanks, *Live Chat: Do You Have a Right to Your Personal Data?*, *SCIENCE* (Jan. 28, 2014, 3:00 PM) <http://news.sciencemag.org/health/2014/01/live-chat-do-you-have-right-your-personal-data>.

436. SACGHS—2008, *supra* note 99, at 2.

437. *See* ANTICIPATE AND COMMUNICATE, *supra* note 5 at 105 (“Federal agencies should continue to evaluate regulatory oversight of direct-to-consumer health services to ensure safety and reliability.”).

sory panels have called for effective regulation of DTC genetic testing. Several important lessons regarding this regulation can be gleaned from the relationship between the industry and FDA over the past four years in particular. FDA will treat DTC genetic tests as medical devices, and they will not fall under the laboratory developed test exemption, or be protected by research use only labeling, if being marketed or knowingly provided to companies for device indications. FDA will treat individual components, such as data, as a medical device if knowingly sold to generate patient-specific information by downstream manufacturers. And while FDA appears willing to consider the most appropriate classification for DTC genetic tests on a case-by-case basis, not validating individual tests might leave manufacturers with their entire service classified as highest risk and requiring premarket approval.

While FDA will face unique challenges engaging with the DTC genetic *interpretation* industry, regulating large-scale genetic and genomic interpretation similarly not as a single device, but as a compilation of genetic medical claims, could allow FDA to effectively target discrete genetic tests on the basis of risk to the consumer. By treating large-scale genetic and genomic interpretation as a compilation of discrete genetic tests, lessons learned from past FDA engagement can be applied to address the most concerning aspects of DTC genetic testing without allowing the unique characteristics of the evolving field to overwhelm the quality assurances already in place, and without prohibiting direct consumer access to valid and useful genetic information.