# 23andMe and the FDA: Negotiating Conceptions of Benefit in the Direct-to-Consumer Genetic Testing Regulatory Debate

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## Abstract

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The oversight and regulation of the direct-to-consumer (DTC) genetic testing industry has been a perennial topic of policy discussion since the emergence of the field in the early 2000s. Despite claiming authority to regulate genetic tests under the 1976 Medical Device Amendments, the U.S. Food and Drug Administration (FDA) had historically exercised enforcement discretion over the industry and not subjected the majority of genetic tests to premarket review. The DTC genetic testing industry was born into an environment of regulatory uncertainty, with stakeholders calling variously for more comprehensive federal oversight and for the minimization of regulatory burdens in order to facilitate innovation. In 2010, the FDA notified DTC genetic testing firms of its intent to regulate the genetic testing services as medical devices, enabling the agency to require premarket review to ensure the safety and effectiveness of the health-related genetic tests. Using tools drawn from discourse analysis and discourse tracing, I examined how stakeholders have framed the benefits and risks of direct-to-consumer genetic testing in justifying the need for – and proposed structure of – regulatory oversight, focusing on the interaction between the FDA and a leading DTC company, 23andMe. My analysis traced the regulatory negotiations, which culminated in a November 2013 FDA Warning Letter to 23andMe which effectively halted the firm's ability to return health-related genetic testing results to their consumers. While 23andMe have framed the benefit of their services in terms of consumer autonomy, empowerment, the potential for disease prevention, and an individual's right to access her own genetic information, many clinicians and researchers have approached

the potential benefit of DTC testing with more skepticism, advocating for an evidence-based evaluation of benefits and harms. FDA's enforcement actions were ultimately constrained by their purview to address concerns about the benefit and harms of DTC genetic testing construed in a narrowly medical way, leaving questions outside of the FDA's scope to regulate – such as issues of cybersecurity, corporate transparency, and responsibility – unresolved.

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## I. Introduction

On November 22, 2013, the U.S. Food and Drug Administration (FDA) sent a warning letter to the consumer genetic testing company 23andMe outlining the company's actions that it determined were in violation of the Federal Food, Drug and Cosmetic Act (FFDCA). (Guttierez, 2013) The FDA argued that 23andMe's Personal Genome Service constituted a medical device under section 201(h) of the FFDCA and was thus subject to FDA regulation. While the FDA defines a medical device as an "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article… intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease," 23andMe had contested the designation of its personal genetic testing service as such. In effectively halting the health-related direct-to-consumer (DTC) genetic testing conducted by arguably the leading company in the field, the FDA sent the most recent of numerous signals of its intent to regulate the emerging health-related DTC genetic testing industry. While some stakeholders welcome greater FDA involvement in the regulation of DTC genetic testing, others argue that such testing is already sufficiently regulated by various other federal agencies and further FDA regulation would hurt the fledging industry more than it would help.

Recent scholarship has treated the interaction between 23andMe and the FDA variously as a competition between risk mitigation and patient empowerment, a struggle between paternalism and free speech, and as a negotiation between autonomy and beneficence. (Downing & Ross, 2014; Green & Farahany, 2014; Nordgren, 2014) In this thesis, I examine this regulatory discourse as a representation of competing stakeholder value claims by asking how the various players conceptualize the consumer benefit of DTC genetic testing. Using tools drawn from discourse analysis, I engage with the debate over the regulation of health-related DTC genetic

tests through a case study of the FDA's public interaction with 23andMe. I examined government texts, academic literature, clinical practice guidelines, industry publications, and the periodical literature to explore how key stakeholders framed, legitimized, and contested conceptions of benefit and risk surrounding DTC genetic testing, and how they used these conceptions to advocate for or against regulatory oversight.

This thesis is organized in 6 sections: In the background (Section II), I survey the history of DTC genetic testing in the U.S. with attention to repeated calls for federal oversight, and present common conceptions of the risks and benefits afforded by the emerging technology that inform these calls. In the background I also outline the evolving regulatory structure and key agencies involved in DTC genetic testing oversight. In Section III, I introduce the methods I employed for this study. Section IV presents the results of this analysis in two parts, first from the perspective of 23andMe's information-based conception of the benefit of DTC genetic testing and then from the perspective of FDA's medical device regulatory mandate. In Section V, I synthesize these perspectives to examine the challenges FDA faced in applying medical device regulations to the DTC industry. Finally, in section VI, I discuss potential implications and challenges of regulating the DTC genetic testing industry.

## II. Background

### 1. Medical Genetic Testing and the Human Genome Project

The human genome, the total complement of an individual's genetic material encoded in deoxyribonucleic acid (DNA), has been the subject of intense research since the term was coined nearly a century ago. The human genome consists of some three billion pairs of bases, assorted into 23 pairs of chromosomes. To the best approximation human chromosomes consist of ~21,000 protein-coding genes, those responsible for patterning the proteins that constitute our

working bodies, as well as non-coding regions which may have regulatory functions. (Pennisi, 2012) While the identification of individual nucleotide variations has led to an increased understanding of gene-disease associations, genetic information is not synonymous with health information. Genetic testing may be used in the clinical context to diagnose monogenic diseases, identify future health risks, facilitate reproductive decision-making, and identify interactions between genotypes and pharmaceuticals. (Brower, 2010) However, genetic testing can also be used as a non-clinical informational tool, such as in genealogical investigation. Direct-to-consumer genetic testing refers to the provision of genetic testing services to the consumer without a clinician intermediary. Broadly, DTC genetic testing encompasses both health- and non-health related genetic tests. For example, some firms advertising services directly to consumers offer tests identical to those utilized in clinical care, such as testing for those mutations causing cystic fibrosis or Fragile X syndrome. (Hogarth et al., 2008) Firms also offer paternity and ancestry testing, which although based on the consumer's same genetic information are generally not considered to be directly related to health outcomes. (Hudson et al., 2007) In this thesis, I focus particularly on the regulation of health-related DTC genetic tests.

Since the commencement of the U.S. Human Genome Project (HGP) in 1990, the rate of innovation in genetic testing technology has been staggering. (Collins & Gallas, 1993) Indeed only three years into the project's initial five-year research plan, Francis Collins, then-director of the National Center for Genome Research, and David Galas reported that, "technological improvements that could not have been anticipated in 1990 [had] changed the scope of the project," allowing more ambitious routes of investigation. (Collins & Galas, 1993 p.43) While the primary motivation behind the HGP was to map and sequence the human genome, other goals included research related to the ethical, legal, and social considerations attendant to the

initiative, exploration of model organisms, development of informatics for data collection and analysis, support for research training, and support for technology development and transfer. (Human Genome Project, 1990)

As the HGP progressed, the multifaceted nature of genetic information became increasingly clear. Collins and Guttmacher, in a 2001 editorial in a special genetics-themed issue of the Journal of the American Medical Association, voiced their belief in the potentiality of the human genome to revolutionize medicine through broad contributions to understanding disease biology: they wrote "…[T]he greatest payoff from understanding the human genome, is likely to be an illumination of the molecular pathogenesis of disorders that are currently poorly understood, and for which treatments are largely empirical and frequently suboptimal." (Collins & Guttmacher, 2001) While only 100 genes had been causally linked to diseases prior to the HGP, by 2014 some 3,195 genes with known phenotype-causing mutations had been identified. (Online Mendelian Inheritance in Man, 2014) The goal was, and largely remains, targeted therapy, or the ability for clinicians to utilize patient genetic risk information to guide and tailor care.

Over the past decade since the completion of the HGP, medical genetic testing has progressed from its origins as a specialist diagnostic service examining genetic disorders such as cystic fibrosis, Huntington's Disease, and Turner's Syndrome, toward a model that aims to capitalize on the potential of pharmacogenetics and the use of genetic risk information to guide medical decisions. Predictions of future health risk based on statistical associations between gene variants and complex disease outcomes, and providing diagnostic results for conditions with variable penetrance and heritability epitomize the intended uses of genetic risk information. (Brower, 2010) Testing for low-penetrance genetic variants associated with common diseases

however, may pose difficulty in interpretation, as the variants alone may be neither necessary nor sufficient to cause disease. This progression towards the return of probabilistic health risk results raises ethical issues central to the DTC regulatory debate, where views about the utility – and therefore the value – of obtaining additional information may differ markedly between users.

Despite the fact that no treatment exists, individuals at risk for Huntington's disease may choose to undergo testing, either to gain knowledge about their future risk or to inform reproductive decision making, while others may elect not to be tested precisely because of the lack of treatment and the inevitability of onset. (Walker, 2007) The value of the information gained from any given genetic test may thus be highly individual-specific. Furthermore, diseases like Huntington's are undeniably serious, and warrant, if not require, the expertise of medical professionals to interpret genetic risk information. But the line between medically relevant or actionable genetic tests and those that are not medically relevant or not clinically actionable is not always clear. Very few mutations confer deterministic outcomes as in the case of Huntington's disease. More often variants suggest a modest increase or decrease in risk of common diseases, such as in the case of polymorphisims at 2q24 and the risk of type 2 diabetes (Burke & Zimmern, 2004; Van Dam, et al., 2010) In the case of diabetes risk factors, the indicated lifestyle modifications such as a healthy diet, adequate exercise and avoidance of smoking do not inherently depend on the identification of genetic variants. It becomes evident that the regulation of genetic tests, and by extension DTC genetic tests, relies in no small part on how genetic tests are defined. In the realm of DTC genetic testing, a distinction has been drawn between "health related" and other forms of genetic tests, posing precisely such a definitional – and regulatory – challenge. (Goddard et al., 2009)

## 2. Federal Regulation of Health-Related Direct-to-Consumer Genetic Tests

DTC genetic tests first emerged on the regulatory radar in force with the advent of the nutrigenomics industry in 2006, in which genetic testing firms purported to tailor lifestyle and nutritional guidance to a consumer's genetic makeup in an effort to address genetically associated health risks. (Bair, 2012) Broader questions regarding the commercial impetus behind genetic testing, however, were noted as early as the 1980s. (Holtzman, 1988) Despite perceiving great potential for the clinical use of genetic information, some researchers and clinicians argued for a growing need for caution regarding the accelerated drive toward commercialization in light of motivations for profit, an insufficient understanding of genetic testing results, and an ability to detect susceptibility variants at a rate that outpaced the ability to provide effective interventions. (Holtzman, 1989) The caution advised in the early days took myriad forms, but a group of voices representing the medical profession sought to keep genetic testing, whether in the clinic or DTC, within the purview of the medical profession. The American College of Medical Genetics, for instance, published a position statement on DTC genetic tests in 2004 that strongly advised consumers to utilize clinicians in the counseling, ordering and interpretation of DTC genetic tests and results. (ACMG, 2004) "Due to the complexities of genetic testing and counseling," the statement argued, "the self-ordering of genetic tests by patients over the telephone or the Internet, and their use of genetic 'home testing' kits, is potentially harmful." Potential harms, it continued, "include inappropriate test utilization, misinterpretation of test results, lack of necessary follow-up and other adverse consequences." (ACMG, 2004 p.60) At that time, relatively few health-related tests were available directly to consumers. By 2006, the field of nutrigenomics had emerged, putting DTC genetic testing directly in the regulatory spotlight and highlighting the complexity in articulating a cohesive strategy for oversight.

The DTC nutrigenomics market claimed, "to provide consumers with the information needed to tailor their diet and exercise programs to address their genetically determined health risks." (Kutz, 2006 p.2) While the companies selling nutrigenomics tests claimed that results were not intended to diagnose disease, the risk predictions they provided were deemed misleading in a Government Accountability Office (GAO) investigation into the legitimacy of the product claims. Notably, the report observed that "…as demand for these new tests continues to rise, it will become increasingly important for consumers to have reliable information in order to determine which tests are accurate and useful." (Kutz, 2006 p.22) In terms of formal regulation, the GAO reported that, "The current regulatory environment provides only limited oversight to those developing and marketing new types of genetic tests." (Kutz, 2006 p.22) While not calling explicitly for more oversight, the GAO report did note that despite a law stipulating that laboratories performing genetic tests for medical purposes must be approved under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), not all the laboratories investigated as part of the report were in fact CLIA approved.

While DTC genetic tests were coming to the attention of Congress (and the GAO) in the early 2000s, several federal advisory committees similarly deliberated the potential options and implications of federal oversight. Two in particular - the Secretary's Advisory Committee on Genetic Testing (SACGT) and the subsequent Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) were chartered to advise the Department of Health and Human Services (DHHS), the umbrella agency that houses the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services (CMS), and the National Institutes of Health (NIH). In examining the federal oversight of genetic tests in the U.S., both committees concluded that major gaps existed. Before exploring the Committees' conclusions relevant to the regulation

of the DTC industry, I first introduce the federal agencies holding primary responsibility for the oversight of genetic testing in the U.S.: the FDA, the CMS, and the Federal Trade Commission (FTC). Their respective roles are outlined below.

### *a. The U.S. Food and Drug Administration*

The FDA is tasked under FFDCA, 21 U.S.C 355(b)(1) with ensuring that those tests that constitute medical devices and that are marketed to patients and consumers are both safe and effective. Many genetic tests are considered medical devices by FDA standards, especially those that contribute to the diagnosis or treatment of disease. A "test to determine a person's risk of developing heart disease," qualifies as a medical device for the purposes of FDA oversight, however "a test to determine ancestry" does not. (Shuren, 2010)

FDA medical device classification is risk-based, with devices stratified into three classes on the basis of the risk they pose to patients and consumers. Based on the risk classification, FDA then determines the level of oversight deemed necessary to adequately ensure safety and effectiveness. FDA risk classification is a highly contested topic with meaningful downstream implications for a device's trajectory on the market. As genetic testing moves toward the evaluation of panels of thousands of genes, or even whole genome sequencing, a single test might provide multiple forms of information, qualifying the device as both medical and non-medical. These complexities present a challenge to the FDA's ability to determine the device's appropriate risk characterization. (McGuire, et al., 2010) Before being legally marketable, medical device manufacturers (sponsors) must submit an application to the FDA requesting exemption, premarket approval (PMA) or 510(k) notification and clearance. The risk class of the device determines which route a manufacturer must pursue for premarket approval.

Class I (low risk) devices are deemed to pose the lowest risk and therefore necessitate

only general control oversight, which are required for all devices. Class I devices generally do not require premarket approval or clearance and may be marketed after registration alone. Class II (moderate risk) devices are subject to general controls as well as special controls, such as performance standards and post-market surveillance. Class III (high risk) devices are subjected to the greatest scrutiny either because of the risk they pose to patients, or because the device has no substantively equivalent device with which to compare its safety and effectiveness.

Class II and Class III devices are subject to 510(k) notification, *de novo* 510(k) notification, or PMA. PMA applications may take substantially longer and require significant financial investment prior to approval. Sponsoring companies must pay submission fees to the FDA, the size of which depends on the type of process (PMA or 510(k)) as well as whether or not the FDA considers the sponsor to be a small business. According to a 2013 white paper published by the Personalized Medicine Coalition, in FY2013 these fees ranged from $2,480 to $248,000. (PMC, 2013 p.9) Between FY2003 and FY2007 only 1% of the ~50,000 devices reviewed by FDA entered the market through the PMA route, compared to 31% via 510(k) and 67% as exempt devices. (GAO, 2009 p.9) Since 2011, medium-risk devices without substantially equivalent devices can also file 510(k) notifications *de novo*, a process somewhere between a 510(k) with a substantially equivalent precursor device and a complete PMA in terms of time investment, evidentiary standards, and financial burden. (FDA, 2011)

Most genetic tests subject to FDA regulation fall into a subset of medical devices termed in vitro diagnostic devices (IVDs), or "those reagents, instruments and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat or prevent disease or its sequelae" under 21 C.F.R. § 809.3(a) 1996. (Shuren, 2010) IVD development can progress through one of two paths before approaching the

FDA for premarket notification or clearance. IVD device manufacturers may develop a test kit to be sold commercially to other laboratories, or a laboratory may develop an IVD to be used internally within the laboratory where it was developed. Such tests are commonly called laboratory-developed tests (LDTs). FDA has "generally exercised enforcement discretion and not enforced applicable regulations with respect to LDTs," since the implementation of the 1976 Medical Device Amendments. (FDA, 2013, p.32) As a result, FDA has not actively regulated most LDTs. Whether the FDA exercises regulatory authority over IVDs, LDTs, or all medical devices has downstream implications not only for the level of scrutiny tests must ultimately undergo, but also in terms of the burden of establishing the device's safety and effectiveness, and how these criteria are to be met. Over the past decade, the FDA has become increasingly involved in the debate over whether and how best to regulate IVDs – and by extension LDTs. According to the FDA, the evolution of IVDs from "relatively simple, well-understood tests… more dependent on expert interpretation… than on the design of the test" to the tests of today, reliant on complex software and non-transparent interpretation, coupled with the increasing volume of LDTs on the market, necessitated an end to the enforcement discretion and more active oversight. (Shuren, 2010)

Health-related DTC genetic tests have posed a particularly challenging problem for FDA regulators. One primary factor has been the lack of definitional clarity about what precisely a health-related DTC genetic test is, and when – or if – a DTC genetic test should be labeled a medical device, and thus subjected to FDA regulation. The DTC genetic testing industry has been marked by regulatory uncertainty since its inception. It was only in 2010 that FDA made explicit its intent to subject DTC genetic tests to premarket approval procedures and end the agency's historic enforcement discretion toward LDTs. "FDA met with some of these companies

starting in 2007," stated Dr. Jeffrey Shuren of the FDA in testimony before the U.S. House of Representatives in 2010, but "never informed [them] that they could lawfully market their tests without FDA oversight." (Shuren, 2010) Health-related DTC genetic tests, FDA argued, were to be classified as, "test kits" and subject to 510(k) notification or PMA clearance prior to marketing.

***b. Centers for Medicare and Medicaid Services***

Under the Clinical Laboratory Improvement Act at 42 USC 263a, CMS oversees clinical laboratories where patient-specific results are reported. Clinical laboratory quality under CLIA evaluates a test's analytic validity, but does not address the clinical validity of a test. Analytic validity refers to the ability of a test to measure or detect the genetic variant or substance it is intended to measure or detect, whereas the clinical validity refers to the strength of the association between (in the case of genetics) the variant identified and a specified health outcome. Under its regulatory authority, CLIA defines a "clinical laboratory" as a "facility for the biological… or other examination of materials derived from the human or for the purpose of providing information for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, human beings" regardless of whether the device is marketed as a kit or as a LDT.

Whereas FDA medical device regulation segregates devices into risk-based categories, CLIA oversight is based on the complexity of tests performed in regulated laboratories. Laboratories performing tests of greater complexity are subject to increasingly stringent personnel, training, and laboratory quality standards, with the goal of ensuring the analytic validity of the tests. Straightforward tests receive a waiver, while laboratories conducting moderate and high-complexity tests must achieve certain performance specifications,

demonstrating precision, analytic sensitivity and specificity to "ensure that their tests are accurate, reliable, timely, and confidential and do not present the risk of harm to patients." (42 USC 263a)

CMS has the power to establish "proficiency testing standards" for each type of test. Proficiency testing entails "the testing of unknown samples sent to a laboratory by a CMS-approved proficiency testing program" as a mechanism of quality control. Stakeholders including the Center for Disease Control and Prevention's (CDC) Clinical Laboratory Improvement Advisory Committee (CLIAC) advocated for the addition of a genetic testing specialty under CLIA for many years, and despite the high complexity of many genetic tests, no such specialty was established. (Holtzman, 1999)

***c. Federal Trade Commission***

The FTC also has purview to oversee DTC genetic testing through the Federal Trade Commission Act, which regulates manufacturers by prohibiting false or deceptive claims and the dissemination of false advertisement. (15 U.S.C. Section 45, 52) The FTC has been involved in the regulation of DTC genetic testing since 2006 when, in conjunction with the FDA and CDC, it published a consumer notice admonishing potential buyers to beware of "the benefits these products supposedly offer." (FTC, 2006) While the main point of the communiqué may have been that "a healthy dose of skepticism may be the best prescription," three more subtle messages were also evident. First, that the scientific evidence upon which the test's conclusions were based was still emerging and un-validated. Second that, "while most other home-use medical tests undergo FDA review to provide assurance of their safety and effectiveness, no at-home genetic tests have been reviewed by the FDA, and the FDA has not evaluated the accuracy of their claims." Third (though unwritten), that there was no evidence suggesting FTC action to

limit the commercial free speech of such DTC genetic testing companies. As such, the only consumer protection available was to be informed of the test's limitations. The only post-market recourse for the FTC was to warn consumers – "buyer beware." The FTC publication warned consumers to be cautious in assuming clinical validity, and encouraged them not to forgo traditional healthcare as a result of DTC genetic testing.

### 3. Metrics for the Evaluation of Genetic Tests

The emergence of a DTC genetic testing industry rested on two related promises: the ability of predictive genetic testing to identify an asymptomatic individual's genetic susceptibilities to future disease, and the ability to "take steps to reduce those risks for which interventions are or will be available." (Collins & McKusick, 2001 p.543; Burke, 2009) With the choice of which tests to pursue, how such tests are defined, and whether they fall within the purview of medicine, come implications for models of health-care delivery. Indeed, despite a growing interest in genetic information, some call into question the utility of the health information being provided. (Caulfield & McGuire, 2012) Whether the risks associated with genetic testing are framed in terms of biology, medicine, consumption, autonomy, or otherwise has downstream implications in terms of the oversight sought – in other words in terms of who is deemed responsible for mitigating those risks. (Bunnik et al., 2014) Thus the criteria and values upon which tests are evaluated constrain and shape the boundaries of the regulatory discourse.

The development and availability of DTC genetic tests highlights the need for clear metrics by which to evaluate the ability of tests to perform as intended or advertised. Three characteristics are often used as the basis for genetic test evaluation: analytical validity, clinical validity, and clinical utility. A fourth characteristic encompassing the ethical, legal, and social implications of the test is also incorporated under the ACCE (Analytic validity, Clinical validity,

Clinical utility, and Ethical, legal, and social implications) framework, the foundation for subsequent analytic methods evaluating genomic testing such as the CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) initiative. (Khoury et al., 2009)

Analytical validity refers to the ability of a test to measure or detect the genetic variant or substance it is intended to measure or detect. A test has a high analytical validity if it not only yields a consistent result over multiple tests, but also yields the correct value consistently. In genetic testing, this might refer to the ability of the test to identify the mutation(s) present consistently and correctly. Analytical validity incorporates test accuracy and reliability.

Clinical validity, meanwhile, refers to the "accuracy with which a genetic characteristic identifies a disease condition or risk." (Burke et al., 2010 p.215) In evaluating a genetic test's clinical validity one may ask: what is the strength of the evidence showing its ability to accurately detect the associated disease or condition? In respect to the test's validity, the sensitivity refers to the conditional probability that the test will denote a positive result in the presence of a positive underlying condition (true positive). Similarly, specificity refers to the conditional probability that the test will denote a negative result given that the condition is truly absent (true negative). (Koepsell & Weiss, 2003) Given that no test is perfect, every test will necessitate a tradeoff between false positive and false negative results, both of which will impact the test's clinical validity and ultimately its utility. Clinical validity incorporates the purpose of the test, the prevalence of the disease or condition for which the test is administered, as well as the level of evidence supporting the clinical validity claims.

Clinical utility "refers to the likelihood that the test will lead to an improved health outcome," and has been interpreted as the usefulness of the test in a clinical setting, as well as the attendant socioeconomic or psychological consequences of administering or taking the test.

(Burke et al., 2002 p.315; Burke et al., 2010) Usefulness in a clinical setting might evaluate whether an improved health outcome resulted from test administration. (Burke, 2009) However, clinical utility has also been interpreted as the value of the information provided by a test, regardless of whether the test leads to an effective treatment or not. For instance, clinical utility could capture the value of a diagnostic test result that reflects merely the benefit of the new knowledge to the diagnosed patient. At the same time as one evaluates the benefits associated with the administration of the test and subsequent treatments, one must evaluate the harms associated with testing, diagnosis, and treatment.

Benefits of DTC genetic testing are often framed in terms of access, autonomy, and empowerment, and include information to guide preventative measures, avoid diagnostic odysseys, contribute to informed decision-making, and receive early treatment due to early diagnosis. (Javitt et al., 2004; Hudson et al., 2007; Palmer, 2012; Freuh et al., 2013) Risks are often framed in terms of the potential for psychological distress from misdiagnosis, misunderstanding of test limitations and inappropriate decision-making, misunderstanding of results due to lack of an intermediary, variable quality (clinical validity, analytical validity, etc.), inapplicability of test results to certain ethnic groups, potential for stigmatization, and physical harms from unnecessary treatment, among others. (Javitt et al., 2004; Hudson et al., 2007; Gniady, 2008; Ng et al., 2009; Freuh et al., 2013) Increasingly, researchers suggest that both the benefits and risks surrounding DTC genetic tests may be equally negligible. (Nordgren, 2014) Psychological stress following testing appears uncommon. (Freuh et al., 2013)

The three metrics – analytic and clinical validity and clinical utility – may each lead to different implications for the balancing of perceived risks and benefits of any given genetic test. An element of subjectivity inherent in the measurement of clinical validity lends the metric to

both support and criticism. In order to evaluate a genetic test's clinical validity one must first establish "credible genetic associations" and then assess "genetic disease associations in relation to the predictive value." (Khoury, et al., 2009 p.4) Because the clinical validity depends on the phenotype or health outcome of interest, the measurement may vary depending on the outcome definition**,** as well as on how one defines a health benefit or harm. Even in the absence of effective health interventions to address risks, a test may still be perceived as valuable by an individual, although such subjective values may be inherently difficult to measure. Other metrics used to evaluate genetic tests include economic cost-benefit or cost-effectiveness analyses, which may similarly vary according to how costs and effectiveness (or benefits) are measured, yet even economic analyses must rely on an external evaluation of test performance such as is provided by measures of utility and validity.

Costs can be taken to mean strictly medical costs, costs to family caregivers and/or society, costs to payers, etc. Furthermore, costs can be compared with costs associated with not testing (or not treating), as well as in absolute terms. Finally, it is important to note that if clinical utility is said to account for the outcomes associated with positive or negative genetic testing results, irrespective of whether they are medical, social, or economic, different risks may be implicated and different weightings of risks and benefits may therefore result.

## 4. Regulating Genetic Tests in the U.S.: Debating the Implications

Despite the lack of a comprehensive U.S. oversight framework addressing genetic tests, numerous agencies, professional-, industry- and consumer-advocacy organizations, as well advisory policy bodies have taken an active role in negotiating the contested regulatory terrain. Central to the debate is the question of whether a given genetic test constitutes the practice of medicine and if so, how it fits within the debate over the government's role in regulating

healthcare. As outlined above, the multifaceted nature of genetic tests obscures an immediate answer to these questions.

The regulatory debate at issue can be summarized as a contest over the implications of additional oversight. One paragraph from the Federal Register announcing a 1999 meeting of the Secretary's Advisory Committee on Genetic Testing (one of the most active and influential policy advisory bodies to have addressed the issue of the regulation of genetic testing in the U.S.) summarizes the debate – and its importance – succinctly:

> The question of whether more oversight of genetic tests is needed has significant medical, social, ethical, legal, economic, and public policy implications. Additional oversight may ensure that genetic tests are appropriately used and accurately interpreted, and it may increase the confidence of providers and individuals in using or having genetic tests. Such oversight might increase the willingness of health insurers to cover the costs of genetic tests if their usefulness can be established, but might also increase the costs of those tests. On the other hand, subsequent acceptance and widespread use of a genetic test may increase the demand for it and thereby lower the costs of a test. The development of genetic tests and their use in clinical practice may be slowed by more oversight measures. Finally, further oversight can be expected to require additional funds. (SACGT, 1999)

Calls for enhanced oversight over genetic testing predated the completion of the HGP, and yet nearly thirty years later stakeholders remain at odds over what form the desired oversight should take. It is the purpose of this analysis to examine how two key players – the FDA and DTC genetic testing firm 23andMe – have framed conceptions of benefit and risk, and how these frames have shaped the regulatory discourse. My methods for this analysis are outlined below.

## III. Methods

Discourse analysis is a qualitative research method rooted in linguistics and semiotics that examines language in use, including the way in which power relationships are constructed and negotiated through conversation. (Gee, 2011) The language and key terms used to frame an issue can be analyzed to understand how stakeholder values are both encoded and instantiated in

discourse. Through negotiation and deliberation, stakeholders can legitimize explanations or call into question competing claims and definitions. Viewing regulatory conversations as negotiations suggests the value of clarity in defining not only the purported benefit of a given product, as is the case with 23andMe's Personal Genome Service, but also in coming to a consensus on what the regulation is trying to achieve.

Issues such as the interactions between FDA and 23andMe lend themselves to discourse analysis because the method offers a way to tease apart how definitions and values are constructed and negotiated by different stakeholders, by examining policy documents, conversations around those documents, and the locations in which the conversations are held. Traditional policy analyses view regulation as an attempt to address market failures, such as the existence of monopolies, externalities, and information asymmetries. (Coglianese et al., 2004) Regulation however, can also be viewed as a "kaleidoscope of lenses" that facilitate the negotiation and accommodation of disparate value claims. (Black, 2002 p.163)

The parameters of discourse construction and negotiation, according to Gee, can be illuminated through close examination of the "seven building tasks" of language. (**Table 1**) These tasks enable participants to construct and enact positions in the world through language. Closely integrated with the building tasks are four tools of inquiry that help delineate how "people build identities and practices and recognize identities and practices that others are building around them." (Gee, 2011 p.28) (**Table 2**) I have incorporated elements of Gee's seven building tasks and four tools of inquiry as well as LeGreco and Tracy's (2009) research design of discourse tracing into my data analysis. In the next section, I outline key elements of these methods.

Discourse tracing "analyzes the formation, interpretation, and appropriation of discursive practices" across levels of discourse, emphasizing close reading of texts and thematic coding guided by structured questions. (LeGreco & Tracy, 2009 p.1518) Texts can take a range of forms, from specific written documents to social narratives. Social narratives reflect operational structures, in both spoken and written forms and represent practices, institutions and contexts that help shape the production, assimilation, and representation of texts.

**Table 1: The Seven Building Tasks of Language***

| Building Task | Definition | Example Question Guiding Reading on DTC GT Policy |
|---|---|---|
| **Significance** | How language is used to render an event, phenomenon, organization, etc. significant or insignificant. | How are policy documents being used to render the practice of DTC genetic testing problematic/significant/revolutionary? |
| **Practices (Activities)** | How language is used to construct and convey socially recognized and/or institutionally supported endeavors. | In examining FDA meeting minutes: what practice(s) are these minutes being used to enact? Establishing the value of formalized deliberation? Stakeholder participation? Maintenance of separation between elite and lay? |
| **Identities** | Persona constructed (implicitly or explicitly) by or for individuals, groups, etc. to situate actor(s) relative to others. | What identity(s) is this industry being used to enact? What other identities (clinician, consumer, policy maker, etc.) does it recognize? What identities does it deny recognition to? |
| **Relationships** | Type or degree of interaction established between identities, participants, audiences, etc. | What sort (formal, informal, clinical, participatory) of relationship 23andMe's discourse enact between the company and the consumer? |
| **Politics/Social goods** | How language is used to convey a stance/perspective on the nature or distribution of social goods. | What perspective on the appropriate use of DTC genetic testing is being conveyed by this text? What is being taken to be 'normal,' 'right,' 'appropriate,' 'valuable'? |
| **Connection** | How language is used implicitly or explicitly to connect or distance ideas, people, etc. | How is 'technological risk' used to distance the DTC debate from concerns over social misuses of technology? |
| **Sign Systems & Knowledge** | How claims to knowledge and beliefs (science, God, etc.), sign systems (Spanish, technical, legal, etc.), are enacted through language. | How do texts privilege certain benefits of DTC genetics (autonomy, cost, participation, etc.) over others? |

**Table 2: The Four Tools of Inquiry***

| Tools of Inquiry | Definition | Example for DTC GT Policy |
|---|---|---|
| **Social Languages** | Styles or varieties of language | Technical vs. vernacular (Necessitating specialized vocabulary or genetic literacy, vs. language for broad consumption) |
| **Discourses** | Ways of utilizing language, symbols, actions, ways of thinking, valuing, tools, etc. to enact a recognizable identity. | Biomedical, macroeconomic, bureaucratic, lay, etc. |
| **Conversations** | Talk surrounding major themes, debates, and motifs common to group or society. | Personalized medicine, genetic education, rational choice, consent etc. |
| **Intertextuality** | Cross-reference or allusion to other texts or types of texts. | Amy Harmon's 2007 NYT article entitled, "my genome, myself: seeking clues in DNA" referring to 23andme, personalized medicine, genetic essentialism, etc. |

* Adapted from Gee, 2011

Attention to the levels of discourse – from local and individual conversations, to the institutional and national – fosters a nuanced examination of how social processes interact to represent, communicate, or contest the prevailing ideologies. LeGreco and Tracy outline research tasks within four overarching phases, which I have adapted for this project. (**Table 3**)

**Table 3: Phases of Research**

| Research Phase | Tasks |
|---|---|
| **1. Research Design** | Define case, conduct literature review |
| **2. Data Management** | Data collection, chronological ordering of texts, initial reading, development of structured questions |
| **3. Analysis** | Interrogation of texts with structured questions, construction of case narrative |
| **4. Evaluation** | Consideration of theoretical and practical implications of the research |

Adapted from LeGreco & Tracy, 2009

Discourse tracing is suited to the study of the controversy over the regulation of DTC genetic tests for several reasons. The systematic case evaluation harnesses techniques from political science, public policy, and economic theory that are needed for the examination of change at the federal policy level over time. At the same time, case analysis seeks to explain how policies are transformed through the interactions of interests and ideologies within and across levels. In this way, "discourse tracing builds upon questions about presence or prevalence, by examining how various levels of discourse interacted with one another to create or transform a certain phenomenon, policy, or action over time." (LeGreco & Tracy, 2009, p.1522) By using the tools of discourse tracing to analyze views surrounding the regulation of DTC genetic tests across stakeholder spheres, I am able to explore the values informing the protracted debate. In doing so, my research informs the larger policy discourse, particularly by identifying locations of overlap as well as conflict.

### 1. The Case

Although 23andMe launched in 2007, the discourse surrounding the regulation of genetic testing can be traced to the emergence of genetic technology in the 1960s. The strands of the

original debate over the application of genetic technology and its ethical implications can be followed to the genetic technology of today, however the primary focus of this paper spans from the launch of DTC testing companies in the early 2000s to the present. (**Table 4**) The 23andMe/FDA debate came to a dramatic head in November 2013, with the FDA's warning letter. This event can be seen as a rupture point in the contested debate regarding oversight of DTC genetic testing and signaling decisive action on the part of the FDA.

Although the prevailing sentiment indicates that neither the risks nor the benefits of DTC genetic testing are particularly cause for concern, the consensus over the past decade has been in favor of some level of oversight, whether at the level of clinical interpretation or federal regulations. (Andrews et al., 1994; Holtzman, 1999; SACGT, 2000; FTC, 2006; Kutz, 2006; Kutz, 2010; SACGHS, 2010) The political climate has shifted dramatically between the mid-1990s and today, spanning three Presidential administrations, economic uncertainties, and partisan gridlock in Congress.

### 2. Data Collection and Management

Data collection in discourse tracing requires that researchers gather from multiple and varied sources. (LeGreco & Tracy, 2009) My goal was to capture the diversity of issues present across stakeholder groups in sufficient detail to enable me to trace discursive processes and to build the case study. This coverage is by no means exhaustive. My search started broadly as a study of formal health policy texts relating to the regulation and oversight of genetic testing, and particularly with documents pertaining to the SACGT and SACGHS. I gradually incorporated other sources, including published studies of participant observations, comments submitted both as part of formal policy making as well as on media sources, blogs, clinical practice guidelines, published academic literature, and notices in the Federal Register.

My search strategy was iterative and often involved following citation trails. Following a broad initial literature review, I sorted texts relevant to the U.S. regulation of DTC medical genetic tests chronologically to facilitate the detection of social processes relevant over time, while also assisting in the identification of which stakeholder voices were present and when/where they were silent.

### 3. Data analysis

My initial reading and coding of texts was informed by my a priori knowledge of the regulation of genetic testing in the U.S. and my reading of existing research suggesting possible explanatory values and claims. Given this background and the case's situation within the broader health policy discourse, I developed a set of probes and structured questions (**Table 5**) to systematically apply to the chronologically ordered texts that focused on paternalism and the role of expertise, autonomous decision-making, conceptions of utility and the tradeoff between perceived benefits and risks. After my initial reading, I annotated and coded all the documents and created tables to facilitate comparison of quotes within and between texts. Finally, I synthesized my research into the narrative presented in the results section.

Exploring the framing of benefits and risks between 23andMe and the FDA proved to be a robust core upon which to build my narrative case. While benefit provides only one avenue of insight into why consensus on DTC test regulation has been so elusive, this central theme bears upon larger recurring themes relating to genetic test regulation more broadly, such as evidentiary standards, the role of payers, informed consent, privacy, utility, and risk.

**Table 4: Timeline of Selected Key Dates, Formal Policy, Practice Guideline Publications, and Industry Activities**

| Year | President | Congress; (House/Senate Majority) | Major Events/ Publications |
|---|---|---|---|
| 1999-2001 | Clinton (D) | 106th; (R)/(R) | SACGT Chartered ('99)<br>SACGT Publication on Genetic Testing Oversight (06.00) |
| 2001-2003 | Bush II (R) | 107th; (R)/(D) | SACGT Publication on Genetic Testing Classification ('01)<br>SACGT Disbanded (09.02)<br>SACGHS Chartered ('02) |
| 2003-2005 | Bush II (R) | 108th; (R)/(R) | Human Genome Project Completed (04.03)<br>ACMG Statement on DTC ('04) |
| 2005-2007 | Bush II (R) | 109th; (R)/(R) | GAO Report on DTC Genetic Testing ('06)<br>FTC Facts For Customers Publication on At-Home GT ('06) |
| 2007-2009 | Bush II (R) | 110th; (D)/(D) | 23andMe Launched ('07)<br>ASHG Statement on DTC GT ('07)<br>FDA Draft Guidance on IVDMIA ('07)<br>ACOG Statement on DTC GT ('08)<br>SACGHS Report on GT Oversight (04.08) |
| 2009-2011 | Obama (D) | 111th; (D)/(D) | SACGHS Publication on DTC Genetic Testing (04.10)<br>FDA Untitled Letters to Industry (06.10)<br>FDA Public Meeting on LDT Oversight (07.10)<br>GAO Publication on DTC (07.10) |
| 2011-2013 | Obama (D) | 112th; (R)/(D) | FDA Advisory Committee Meeting (03.11)<br>23andMe submits 510(k) ('12) |
| 2013-2015 | Obama (D) | 113th; (R)/(D) | FDA Warning Letter to 23andMe (11.13)<br>FDA Accepts 23andMe 510(k) (06.14)<br>FDA Intent to Issue Draft Guidance LDT (07.14) |

**Table 5: Structured Questions**

| Type | Structured Question |
|---|---|
| **Philosophical** | What is the perceived purpose of regulating DTC genetic tests? |
| **Procedural** | How is language used to define relationships between stakeholder groups? |
| | How is language used to privilege certain forms of expertise over others? |
| **Policy Concepts** | How are benefits/ risks framed in relation to regulation of DTC genetic tests? |
| | How is language used to render the use of DTC genetic tests with/without a clinician intermediary significant? |
| **Policy Specific** | How are arguments in favor/ against regulation of DTC GT framed? |
| | What recommendations are offered for oversight of DTC genetic tests? |

## IV. Results

Examining the discourse around DTC genetic testing regulation revealed a complex network of stakeholders and interests. (**Table 6**) The seven stakeholder clusters are themselves a generalization of an almost infinitely broad stakeholder group, if stakeholders in the DTC genetics debate are taken to be essentially everyone participating in some way with the U.S. healthcare system or biotechnology.

Despite efforts to bolster CMS/CLIA's scrutiny over the genetic testing industry through the establishment of proficiency testing standards, initial promises ultimately went undelivered. Although FDA was slow to react to the emerging DTC industry, stakeholder advocacy in favor of the agency's oversight eventually helped catalyze action. The primary interaction between 23andMe and the regulatory agencies has been through the FDA. I focus my analysis therefore on the two principle stakeholders, 23andMe and the FDA, and reference other stakeholders as their narratives and interests intersect.

The two sections that follow examine how FDA and 23andMe each conceptualize consumer benefit, and as a result how each envisions, challenges, and instantiates regulations. First, I analyze how 23andMe and the FDA conceptualize and frame the benefits and risks of DTC genetic testing. I argue that 23andMe frames benefits so as to challenge the medical establishment's monopoly over the generation and dissemination of genetic information. Appealing to the rhetoric of consumer autonomy, the democratization of medicine, and the revolutionary nature of their new research paradigm, 23andMe offers a conception of benefit that identifies access to personal information as a desirable end. Then I analyze how the FDA frames consumer benefits. In my analysis of the FDA and the constraints on the agency's ability to regulate the emerging field under the medical device paradigm, I argue that FDA pursued a

conception of benefit rooted in questions of clinical utility, risk, and uncertain evidentiary standards. The oversight of genetic testing broadly has been on the regulatory radar since the HGP, and debates over regulations were particularly concentrated in the clinical genetics community. Political, economic, and circumstantial factors aligned in 2013 that finally prompted FDA to act with regards to 23andMe, however there was nothing swift or inevitable about the agency's actions. Section V presents my discussion of how FDA was able to address the evolving offer of 23andMe using medical device oversight, despite being imperfectly suited for the task. I conclude in Section VI by highlighting some possible implications of the regulatory negotiation between FDA and 23andMe, particularly in terms of information access, and privacy. I point to questions left unanswered by FDA's attempt at regulating the DTC genetic testing industry as a medical device, and suggest that opportunities for oversight outside of federal regulations may prove to be an important agenda for policy research going forward.

**Table 6: Stakeholders**

| Stakeholder | Generalized Views on Oversight of DTC Genetic Tests | Dominant Theme(s) |
|---|---|---|
| DTC Genetics Industry | • Unclear regulatory environment – in favor of clarification<br>• Potential for regulation to stifle innovation<br>• Unsuccessful attempts at industry self-regulation<br>• Question whether DTC genetic testing should be classified as a medical device under FDAA – Information industry. | • Right to genetic information – access<br>• Biomed research revolution<br>• Empower consumer/ patient - education<br>• Data generation<br>• Value in databases & partnerships |
| Clinicians | • In favor of oversight<br>• Advocate risk-stratification to prioritize oversight; no consensus on basis of stratification<br>• Advocate continued clinician involvement, evaluation of health claims, advertisement<br>• General consensus of need for assessment analytic validity at minimum<br>• Implications for practice of medicine? Resource utilization. Provider education. Reimbursement. | • Clinical validity, clinical utility.<br>• Expertise not synonymous with paternalism<br>• Mitigate risk to patients<br>• Incentivize research |
| Consumers/ Patients/ Research Subjects | • Wary of regulations stifling access<br>• Advocate for autonomy in decision-making, wary of paternalism in medicine<br>• Expect government to protect public health<br>• Unclear implications for privacy | • Empowerment rhetoric<br>• Personal utility<br>• Transparency & Trust<br>• Multiple uses, including non-medical<br>• Variable genetic literacy |
| Academia | • Generally in favor of oversight – balanced, not over-burdensome<br>• Debate how to prioritize risks<br>• Questions over ability of federal agencies to enforce regulations<br>• Questions surrounding evidentiary standards – influence coverage<br>• Consideration of social risks | • ELSI of DTC genetics<br>• Metrics for test evaluation<br>• Metrics for risk assessment<br>• Incentivize research |
| Payers | • Need for coverage decisions re: medical genetic testing<br>• Questions surrounding evidentiary standards, role of government payment decisions and incentives for tech development | • Evidence-based decisions<br>• Coverage with evidence |
| Regulators | • Constrained by mandate and funding<br>• Potential for redundancies, question of purview<br>• Balance incentives for evidence generation against risks to public health – minimal burden<br>• Responding to stakeholder interests, political climate | • Research – need for collaboration<br>• Role in basic and translational science<br>• Evidentiary standards<br>• Benefit & metrics for evaluation<br>• Risk-stratification |
| Advocates/ Advisors | • Generally in favor of oversight<br>• Poly-vocal stakeholder representation – difficulty reaching consensus on form oversight should take<br>• Incentive industry growth<br>• CLIA expansion advocated<br>• Advocated for industry, regulator collaboration | • ELSI of DTC genetics<br>• Metrics for test evaluation<br>• Metrics for risk assessment<br>• Incentives for research<br>• Role of expertise<br>• Role of advocacy in research agenda |

### 1. 23andMe and the Provision of Personal Genetic Information

When 23andMe launched in 2007, the Mountain View, CA company held as its mission, "empowering individuals to access, explore, share and better understand their genetic information, [by] making use of recent advances in DNA analysis technologies and proprietary web-based software tools." (23andMe, 2007a) Rhetorically the mission focuses on exploration, education and discovery, is unabashedly individual-centric, and encourages customers to "Search and explore their genomes… Learn how the latest research studies relate directly to traits identified in their genome…and Discover their genetic roots and find where they sit on the tree of human genetic history." (23andMe, 2007b) In less dynamic tones, but importantly for the future evolution of 23andMe, consumers were also given "the option to actively participate in a new research approach." (23andMe, 2007b) This early iteration of 23andMe was not as yet conducting the in-house research that would become a hallmark of the firm, but they worked to build a consumer base by providing $999 reports that included results from genetic analyses on ancestry, personal traits, and risks of developing specific diseases.

For $999, 23andMe would send customers a mailer with a barcoded tube for customer saliva collection that was sent to 23andMe's contracted lab. At the lab, the customer's DNA was extracted and more than half a million points in the individual's genome, including a proprietary set chosen by 23andMe scientists, were read by "a microchip-like device made by Illumina, a leading developer of genetic analysis tools," in order to "produce a detailed genetic profile." Using private login tools on 23andMe's secure website, consumers could "explore their ancestry, see what genetic research means for them and compare themselves to friends and family members." The service would allow consumers to "ultimately … become part of a community

that works together to advance the overall understanding of the human genome." (23andMe, 2007b)

23andMe worked diligently to distance its products from the nutrigenetic tests that had attracted the FDA and FTC's attention a few years prior in 2006. (FTC, 2006) Indeed, only ten days after the launch, on November 29, 23andMe announced that the World Economic Forum had selected the startup as a 2008 Technology Pioneer. (23andMe, 2007c) The theme of the World Economic Forum Annual Meeting that year was "The Power of Collaborative Innovation." (World Economic Forum, 2008) 23andMe was one of 12 companies to be honored as pioneers in the biotechnology/health category. The blurb in the Forum Brochure frames the company as both an avenue to personal information and as the harbinger of personalized medicine:

> "The company builds on recent advances in DNA analysis technologies to enable broad, secure and private access to trustworthy and accurate individual genetic information. …Since the sequencing of the human genome, the concept of personalized medicine has often been discussed, but rarely has its promise been rendered tangible. The founders of 23andMe have been able to envisage a way to generate valuable, personalized profiles based on the core of an individual's DNA." (World Economic Forum, 2008)

Whether 23andMe has delivered on the promise of personalized medicine is beyond the scope of this paper. However, the economic, political, and scientific underpinnings of this thought – that 23andMe had rendered the promise of the genomic era as tangible and valuable - deserves further exploration, as it represents one of the 'benefits' being advertised to consumers early in the firm's evolution.

Undoubtedly 23andMe's mission was written precisely to leverage the science and use the lure and prestige of genetic testing to recruit new customers and study participants. 23andMe's launch was directed toward this market, but the focus of their marketing was simultaneously an attempt to selectively capitalize on the medical frame. The U.S. is a

worldwide leader in medical device development, particularly in the market for personalized medicines, which according to some calculations include genetic testing. According to a 2009 PricewaterhouseCoopers LLP publication, the market valuation for personalized medicine is a staggering $232 billion, with a projected 11 percent annual growth rate. (PWC, 2009) "We are now seeing a blurring of the lines between traditional healthcare offerings and consumer oriented wellness products and services," argued David M. Levy, MD, global healthcare leader at PricewaterhouseCoopers. "The market potential is enormous for any company that learns to leverage the science, target individuals and develop products and services that promote health." (PWC Newswire, 2009)

In 2007, both 23andMe and its main competitor, Navigenics, eschewed obtaining CLIA certification for their testing laboratories. In their first iterations, both firms were focused on genealogy and a very limited set of health conditions. By May 2008, 23andMe had extended their offer to include a program to recruit and compile participant data toward more explicitly health-related research, thereby developing a consumer-driven health-research paradigm. (23andMe, 2008b) 23andMe also capitalized on technological innovations that allowed the firm to reduce the price of their Personal Genome Service from the initial $999 to $399. The firm hoped that reducing the price would incentivize participation, advertising the reduced-price test as containing a "broader range of Single Nucleotide Polymorphism (SNP) variations and rare mutations… thereby providing more relevant data on published associations, as well as maternal and paternal ancestry." (23andMe, 2008c)

Amidst the expansion and the seeming federal oversight vacuum, states began to directly engage with the DTC genetics industry. (Herper, 2008) 23andMe received warning letters from both New York and California for conducting clinical laboratory testing without the appropriate

license or registration and for offering a clinical laboratory test to consumers without a physician order. (Ray, 2008) 23andMe opted to shift its DNA extraction and processing to a CLIA certified lab in an apparent concession to those designating the Personal Genome Service as a test producing medically relevant results. Reporting the regulatory change on the firm's blog, founders Anne Wojcicki and Linda Avey noted that, "Because 23andMe is creating an entirely new kind of business in delivering personal genetic information, the regulatory requirements we face are both complicated and uncertain… Though CLIA certification and oversight are appropriate for specific health and disease-related testing, we are complying with these guidelines to be consistent with other types of laboratory testing." (23andMe, 2008a) The statement was in essence a demonstration of the firm's understanding that, while not a medical device or a clinical testing laboratory, there was a threat to the business if it appeared to evade regulation or seemed unwilling to participate in the policy negotiations.

Selective distancing from the medical frame did not stop 23andMe from also selectively pursuing oversight when it was in the firm's interest – particularly in efforts to create a level playing field and establish a degree of favorable regulatory standardization. (Philippidis, 2014) 23andMe partnered with California state Senator Alex Padilla (D-San Fernando Valley) in 2009 to draft SB 482, a bill which proposed to exempt "algorithmic interpretation done by a computer after the actual generation of the raw data in a CLIA lab" from elements of CLIA oversight, in essence removing "regulatory barriers to operation for companies providing personal genome services." (Javitt, 2009) The bill attempted to separate bioinformatic firms such as 23andMe from the laboratories generating genomic information for the purposes of oversight, however the proposal was largely seen as an additional complexity rather than an operational solution. The bill was subjected to scrutiny but did not pass. (Ray, 2009a; 2009b)

Challenges to the medical establishment by 23andMe and the DTC genetic testing industry were not confined to dodging CLIA regulations. 23andMe also challenged the need for medical intermediaries with respect to fulfilling an individual's "right to genetic information." Their policy page states: "23andMe believes people have the right to access their personal genetic information. …Genetic information is a fundamental element of a person's body, identity, and individuality. As such, the rights that people enjoy with regard to financial, medical and other forms of personal information should apply to genetic information as well." (23andMe, 2014a)

In 2009, Kaiser Permanente announced plans to construct a genetic database funded by a $25 million NIH research grant. The Research Program on Genes, Environment & Health (RPGEH) project proposed to genotype 500,000 Kaiser patients and combine the genomic information with phenotypic information from participants' health records and study-specific survey data to create one of the largest such databanks in the United States. (Vorhaus, 2009) Individual patient/participants did not stand to directly benefit, however, and were informed of this on the study's frequently asked questions (FAQ) web page: "You will not receive personal health or medical results from taking part in the RPGEH. …We do not expect that results from the RPGEH will be the kind of information that can be used by you or your health care provider to make decisions about your current health care." (RPGEH FAQ cited in Vorhaus, 2009) This stance on the return of individual research results to participants was counter to 23andMe's rhetorical appeal to the "democratization" of personal genetic information. Upon learning that the RPGEH study did not intend to return individual results to participants, 23andMe CEO Anne Wojcicki wrote a strongly worded post for the 23andMe blog expressing her disappointment:

> "I strongly disagree that one's genome is currently only useful in research and not for individual use. There are a number of highly useful genetic results that may be generated.

> …Even if genetic research is at an early stage today, having one's genetic data will be of increasing utility as research progresses." (23andMe, 2009a)

Wojcicki's sentiment stood in sharp contrast to medical information regulation by standing firm in its belief that simply having the genetic information *is* the benefit. Of course 23andMe had a vested interest not only in enabling patients/consumers to access their genetic information, but also in enticing patients/consumers to participate in *their* research database. Introduced in 2009 as a "Do-It-Yourself Revolution in Disease Research," 23andMe's rhetoric capitalized on the patient in each person: "There's a high likelihood that a disease of some sort affects you or one of your relatives – every family seems to have ripples in its gene pool that define and shape its health dynamics." (23andMe, 2009b) While both the RPGEH and 23andMe participants could claim a space in the participatory science revolution, 23andMe was proposing a radically different model: not only will the consumer/participant/patient cultivated by 23andMe derive direct benefit from participating in a research project, they will be invested in it in different ways because they *paid* to participate. Given the commodification of genetic information participation advocated by 23andMe, withholding participant information seemed antithetical to the "'virtuous cycle' of research and self-knowledge" they rhetorically espoused. (Palmer, 2012 p.488)

23andMe's insistence on claiming that the results they provided were for "research and educational purposes only" while simultaneously encouraging consumers to claim their right to access their genetic information based on potential future utility are not at as incompatible as it might seem. Key to the resolution is the idea that firms like 23andMe are selling the promise of *future* benefits, in exchange for participation today. The idea of potentiality is central to the creation of a market for personal genetic information, and signals a fundamentally different kind of researcher/ subject/ clinician/ patient/ consumer relationship than the pre-genome research

model, one that reformulates the consumer as a research subject and advocate, while also signaling a departure from the paradigm under which the FDA medical device regulations operate. (Lee, 2013)

### 2. FDA Medical Device Regulation and DTC Genetic Testing

In this section, I discuss how the FDA framed DTC genetic testing benefit in terms of medical device assessment, which justified allowing the agency closer scrutiny of 23andMe's unverified health claims and risks to consumer health outcomes. I first situate FDA's interest in regulating DTC genetic tests within the larger genetic testing regulatory debate to elucidate the difficult position the FDA faced in simultaneously attempting to incentivize innovation while also attempting to exert greater control over the emerging industry.

As discussed in the introduction, FDA historically exercised enforcement discretion over LDTs under the assumption that they were "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." (FDA, 2010) Although FDA's actions toward 23andMe seem heavy-handed, they are understandable in the context of the regulation of medical devices with which FDA is tasked. Multiple stakeholders – from the clinical realm, research, industry, and consumers – called on FDA to exercise greater regulatory authority over genetic testing over the years preceding the rise of the DTC industry. I argue that ultimately FDA felt compelled to provide oversight of the industry despite the fact that the regulatory tool available to the agency – medical device regulations – did not provide an optimal fit for the issue at hand.

#### *a. Genetic Testing on the Policy Radar*

The emergence of DTC genetic testing in the U.S. is best understood in the larger context of the HGP. The Secretary's Advisory Committee on Genetic Testing (SACGT) was chartered to

advise the Department of Health and Human Services (DHHS) and particularly asked to, "assess whether current programs for assuring the accuracy and effectiveness of genetic tests are satisfactory or whether other measures are needed." (SACGT, 2000) The Committee was comprised of clinicians, academics, legal scholars, ethicists, as well as ex officio representatives from administrative agencies. The first report of the SACGT, published in 2000 and entitled "Enhancing the Oversight of Genetic Tests," addressed five major issues relevant to regulation through a public consultation process: 1) the criteria used to assess the benefits and risks of genetic testing, 2) how to differentiate between categories of tests, 3) the process used to collect, evaluate, and disseminate data on tests in each category, 4) options for oversight and their respective advantages and disadvantages, and 5) the appropriate level of oversight for each category of genetic tests.

The SACGT report distinguished between risks posed by the "technical aspects of a given test" and risks posed by the interpretation of test results. The greater the technical complexity inherent in test interpretation, SACGT argued, "the greater the possibility that the clinical utility may not be well-understood." (SACGT, 2000 p.16) Determining clinical utility necessitated a test-by-test examination of outcomes associated with positive and negative test results – but only individuals undergoing testing, the committee argued, could ultimately weigh and balance the attendant risks. This conclusion highlighted the need for both provider and patient education on the promise, limitations, and applicability of genetic testing. "A clinically valid test in the hands of a poorly trained health care provider can pose as much risk as a less valid or accurate test that is correctly interpreted," the SACGT concluded. (SACGT, 2000 p.16) And yet, the level of nuanced genetic understanding needed for patients to correctly interpret and weigh results seemed nearly unattainable, not simply because of shortcomings in education but

because “for many genetic tests, particularly those that are predictive or presymptomatic, knowledge of a test’s clinical validity may be incomplete for many years after the test is developed.” (SACGT, 2000 p.17) In other words, there wasn’t necessarily a way *to ascertain* the genetic test’s clinical validity in advance of making an informed decision on its use before the test had come to market.

SACGT recommended that all new genetic tests, including LDTs, be subjected to FDA review *before* clinical or public health use, with particular attention to be given to the expeditious evaluation of pre-market data as well as increased post-market data collection and evaluation. (SACGT, 2000) Suggesting that not all tests warranted equal scrutiny, SACGT recommended that FDA tailor the level of oversight applicable according to the risks posed to consumers, patients, or society. Despite concluding that genetic tests warranted additional federal oversight, SACGT however, was unable to articulate precisely how FDA ought to determine the level of scrutiny a given test warranted. (SACGT, 2001)

In response to SACGT’s report, and on the day before Republican President George W. Bush took office, outgoing Secretary of Health and Human Services Donna Shalala penned a four-page letter to the members of the SACGT providing an overview of what “the Department is prepared to undertake to enhance oversight of genetic tests and genetic testing.” (Shalala, 2001) The oversight plan called for implementation of the SACGT proposals, “to the extent possible,” and broader interagency cooperation that capitalized on existing statutes and regulations – particularly CLIA and the Medical Device Amendments to the FDAA. Furthermore, Secretary Shalala’s letter called for the FDA to coordinate oversight in its capacity to review, approve, and label “all new genetic tests that have moved beyond the basic research phase.” (Shalala, 2001) Despite the DHHS’ express interest in coordinating the oversight of genetic tests

through an interagency approach, the administration change in 2001 set in motion a policy swing that favored more limited agency oversight of business, as outlined below. While calls for FDA oversight of genetic tests were on the federal government's radar, the political urgency of FDA action suggested by the SACGGT diminished after 2001, only to be rekindled in the excitement following the completion of the HGP in 2003 and then subsequently with the emergence of the DTC industry.

Tommy Thompson, President Bush's appointee for HHS Secretary, was confirmed by the Senate on January 24, 2001. SACGT continued to work towards a framework for genetic testing classification, but the Committee was rather abruptly disbanded in September 2002 and a new Advisory Committee established. As presented by SACGHS Executive Secretary Sarah Carr, the decision on the part of the DHHS to disband SACGT came after a needs assessment, where it was determined that a broader scope for the Advisory Committee was preferable to the narrow charge of SACGT. (Carr, 2003)

Whereas the SACGT had called for rigorous pre-market review of genetic tests as well as enhanced FDA and CLIA scrutiny before introduction of tests into clinical use, the SACGHS started a shift away from those recommendations and toward enhanced post-market surveillance, a shift that encouraged market forces over federal regulatory intervention.

As genetic testing evolved, and with the completion of the HGP, proponents of the clinical application of genetic testing argued for policies that would favor the establishment of new genetic tests in clinical use. At the same time, the DTC provision of genetic risk information raised concerns among clinicians who saw certain applications as premature and risky. Some stakeholders hypothesized that genetic risk information could increase patient anxiety, and these

concerns might be magnified in the DTC arena where supervision and interpretive assistance were minimal or absent. (SACGT, 2000; Kutz, 2006)

The Government Accountability Office is the audit, evaluation and investigative arm of Congress. In 2006, the GAO was asked to investigate the "legitimacy" of certain DTC industry claims and concluded that the companies investigated "made medically unproven" disease predictions and that results "may mislead consumers by promising results they cannot deliver." (Kutz, 2006, p.22) Further, the GAO concluded that the minimal oversight of DTC genetic tests provided under FDA LDT regulation coupled with the lack of a genetic testing specialty under CLIA, "makes it difficult for consumers to determine whether a genetic test provides meaningful, scientifically based information." (Kutz, 2006 p.2) This was the first GAO investigation after the completion of the HGP and reflected pockets of skepticism toward the early commercial fruits of the project.

With DTC genetic testing on Congress' radar, Senators Kennedy (D-Mass.) and Smith (R-Ore.) introduced the Laboratory Test Improvement Act in 2006 to expand FDA's oversight of all clinical laboratory tests. The Act was re-submitted in 2007 (S. 736, 110th Cong. §§1-9 (2007)), along with the Genomics and Personalized Medicine Act (S. 976, 110th Cong. §§1-7 (2007)) sponsored by Senators Obama (D-Ill.) and Burr (R-N.C.). The Genomics and Personalized Medicine Act would be re-introduced in 2008 and in 2010 in the House, however each such attempt at articulating comprehensive oversight of genetic testing and personalized medicine has stalled in Congress. Despite garnering Congressional attention, these legislative attempts to address the regulation of personalized medicine and DTC genetic testing were not perceived as urgent, particularly when regulatory coffers were tight.

The FDA, meanwhile, was itself trying to make inroads in regulating genetic testing, but meeting with stakeholder resistance. In 2006, FDA published a draft guidance document outlining its intent to regulate in vitro diagnostic multivariate index assays (IVDMIAs), a subset of LDTs the agency believed to pose a higher risk because of their greater complexity. (FDA Draft Guidance, 2006) Stakeholders representing the medical device industry, laboratory testing community, clinicians, and the DTC industry were torn in their support or criticism for the FDA's intent to expand oversight. The Washington Legal Foundation (WLF), a public interest law and policy center, submitted a Citizen's Petition on behalf of stakeholders in the laboratory testing community in opposition to what it perceived as FDA interference outlined in the IVDMIA draft guidance. The petition stated:

> "[the] FDA should not interfere with those who practice 'laboratory medicine' in highly innovative and skilled labs around the country and who are regulated federally under CLIA as well as under state laboratory and medical practice acts. This is an essential part of the U.S. medical and public health infrastructure that cannot afford to be degraded, however inadvertently." (Popeo & Samp, 2006)

While the WLF opposed FDA oversight of LDTs, other stakeholders, such as the biotechnology corporation Genentech viewed FDA's actions as a step in the right direction. In a 2008 citizen's petition, Genentech advocated for FDA oversight of all "*in vitro* diagnostic tests pursuant to the risk-based classification system it uses for medical devices," under the premise that a risk-stratified approach would allow FDA to target oversight on high-risk tests, whether initially classified as LDTs or kits. (Johnston, 2008)

Between 2007 and 2010, several factors aligned to not only raise DTC genetic testing on the FDA's agenda yet again, but also finally to provoke the agency to act. In 2007 – and for the first time since 1995 – both houses of Congress were controlled by Democrats, which gave the party an operational majority to strengthen the capacities of the various agencies, including the FDA. In May 2008, after twelve years of debate and negotiation, the Genetic Information

Nondiscrimination Act (GINA) passed in the Senate (95-0) and the House (414-1) and was signed into law by President Bush. It was in the midst of these shifting political sentiments, that 23andMe emerged on the market, along with several other new DTC firms.

As an increasing number of DTC firms launched, multiple concerns were voiced by the clinical genetics community, including fears of inappropriate test utilization, concerns about differential test standards, the potential lack of necessary consultation and follow-up, concerns over the fragmented regulatory environment, and a shortage of clinicians trained to interpret genetic results. These concerns pointed repeatedly toward two main recommendations: (1) greater oversight of laboratory claims through a bolstered CLIA, and/or (2) a risk-stratified FDA-based approach that would provide both clinicians and consumers with meaningful information upon which to judge DTC test claims. (ACMG Statement, 2004; Hudson et al., 2007)

***b. The Perfect Storm***

In 2010, the SACGHS published a report explicitly examining DTC genetic testing oversight. Drawing heavily on prior SACGHS publications, the Committee concluded that gaps in federal oversight limited the "ability of consumers to make informed decisions about DTC genetic testing services." (SACGHS, 2010) In particular, the Committee found that a lack of FDA/FTC review could pose several dangers to consumers through the provision of false and misleading marketing claims, incomplete evidence of clinical validity and/or clinical utility which could impede informed decision-making, insufficient privacy and research protections, and gaps in provider and consumer knowledge leading to potential misuse or misinterpretation of results. As a result, SACGHS recommended that FDA and CMS, develop guidance and/or regulations to close the oversight gaps, in conjunction with stakeholders such as clinicians, the DTC industry, consumers, and patients. Additionally, SACGHS recommended the creation of a

mandatory federal laboratory test registry that would include DTC genetic tests, expanded FTC evaluation of DTC company claims, research spearheaded by the HHS Office for Civil Rights into privacy protections, and HHS broad-reaching genetics education initiatives. (SACGHS, 2010)

Not long after the publication of SACGHS' examination of the DTC industry, another DTC genetics firm, Pathway Genomics announced its intentions to sell its genetic testing product at Walgreens drugstores in the U.S. (Vorhaus, 2010a) Reactions to the announcement were starkly divided, in keeping with general sentiments toward the DTC genetics industry. On one side were those who worried that selling spit kits in stores would release Pandora-like unforeseen consequences that consumers would be unprepared to weather without professional guidance. On the other side were those who viewed the uproar as an elitist attempt to control a technology that had already been on the market for over three years. (Stein, 2010) Most notable however, was the response by Alberto Gutierrez, the FDA's director of the office of in-vitro diagnostics: "They are making medical claims. We don't know whether the test works and whether patients are taking actions that could put them in jeopardy based on the test." (Stein, 2010) Making unvalidated medical claims based on unverified tests suggested the necessity – and appropriateness – of FDA medical device oversight.

The political climate in 2010 represented a perfect storm as far as increased federal oversight was concerned, as unresolved tensions regarding broader genetic testing regulation gained increasing scrutiny. The Democratic Congress and President Obama were both willing to expand the FDA's scope of attention. Indeed, FDA's focus on the DTC industry was, as a noted legal scholar and analyst commented, only one arm of the agency's "intent to much more aggressively regulate the entire field of LDTs." (Vorhaus, 2010b) Another GAO investigation

had been launched into DTC genetics company claims, and 23andMe was among the four firms investigated. Each firm was sent ten undercover tests, representing two samples each from five unique donors. Each donor submitted one test with accurate information, and one with fictionalized information. When donors received differing disease risk predictions from all four firms, including "DNA-based disease predictions that conflicted with their actual medical conditions," the GAO concluded that the tests were misleading and questionable in terms of validity. (Kutz, 2010) GAO briefed FDA on May 25, 2010, NIH on June 7, and FTC on June 17 on the findings of their investigation and "referred all the companies… to FDA and FTC for appropriate action." (Kutz, 2010 p.19) FDA sent its first Untitled Letter to the DTC firms on June 10th.

The expanding offer of DTC firms, both in respect to the assessment of high-risk disease variants as well as the advertisement and the provision of their services to an ever-widening commercial audience, coupled with concerns about the validity of the health claims being made, provoked FDA to intervene. (Guttierez, 2010a) 23andMe received one of the 23 FDA Untitled Letters sent in the summer of 2010 to DTC firms notifying them of their potential violations of medical device regulations. (Guttierez, 2010b) These Untitled Letters provided "an initial correspondence with regulated industry that cites violations that do not meet the threshold of regulatory significance for a Warning Letter." Without information from 23andMe on the analytical or clinical validity of their Personal Genome Service, and given that consumers "may make medical decisions in reliance on" the information the system provides, the FDA determined that the Personal Genome Service constituted a device and was subject to premarket regulation. (Guttierez, 2010b) Many DTC genetic testing firms changed their business models to require a clinician intermediary as a result of these initial FDA letters, but 23andMe chose to

pursue 510(k) notification in compliance with FDA Medical Device regulations instead. (23andMe, 2012)

FDA was only able to exert oversight over genetic tests to the extent that the test being regulated fit within their purview. Experts, and particularly clinicians, remained concerned that DTC genetic test results could mislead consumers and lead to harm. After two years of deliberating its final IVDMIA guidance, and in part because of the rapid expansion of DTC genetic testing, in 2010 FDA decided that rather than attempt to devise regulations covering only IVDMIAs, the agency would instead exert oversight over all LDTs. Citing the SACGHS recommendation that "FDA should address all laboratory tests in a manner that takes advantage of its current experience in evaluating laboratory tests," FDA admitted that while enforcement discretion over LDTs may have made it easier for laboratories to innovate rapidly, the inconsistent application of oversight created an unlevel playing field that may not have provided "reasonable assurance of safety and effectiveness" of tests that made it to market. (FDA, 2010)

Despite the drama of the summer of 2010, nothing happened quickly. When the FDA sent 23andMe its Warning Letter in 2013, the agency cited two major reasons for intervention: (1) "the potential health consequences that could result from false positive or false negative assessments for high-risk indication" such as BRCA-related genetic cancer risk and pharmacogenetic drug responses, and (2) the agency's lack of assurance in the analytic or clinical validity of the 254 disease and risk reports offered by the firm. (Guttierez, 2013) The agency's concerns were both that individual consumers might use information inappropriately, and that the information upon which consumer decisions were based might itself be inaccurate. Despite multiple prior interactions, the agency argued that 23andMe had not only made insufficient effort to provide missing evidence, but had also ramped up "new marketing

campaigns," which indicated a "plan to expand the Personal Genome Service's uses and consumer base without obtaining marketing authorization from FDA." As a result, the FDA concluded it would assess the entire Personal Genome Service as a Class III medical device.

The fact that the FDA framed its dissatisfaction with 23andMe's services in the context of BRCA analysis is noteworthy, and evidences the difficulties facing the FDA in attempting to regulate the DTC genetics industry in terms of medical devices. Concerns about unvalidated claims in the nutrigenomics industry did not cause FDA to intervene in 2006 after the first GAO investigation. An element of internal self-regulation among firms undoubtedly helps to raise the standard among all firms surviving to compete. But despite this, as Murray et al. note, the "DTC genetic testing industry exhibits a continuum of practices," and even within a firm, "some …offer tests over the entire range." (Murray et al., 2010, p.460) 23andMe was one such firm, at one point offering a package comprised of 166 tests of which 99 were based on variants "categorized as 'preliminary research' because the genetic association data have not yet been replicated." (Murray et al., 2010 p.460) 23andMe utilized a three-star rating system to visually present the strength of the science underlying the results they presented. 1-star tests at 23andMe included variants to the D2 dopamine receptor associated with 'avoidance of error' and 'obsessive compulsive disorder' each based on single studies with small samples. Three-star tests could still be ranked highly despite failing four replication studies, such as with a 3-star test for Lou Gehrig's Disease (ALS). (Murray, et al., 2010) Arguably, the tests the FDA was targeting in its 2013 Warning Letter were among those with the most clearly discernable clinical value. Although there were stronger examples of tests providing questionable results, FDA constrained its critique to those tests 23andMe reported which were clearly medical in nature – precisely

because they provided the basis for FDA's purview, and were potentially of greatest interest to consumers as well.

FDA's dissatisfaction stemmed in part from the fact that 23andMe spurned the regulatory system after making its initial 510(k) submission. That the firm failed to provide sufficient validation data while ramping up its advertising campaign indicated to the FDA that it did not take its discussions with FDA seriously and intended to proceed without appropriate regulatory standing. While 23andMe claimed to be for "research, informational, educational" use only, FDA did not share this view. (23andMe, 2014b) Instead, FDA considered the Personal Genome Service "misbranded" because it viewed the firm's marketing of health reports as "a first step in prevention" that claimed to enable consumers to "take steps toward mitigating serious diseases," and thus was reflective of the marketing of a medical device. (Guttierez, 2013)

In contrast to 23andMe's interpretation of benefit that values access to genetic information even in the absence of definitive clinical utility, FDA argued that unverified claims and inaccurate data carried their own risks and potential harms to consumers and patients. The notion of wanting to ensure that the information being disseminated to consumers was "correct" was raised both in 2010 and 2013, and each time Agency representatives made a point to underscore that FDA's actions were not motivated by a paternalistic desire to keep information out of the hands of consumers, but rather that incorrect or unvalidated information could be worse than no information at all. (Pollack, 2010)

***c. Looking Ahead***

Since November 2013, 23andMe has made strides toward re-forging a relationship with the FDA, all the while continuing to frame access to personalized genetic information as inevitable. (Farr, 2014) Although the firm has noted the negative effects the warning letter had

on its ability to recruit new consumers (Ray, 2014) communications have emphasized the firm's commitment to keep researching, keep publishing, and keep recruiting – in order to, in the words of CEO Wojcicki, "return to delivering health information." (Wojcicki cited in Farr, 2014) Indeed 23andMe can be said to have successfully reinvigorated its business image in the past year, establishing partnerships with pharmaceutical companies interested in mining its genetic database, as well as securing a two-year NIH grant to develop a collaborative research platform for the 23andMe database to allow researchers access to the aggregated de-identified dataset. (23andMe, 2014d)

In 2014, 23andMe submitted, and the FDA accepted the firm's first 510(k) notification, signaling the firm's intent to continue in the slow slog through the FDA medical device regulatory process, as well as its intent to regain its ability to market the Personal Genome Service. Kathy Hibbs, 23andMe's Chief Legal and Regulatory Officer wrote, "This submission is for one health report, and is part of the FDA's regulatory review of our health product." (23andMe, 2014c) Perhaps subtly signaling defiance amidst the firm's intent to appease the FDA, Hibbs did not refer to the Personal Genome Service as "our health-related genetic test," but rather as our "health product." This semantic sidestep suggests that 23andMe still does not consider the Personal Genome Service a device – or a test – at all. In the absence of a truly appropriate regulatory framework that views 23andMe as the data-generating and interpretation-formulating bioinformatics firm it advertises itself to be, such single-test submissions may be the only available solution for both the FDA and 23andMe.

## V. Discussion

Despite being imperfectly suited for the task, FDA marshaled its tools for regulating medical devices to provide oversight over the DTC genetic testing industry where firms

increasingly provided health-related claims. The interesting interaction between the FDA and 23andMe has brought to light several difficulties inherent in attempting to regulate genetic technologies under the medical device paradigm.

Although many scholars called for FDA to take on the primary responsibility of regulating DTC genetic tests, the medical device regulatory framework requiring evidence of safety and efficacy "is poorly suited to predictive genetic tests or genomic services," where evidence of benefit or utility may not manifest for years or decades. (Palmer, 2012 p.494) Predictive genetic tests present an inherent challenge to oversight, and particularly to the FDA medical device regulations because of different perceptions of their value to consumers. Though incorporating the personal value placed on genetic information by consumers might give a better demonstration of the perceived benefits obtained from the provision of information such as with 23andMe, eliciting such values and utilizing them to facilitate comparisons between tests would be challenging because of their very subjective nature. Relying solely on medical outcomes in the enumeration of benefits and the calculation of utility, on the other hand, may underestimate the true value of the information.

Evidentiary questions can be viewed in two different, yet equally important ways. The FDA's evidentiary questions revolved around the accuracy and validity of the risk information being generated and returned to consumers. To resolve such questions would require either large-scale pre-market trials such as those characterizing the RCT paradigm in drug testing, or large-scale genotype/phenotype/pharmacogenetic databases upon which to conduct post-market surveillance. 23andMe's evidentiary question was very different. The firm's business model required a continual appeal to the incompleteness of human genetic knowledge in an effort to encourage participation in research, and thereby in the expansion of the company's database. The

value of the intersection between the two views – the collaboration between regulatory agencies and DTC firms to incentivize the creation of large genomic databases – has not escaped the attention of either 23andMe or the FDA. (Ray, 2008) Instead of relying primarily on premarket studies to address questions of safety or effectiveness, a solution might lie in "focusing additional effort on postmarket surveillance and regulation." Such a program however, "would probably require new legislation to give FDA" broader powers to regulate medical devices, which has not been politically emphasized thus far. (Evans, 2010; McGuire, et al. 2010, p.182) Further complicating any new legislative attempt to regulate genetic tests as medical devices is the perennial question of evidence thresholds, or where to set the balance between incentivizing innovation and facilitating translation of new technologies into clinical practice, versus allowing underdeveloped tests of poor value and unsubstantiated claims onto the market. This question suggests the need for investment not only in basic research, but translational research as well. (Khoury et al., 2009) Although the FDA has not yet partnered with 23andMe to create such a post-market validation database, the NIH recognized potential in the firm's research platform and recently awarded them with a grant to expedite research collaborations. (23andMe, 2014d)

What the future holds in terms of 23andMe's research database is yet unclear. What has become clear is that the firm's business model is integrally tied to recruiting more consumer/ participants. "The long game here is not to make money selling kits," a 23andMe board member is quoted as saying. "Once you have the data, [the company] does actually become the Google of personalized health care." (Seife, 2013) One of the unintended consequences of FDA's forceful treatment of 23andMe – and indeed the DTC genetic testing industry more generally – has been the compartmentalization of the testing process into distinct silos: sample collection, data generation/ sequencing, data curation and storage, data interpretation, and the return of results.

When 23andMe first began offering its Personalized Genome Service in 2007, these steps were bundled together. However, the November 2013 Warning Letter effectively disallowed 23andMe from returning its personalized risk information to consumers, yet it did not prevent the company from returning un-interpreted genetic results (i.e., sequence information without interpretation in terms of health risks) or ancestry information, nor did it prohibit the firm from adding to their database, all of which the company continues to do. While 23andMe sees the value proposition in collecting consumer genetic information and partnering with pharmaceutical firms and researchers, consumers are still looking for firms to interpret the raw data that 23andMe returns.

Even prior to 2013, free internet-based interpretation services such as Promethease began to appear (Palmer, 2012 p.426). This bifurcation of the DTC genetic testing industry between firms producing raw genetic data and those providing interpretation, has implications for FDA's continuing ability to control the process and products of DTC genetic services as medical devices. Several scholars have pointed out the difficulty FDA will likely face in enforcing medical device regulations against information-only products, such as open-source interpretation websites, particularly in light of potential First Amendment scrutiny. (Javitt et al., 2004; Spector-Bagdady & Pike, 2014) As a result, stakeholders must consider whether the promulgated regulations and current oversight pathways are achieving – or can achieve – their intended effects.

The interaction between 23andMe and the FDA has erroneously – but understandably – been interpreted by some as a form of governmental paternalism. Berin Szoka of TechFreedom wrote: "…the FDA think that Americans can't be trusted with more information about their potential health risks because some people might make rash decisions with it." (Szoka, 2013) Szoka concludes that banning personal genomics isn't the answer; I would agree, but I would further argue that Szoka is addressing only a sliver of a much broader issue. Szoka frames FDA's

actions as meddlesome: “Doctors and patients will both adapt to the new reality of medical care personalized for our genes – but only if the FDA gets out of the way.” But as I have shown, FDA acted forcefully with 23andMe precisely out of an attempt to address concerns about benefit construed in a narrowly medical way. Without disregarding the paternalism critique, the agency’s actions are understandable in light of the medical framing of benefit it is charged with addressing. From the consumer perspective however, regulatory action based on the logic of medical benefits leaves important questions unanswered. Consumers are left wondering not only whether they ought to have access to their genetic information, but also what researchers, pharmaceutical companies, and the DTC genetics industry intend to do with their genetic information, and if they stand to benefit. These questions point to further issues of resource allocation, equity, costs, responsibility, genetic information privacy, cybersecurity, consumer/ patient consent, corporate transparency, and research data sharing – all of which will necessitate a more explicit discussion of underlying stakeholder value claims, and all of which FDA’s medical device regulations would be ill equipped to address alone.

## VI. Conclusion

The regulation of human genetic testing, and the DTC genetic testing industry in particular, has been the epicenter of a longstanding and complex controversy for the past 20 years. In this thesis, I used the tools of discourse tracing and analysis to explore the differential framing of consumer benefit pursued by the FDA and 23andMe and how these frames affect perceptions of regulatory pathways. My analysis revealed the ways in which 23andMe positioned itself in dynamic tension with the clinical model of genetics while opportunistically aligning with the establishment to further their own policy goals, as well as ways by which FDA was constrained by its medical device purview in its actions toward the DTC industry. The multifaceted nature of the testing services being offered, as well as the seemingly limitless

personal motivations for participation, makes finding a single regulatory solution unlikely. Rather, the regulatory negotiation between the FDA and 23andMe and the oncoming deluge of genetic information point to consumer protection issues that extend beyond FDA's medical device regulatory paradigm – such as what consent entails in the genomic age, the need for international harmonization of research practices, and the economic implications of consumer genomics – issues that are due for reexamination.

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