Genetic Gatekeepers: Regulating Direct-to-Consumer Genomic Services in an Era of Participatory Medicine

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> Those who seek to censor or burden free expression often assert that disfavored speech has adverse effects. But the fear that people would make bad decisions if given truthful information cannot justify content-based burdens on speech. The First Amendment directs us to be especially skeptical of regulations that seek to keep people in the dark for what the government perceives to be their own good.[1]

> The FDCA's product-focused requirements provide an odd-fitting framework for regulating what is basically an information service.[2]

Introduction

In June 2010, a representative of the Government Accountability Office ("GAO") appeared before a congressional subcommittee to report the results of GAO's latest undercover investigation of direct-to-consumer ("DTC") genomic testing services.[3] The testimony was scathing. Gregory Kutz, director of the GAO investigation, reported that the DTC services offered "test results that are misleading and of little or no practical use,"[4] including predictions "that conflicted with our donors' actual medical history."[5] Kutz explained that two services reported that a man who had suffered from irregular heartbeat for thirteen years had a *reduced* genetic risk of irregular heartbeat. Holding up the man's worn-out pacemaker, Kutz asked, "is [DTC testing] science or is this art?"[6] One subcommittee member—a physician—speculated that DTC test results could turn hypochondriacs into maniacs, or cause patients to "jump off a building . . . simply

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1 Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2670–71 (2011) (internal quotations and citations omitted).

2 Richard A. Merrill, *Genetic Testing? A Role for FDA*, 41 Jurimetrics 63, 65 (2000).

3 GAO, GAO-10-847T, Direct-to-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices 1 (2010) [hereinafter 2010 DTC Investigation].

4 *Id.*

5 *Direct-to-Consumer Genetic Testing and the Consequences to the Public Health: Hearing before the Subcommittee on Oversight and Investigations of the House Energy and Commerce Committee*, 112th Cong. (July 22, 2010) (Statement of Gregory Kutz, Managing Director, Forensic Audits and Special Investigations, GAO).

6 *Id.*

out of fear or ignorance."[7] And a representative of the Food and Drug Administration ("FDA") expressed chagrin: "if there's any issue here with the FDA, quite frankly, and I'll say this, it's why didn't we act sooner?"[8]

Unfortunately, both the investigation and the subcommittee hearing misconceived the role of DTC genomic services, which are incapable of diagnosing the vast majority of diseases. Genetic tests yield information that is "probabilistic and not deterministic."[9] They can identify carrier status for inherited disorders; they can also make qualified predictions about future disease risks, medication response, and other physical and metabolic characteristics. But even a perfect genetic test could not predict a complex health condition with environmental factors—like heart disease—with certainty. Only through the looking-glass of genetic exceptionalism,[10] which ascribes near-mystical predictive powers to genetic science, would information of such uncertain value traumatize its recipient into jumping off buildings.

Historically, FDA has regulated few genetic tests. It has not regulated DTC genomic tests at all. But shortly before the June 2010 hearing, FDA notified certain DTC companies that their services constituted medical devices within FDA's statutory jurisdiction, suggesting that the agency may soon take a larger role. Nearly two years later, scholars, DTC enthusiasts, and the medical community remain deeply divided on the best regulatory approach.[11] Some commentators warn of an "incipient culture war"[12] between two factions: bioethicists and clinicians who fear that "health information is 'powerful and important and likely to be misinterpreted by people to their own harm'"[13] unless mediated by expert gatekeepers, and DTC consumers[14] who dismiss those concerns as paternalistic and assert a "right" to access personal genetic data.[15]

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[7] *Id.* (Statement of Rep. Phil Gingrey).

[8] *Id.* (Statement of Jeff Shuren, Director, Center for Devices and Radiological Health, FDA).

[9] Gail H. Javitt, Erica Stanley, & Kathy Hudson, *Direct-to-Consumer Genetic Tests, Government Oversight, and the First Amendment: What the Government Can (and Can't) Do to Protect the Public's Health*, 57 OKLA. L. REV. 251, 260 (2004); Gina Kolata, *Capacity of Genome to Predict is Limited*, N.Y. TIMES D5 (Apr. 3, 2012) ("[e]ven if you know everything about genetics, prediction will remain probabilistic and not deterministic" (quoting David Altschuler)).

[10] Genetic exceptionalism is the practice of treating genetic information as unique, such that it warrants greater regulation or protection than other health information. *See, e.g.*, Michael J. Green & Jeffrey Botkin, *"Genetic Exceptionalism" in Medicine: Clarifying the Differences Between Genetic and Nongenetic Tests*, 138 ANN. INTERN. MED 571, 572 (2003); Lainie Friedman Ross, *Genetic Exceptionalism vs. Paradigm Shift: Lessons from HIV,* 29 J. L. MED ETHICS 141, 142 (2001); Lawrence O. Gostin & James G. Hodge, *Genetic Privacy and the Law: an End to Genetic Exceptionalism,* 40 JURIMETRICS 21, 31 (1999).

[11] *See, e.g.*, Andrew S. Robertson, *Taking Responsibility: Regulations and Protections in Direct-to-Consumer Genetic Testing*, 24 BERKELEY TECH. L. J. 213, 238 (2009) (arguing that FDA should treat DTC services "with medical purposes" as medical devices requiring approval).

[12] James P. Evans & Robert C. Green, *Direct to Consumer Genetic Testing: Avoiding a Culture War*, 11 GENETICS IN MED. 568, 569 (2009).

[13] ROUNDTABLE ON TRANSLATING GENOMIC-BASED RESEARCH FOR HEALTH, BD. ON HEALTH SCIENCES POL'Y, INST. ON MED., INTEGRATING LARGE-SCALE GENOMIC INFORMATION INTO CLINICAL PRACTICE: WORKSHOP SUMMARY 49 (Nat. Acad. Press 2012) (quoting Hank Greely) [hereinafter IOM INTEGRATION WORKSHOP SUMMARY].

[14] This Article will call individuals who purchase DTC genome services "consumers," rather than "patients." Although "consumer" lacks the ethical dimension usually associated with health care, s*ee, e.g.,* Raisa B. Deber et al., *Patient, Consumer, Client, or Customer: What Do People Want to Be Called?* 8 HEALTH EXPECTATIONS 345, 345–47 (2005), DTC genomic services do not provide health care, not all DTC users are patients, and genetic information has intangible value apart from any medically actionable implications. As Dan Vorhaus has noted, FDA itself has used both "patient" and "consumer" in its letters to DTC companies—sometimes in the same paragraph. Dan Vorhaus, *What Five FDA Letters Mean for the Future of DTC Testing*, GENOMICS LAW REPORT (June 11, 2010), http://bit.ly/a16QoI (last visited Apr. 29, 2012).

[15] *See, e.g.*, Caroline Wright et al., *People Have A Right To Access Their Own Genetic Information*, GENOMES UNZIPPED (Nov. 3, 2011), *available at* http://bit.ly/iiVpGC (last visited Apr. 29, 2012); Andrew Pollack, *F.D.A. Faults Companies on Unapproved Genetic Tests*, N.Y. TIMES (June 11, 2010) ("we believe that people have the right to know as much about their genes and their bodies as they choose" (quoting a

The best-known DTC genomic service, 23andMe, is thriving despite the long shadow of regulatory uncertainty; it has expanded its role beyond mere provider of genetic information, to organizer of crowd-sourced genetic research projects, facilitator of genetic networking, and producer of peer-reviewed publications. But many of 23andMe's former competitors have quit the DTC market entirely.

Genetic tests implicate a host of legal, social, ethical, and policy issues, including data privacy, informed consent, tort liability, genetic discrimination, and health care resource allocation. However, this Article asks a narrower question: given the current state of the DTC industry, should FDA become a regulatory gatekeeper, tightly controlling access to DTC genomic services, as it already does for medical devices? The potential benefits of a unified federal approach include quelling regulatory uncertainty, harmonizing a patchwork of inconsistent state requirements, and fostering investment in the genomic innovation sector. But a unified federal approach does not necessarily require that FDA act as gatekeeper. Although FDA has the requisite statutory jurisdiction and scientific expertise, it is not at all clear that the agency should intervene. FDA lacks sufficient resources to monitor the constantly evolving scientific and medical consensus on thousands of genetic variants. Furthermore, its risk-based safety and effectiveness framework is ill-suited to genomic services,[16] because regulation in this area pits intangible values like autonomy, identity, and participation against speculative future harms. If FDA should intervene, it might be prudent to opt for a limited role, in cooperation with other federal agencies.

Importantly, a regulatory approach that distinguishes FDA's handling of genomic services from its handling of medical devices, or other "homebrew" clinical laboratory tests, need not entrench the fallacy of genetic exceptionalism. Rather, such an approach would acknowledge that medicine is in a crucial transitional phase. Affordable whole-genome DNA sequencing will soon generate a flood of data far beyond the scope of today's DTC tests, and researchers are exploring ways to monitor, analyze, and leverage other physiological datasets, like the proteome and metabolome.[17] Genomic information is a crucial ingredient in participatory research, a decentralized user-driven movement that has the potential to complement traditional clinical research, spark innovation, and generate novel social benefits. Health care is becoming more complex, information-rich, and participatory. Accordingly, federal agencies—including FDA—have made substantial commitments to personalized medicine, patient empowerment, and access to personal medical information.[18] These aspirational principles would be difficult to reconcile with a regulatory regime in which healthy individuals are kept ignorant of their own genetic code: "Who has authority to tell an individual what they are allowed to know about themselves?"[19]

23andMe statement)); Cynthia Marietta & Amy L. McGuire, *Direct-to-Consumer Genetic Testing: Is It the Practice of Medicine?* 37 J. L. Med & Ethics 369, 370 (2009) ("we agree that competent adults generally have a right to purchase available information about themselves and their DNA").

[16] *Cf.* Richard A. Merrill, *Genetic Testing? A Role for FDA*, 41 Jurimetrics 63, 65 (2000) ("[T]he FDCA's product-focused requirements provide an odd-fitting framework for regulating what is basically an information service.").

[17] Rui Chen et al., *Personal Omics Profiling Reveals Dynamic Molecular and Medical Phenotypes*, 148 Cell 1293, 1293 (2012).

[18] *See, e.g.*, Andrew C. von Eschenbach, *Navigating the Molecular Revolution: FDA Leadership in a Time of Transition, in* Perspectives on Risk and Regulation: the FDA at 100, 149–56, at 18 (Arthur Daemmrich & Joanna Radin, eds., 2007) (discussing FDA's Critical Path Initiative, intended to leverage "advances in genomics and proteomics" in a "health care system of the future [that] will be not only personalized but also predictive, preemptive, and more participatory").

[19] Lisa Krieger, *UC Berkeley Drops Plans to Release Personal Genetic Information to Incoming Freshmen*, San Jose Mercury News (Aug. 12, 2010) (quoting Dean Mark Schlissel's response to a Department

Part I of this Article offers a brief primer on genetic science and personalized medicine, describes the DTC genomic service industry, and explains how DTC genomic services relate to new models of participatory, publicly driven research. Part II summarizes FDA's statutory authority over medical devices and in vitro diagnostics, and the agency's historical ambivalence toward genetic tests. Part III concludes that while FDA likely has the authority to regulate genomic services, there is reason for caution, particularly with regard to assessing safety and efficacy. Part IV argues that FDA should adopt a limited role in controlling access to genomic information, but should also work with other agencies and industry to develop standards, improve public genetic literacy, and implement a post-test adverse event reporting system that would facilitate evidence-based evaluation of the risks of genomic testing, should those risks eventually materialize.

I. GENOMIC MEDICINE

Genetic tests involve the analysis of DNA, RNA, chromosomes, proteins, or metabolites in order to detect variations related to health and disease.[20] In recent years, optimistic rhetoric about the power of "genetic 'crystal balls' and genome-based panaceas"[21] to diagnose, predict, and prevent disease has become nearly ubiquitous.[22] However, such rhetoric reflects deterministic misconceptions about the influence of genes on future health and overstates the maturity of the underlying scientific research. Genetic tests, while powerful, are flawed crystals. That fallibility is what makes them so challenging to regulate.

A. *A Genetic Primer*

Genes, which encode proteins, are the functional units of deoxyribonucleic acid ("DNA").[23] A complete set of genes—in humans, approximately 21,000 genes, on 46 chromosomes—is called a "genome."[24] Each chromosome consists of two complementary strands of DNA nucleotides (A, T, C, and G) paired like a zipper.[25] There are three billion pairs of nucleotides, or "base pairs," in the human genome.[26] Any two individuals' DNA is 99.9 percent similar; the remaining 0.1 percent, in combination with environmental and epigenetic factors, produces the many physical differences among us.[27]

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of Public Health ruling that the University of California, Berkeley, could not test incoming freshman for "noncontroversial" genetic variants as an educational exercise).

[20] *See* SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, AND SOC'Y, U.S. SYSTEM OF OVERSIGHT OF GENETIC TESTING: A RESPONSE TO THE CHARGE OF THE SEC'Y OF HEALTH AND HUMAN SERVS 17 (2008) [hereinafter SACGHS OVERSIGHT REPORT]. *See also What is Genetic Testing?,* GeneTests Med. Genetics Information Resource, http://www.ncbi.nlm.nih.gov/projects/GeneTests/static/concepts/primer/primerwhatistest.shtml (last visited Apr. 29, 2012).

[21] Eric S. Lander, *Initial Impact of the Sequencing of the Human Genome*, 470 NATURE 187 (2011).

[22] *See, e.g.*, Lauren B. Solberg, *Over the Counter but Under the Radar: Direct-to-Consumer Genetic Tests and FDA Regulation of Medical Devices*, 11 VANDERBILT J. ENT. & TECH. L. 711, 713 (2009) ("Genetic tests offer consumers a figurative crystal ball"); Juliana Han, *The Optimal Scope of FDA Regulation of Genetic Tests: Meeting Challenges and Keeping Promises*, 20 HARV. J. L. & TECH. 423, 423 (2007) ("Soon, [genetic] tests will function as medical crystal balls, forecasting risks of disease years into the future.").

[23] *See generally* JAMES THOMPSON & MARGARET THOMPSON, GENETICS IN MEDICINE 4–6 (Robert L. Nussbaum, Roderick R. McInnes & Huntington F. Willard eds., 6th ed. 2004).

[24] Lander, *supra* note 21, at 188.

[25] *See generally* THOMPSON & THOMPSON, *supra* note 23, AT 17–19.

[26] Lander, *supra* note 21, at 187–88.

[27] Isaac S. Kohane & Russ B. Altman, *Health-Information Altruists — A Potentially Critical Resource*, 353 N. E. J. MED. 2075, 2075 (2005).

Early advances in genetic medicine involved disorders caused by inherited mutations in single genes.[28] These classic "Mendelian" disorders include cystic fibrosis, sickle-cell anemia, and Huntington's disease. Huntington's disease is a dominant disorder: only one copy of the mutated gene is necessary to cause symptoms of the disease. In contrast, cystic fibrosis, a recessive disorder, will only manifest if two copies of the mutated gene are inherited.

Importantly, one's genetic code (or genotype) cannot necessarily predict one's physical state (or phenotype). Huntington's disease is highly penetrant, meaning that almost all individuals with a mutated gene will eventually develop the disease.[29] A genetic test for Huntington's disease is thus highly predictive: the presence of a mutated gene correlates with an estimated lifetime disease risk of 100%. But most diseases are significantly less penetrant. Some individuals with mutated disease genes may never develop any symptoms at all. And genetic diseases have variable expressivities, meaning that individuals who do develop the disease will experience symptoms of varied severity.

Although the study of genetics is over a century old, the last few decades have seen a dramatic, technology-driven increase in knowledge. When the Human Genome Project launched in 1990, the best-equipped research laboratories could read only one thousand DNA base pairs a day, at a cost of about $10 per pair.[30] By the time the Human Genome Project published a draft sequence of the human genome in 2001, its twenty laboratories "were collectively sequencing 1,000 base pairs per second, 24/7."[31] Before the Human Genome Project, only 100 disease genes had been identified; today, almost three thousand Mendelian disease genes are known.[32]

Genetic tests can reliably identify Mendelian disorders like Huntington's disease, although such diseases unfortunately remain difficult to treat. But most common disorders—like heart disease, obesity, addiction, and diabetes—are influenced by a complex interplay of genetic and environmental factors. No single gene determines whether a person will develop these disorders. As a result, these disorders have proven harder to study, understand, and predict.

To identify the genetic basis for complex common diseases, genetic researchers turned to single-nucleotide polymorphisms ("SNPs"). SNPs are letters in the genetic code that vary from person to person and can serve as landmarks for nearby genes.[33] Although SNPs constitute less than one percent of the human genome, a SNP-based screen can capture most of the genetic variation between individuals.[34] Genome-wide association studies ("GWAS") use microarray devices (also called "gene chips" or "SNP chips") to screen half a million to a million SNPs at a time.[35] By aggregating SNP data from many participants, researchers can tease out small statistical associations between SNPs and

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[28] *See generally* Thompson & Thompson, *supra* note 25, at 51–63.

[29] *Id.*, at 240–42.

[30] Paula Stephan, How Economics Shapes Science 88 (2012).

[31] *Id.*

[32] Lander, *supra* note 21, at 191.

[33] "SNPs" is pronounced "snips." NIH, *What Are Single Nucleotide Polymorphisms (SNPs)?* Genetics Home Reference (Apr. 24, 2012), http://ghr.nlm.nih.gov/handbook/genomicresearch/snp.

[34] *Id.*; Lander, *supra* note 21, at 191.

[35] *See* SACGHS Oversight Report 60. Because SNPs are much smaller than genes, testing for SNPs is usually described as "genotyping" or "screening" rather than gene "sequencing." *See generally* NIH, *Microarray Technology*, Genetics Home Reference (Apr. 24, 2012), http://ghr.nlm.nih.gov/glossary=microarraytechnology.

various health conditions.[36] More than a thousand genetic variants linked to common disorders have been identified—nearly all within the last five years.[37]

Most investigational genetic studies are not intended to develop predictive tests, but to elucidate the molecular basis of disease and inform the development of treatments.[38] The statistical associations they find are small, difficult to replicate,[39] and not readily translatable to patients in a clinical setting.[40] Nevertheless, "genetics is transforming our notion of what it means to be healthy when one may be genetically 'at risk,'"[41] and interest is growing in predictive models that could identify pre-disease states in asymptomatic patients and facilitate early interventions.

Clinical genetic tests are typically evaluated using the four dimensions of the ACCE framework: analytical validity, clinical validity, clinical utility, and ethical, social and legal implications.[42] Analytical validity represents the accuracy and reliability of the genotyping or sequencing process in detecting a DNA variation.[43] Clinical validity represents the test's predictive value, which depends on the strength of the association between a genetic marker and a disease.[44] Clinical utility is a complex factor, taking into account the test's usefulness in guiding treatment decisions and whether its clinical benefits outweigh its risks.[45]

As of April 2012, genetic tests were available for 2,612 diseases;[46] however, few of these tests have been evaluated under the ACCE framework. Generally, the analytic validity of SNP-based tests should be high if the clinical laboratory uses the proper procedures,[47] although whole-gene sequencing remains the gold standard. However, SNP genotyping has certain technical limitations: it cannot detect rare mutations, such as deletions or duplications of DNA, and in some people (or ethnic populations), a given SNP may not be an accurate proxy for a nearby mutation. Clinical validity and clinical utility are difficult to evaluate, since they depend on the strength of the underlying

[36] Published studies typically report the likelihood that an individual with a given health disorder has a certain SNP genotype as an "odds ratio" (the odds of an individual with a variant having the disorder, divided by the odds of an individual without the variant having the disorder). These studies sometimes confuse lay readers, because odds ratios are not equivalent to relative risk. *See* Lisa M. Schwartz, Steven Woloshin, & H. Gilbert Welch, *Misunderstandings About the Effects of Race and Sex on Physicians' Referrals for Cardiac Catheterization*, 341 N.E.J.M. 279, 280–82 (1999) (describing how mainstream media outlets misunderstood a genetic study and misreported its findings on risk). In this paper, "risk" and "genetic risk" are used in the general, nontechnical sense most familiar to lay audiences.

[37] Lander, *supra* note 21, at 191.

[38] *Id.* at 193.

[39] A. Cecile J. W. Janssens et al., *A Critical Appraisal of the Scientific Basis of Commercial Genomic Profiles Used to Assess Health Risks and Personalize Health Interventions*, 82 AM. J. HUM. GEN. 593, 593 (2008).

[40] Peter Kraft et al., *Beyond Odds Ratios — Communicating Disease Risk Based on Genetic Profiles*, 10 NATURE REV. GEN. 264 (2009).

[41] Ross, *supra* note 10, at 142.

[42] Caroline Fiona Wright & Mark Kroese, *Evaluation of Genetic Tests for Susceptibility to Common Complex Diseases: Why, When and How?* 127 HUMAN GENETICS 125, 127 (2010); Muin J. Khoury et al., *The Scientific Foundation for Personal Genomics: Recommendations from a National Institutes of Health–Centers for Disease Control and Prevention Multidisciplinary Workshop*, 11 GENETICS IN MED. 561, 561 (2009).

[43] *See generally* SACGHS OVERSIGHT REPORT 67–72.

[44] *Id.* 85–91; Khoury, *supra* note 42, at 561–62.

[45] *See generally* SACGHS OVERSIGHT REPORT 115–31; Khoury, *supra* note 42, at 562–63.

[46] GENETESTS MED. GENETICS INFORMATION RESOURCE, http://www.ncbi.nlm.nih.gov/sites/GeneTests/ (last visited Apr. 29, 2012).

[47] *See, e.g.,* Pauline C. Ng, Sarah S. Murray, Samuel Levy & J. Craig Venter, *An Agenda for Personalized Medicine*, 461 NATURE 724, 724 (2009) (reporting high accuracy and greater than 99.7% agreement in raw genotype data reported by 23andMe and Navigenics); PERSONALIZED MEDICINE COALITION (PMC), PERSONAL GENOMICS AND INDUSTRY STANDARDS: SCIENTIFIC VALIDITY (July 2008) (23andMe, Navigenics, and deCODE estimated that their genotype data had 99% accuracy) *available at* http://bit.ly/KpJenC (last visited Apr. 29, 2012).

research and the availability of treatments or preventative strategies.[48] Predictive SNP-based tests that aggregate small contributions to future disease risk require different approaches to evaluating clinical validity and clinical utility than diagnostic tests for high-penetrance genetic disorders.[49] Since genetic diagnostics are rarely evaluated in prospective clinical studies, evidence of clinical validity and utility is often unavailable.[50] In general, tests for genetic variations with weak predictive power are unlikely to have demonstrable clinical validity and/or utility at this time.

B. *Personalized Health Care*

"Personalized health care" is often described as the effort to "shap[e] preventive and diagnostic care to match each person's unique genetic characteristics."[51] Federal efforts like the Secretary of Health and Human Services ("HHS") Personalized Health Care Initiative and FDA's Critical Path[52] have invested significant resources in "information-based health care" built on basic genetic research, clinical applications, health information management, and decision-supporting technologies,[53] in order to promote patient empowerment:

> An important ideal of personalized health care is to better enable patients themselves to be participants and guides in their own health care. . . [p]atients will increasingly possess both the information and the sense of authority that will help them become partners in their own care, helped by professionals who are increasingly seen as advisors and "coaches."[54]

The centerpiece of personalized health care is arguably pharmacogenomics—the study of how genetic differences affect an individual's response to drugs.[55] Pharmacogenetic tests are expected to transform clinical practice by informing medication selection and dosage, reducing the risk of over- or under-treatment, and avoiding toxicity.[56] Pharmacogenetic targets include genes like CYP2D6, which encodes an enzyme that metabolizes approximately one-fourth of currently used drugs, including many antidepressants, painkillers and beta-blockers.[57] CYP2D6 enzyme activity varies among individuals, with significant therapeutic consequences.[58] Some clinicians screen patients for CYP2D6 polymorphisms before prescribing a new medication.[59] FDA has

[48] *See, e.g.*, Monica R. McClain et al., *A Rapid-ACCE Review of CYP2C9 and VKORC1 Alleles Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding*, 10 Genetics in Med. 89 (2008) (applying the ACCE framework to pharmacogenomic markers); Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, *Recommendations from the EGAPP Working Group: Testing for Cytochrome P450 Polymorphisms in Adults With Nonpsychotic Depression Treated With Selective Serotonin Reuptake Inhibitors*, 9 Genetics in Med. 819, 820 (2007) (similar).

[49] Khoury, *supra* note 42, at 561–64.

[50] *See, e.g.*, SACGHS Oversight Report 4.

[51] DHHS, *Personalized Health Care*, http://www.hhs.gov/myhealthcare/ (last visited Apr. 29, 2012).

[52] *See* von Eschenbach, *supra* note 18, at 151.

[53] DHHS, Personalized Health Care: Opportunities, Pathways, Resources, 2, 7–8, 9–12 (2007).

[54] *Id.* at 13.

[55] Sec'y's Comm. on Genetics, Health, and Soc'y, Realizing the Potential of Pharmacogenomics: Opportunities and Challenges 9 (2008), *available at* http://oba.od.nih.gov/oba/sacghs/reports/sacghs_pgx_report.pdf.

[56] *Id.* 1–2; *see also id.* at 15–16 (discussing how genetics affects dosing of the blood thinner warfarin).

[57] Shu-Feng Zhou, *Polymorphism of Human Cytochrome P450 2D6 and its Clinical Significance: Part I*, 48 Clinical Pharmacokinetics 689, 691 (2009).

[58] Shu-Feng Zhou, *Polymorphism of Human Cytochrome P450 2D6 and its Clinical Significance: Part II*, 48 Clinical Pharmacokinetics 761, 792 (2009).

[59] *Id.*

required that some drug manufacturers include information about CYP2D6, and/or recommendations for CYP2D6 genotyping, in their products' labeling.[60]

Pharmacogenomics also has the potential to target new drugs to certain patient populations, and thereby facilitate FDA approval. In even the most carefully designed clinical trials, subjects display a range of treatment responses.[61] Where this variability correlates with known genetic markers, manufacturers have developed "companion diagnostics" to identify those patients most likely to respond favorably.[62] Some of the more complex diagnostic tools intended to guide clinician decisionmaking arguably blur the line between product and medical practice;[63] Genomic Health's Oncotype DX, for example, "helps patients and their doctors make informed, individualized treatment decisions" about chemotherapy by reporting a "Recurrence Score," using a complex algorithm based on the relative activity of multiple cancer genes.[64]

The ultimate goal of genomic medicine is to anticipate and prevent future health conditions.[65] However, skeptics point out that genetic variation currently accounts for only five to fifty percent of the genetic risk of a given disease.[66] Environmental factors, family history, and behaviors like smoking are better indicators of disease risk than most genetic variants, prompting pessimism about the benefits of predictive genetic testing.[67] For example, one study found that screening eighteen SNPs linked to Type 2 diabetes gave a risk estimate "essentially no better" than one based on the patient's body mass index, age, and sex.[68] And in a study of statin drug response, the best two SNPs had weaker predictive value than age and gender.[69]

Predictive genetic tests are also difficult to integrate into medical practice, because they can't give a "yes/no" prognosis for most diseases.[70] Many clinicians lack the genetic training needed to evaluate risk estimates or explain risk to their patients; health facilities may not have the recordkeeping infrastructure to maintain genetic data in accessible and useful formats; and even the most accurate genetic information can do little to improve

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[60] *See, e.g.*, Leslie Sinclair, *Med* Check, 47 PSYCHIATRIC NEWS 30, 30 (JAN. 20, 2012) (reporting that FDA had updated the required labeling for Orap (pimozide) to recommend CYP2D6 genotyping for patients receiving high doses).

[61] *See* Barbara J. Evans, *Seven Pillars of a New Evidentiary Paradigm: The Food, Drug, and Cosmetic Act Enters the Genomic Era*, 85 N. D. L. REV. 468 (2010) (discussing how variable treatment response undercuts FDA's premarket clinical trial requirements).

[62] *See* SEC'Y'S COMM. ON GENETICS, HEALTH, AND SOC'Y, *supra* note 55, at 26–28; FDA, *Draft Guidance for Industry and Food and Drug Administration Staff--In Vitro Companion Diagnostic Devices* 6–7 (July 14, 2011).

[63] Barbara J. Evans, *Distinguishing product and practice regulation in personalized medicine*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 288, 288–90 (2007).

[64] *Oncotype DX Overview*, GENOMIC HEALTH, http://www.oncotypedx.com/en-US/Breast/PatientsCaregiversInvasive/OncotypeDX/Overview (last visited May 31, 2012).

[65] *See* Evans, *Seven Pillars, supra* note 61, at 460–61 (2010) (discussing the role of genomic medicine in enhancing predictive judgments and prognosis).

[66] Carlos D. Bustamante, Esteban González Burchard & Francisco M. De La Vega, *Genomics for the World*, 475 NATURE 163, 164 (2011).

[67] *See, e.g.*, Nicholas J. Roberts et al., *The Predictive Capacity of Personal Genome Sequencing*, SCI. TRANSL. MED. (2012) (estimating that for most individuals, whole genome sequencing would have little predictive value, and that "in the best-case scenario," ninety percent of patients "might be alerted to a clinically meaningful risk for at least one disease"); Kolata, *supra* note 9; Jocelyn Kaiser, *A Reality Check for Personal Genomes*, SCIENCENOW (Apr. 2, 2012), http://news.sciencemag.org/sciencenow/2012/04/a-reality-check-for-personal-gen.html ("'we're not going to have a huge impact' on the average person with genome sequencing" (quoting Harvard University epidemiologist Peter Kraft)).

[68] Clifton Bogardus, *Missing Heritability and GWAS Utility*, 17 OBESITY 209, 210 (2009).

[69] SEC'Y'S COMM. ON GENETICS, HEALTH, AND SOC'Y, REALIZING THE POTENTIAL OF PHARMACOGENOMICS: OPPORTUNITIES AND CHALLENGES 29–30 (2008), *available at* http://oba.od.nih.gov/oba/sacghs/reports/sacghs_pgx_report.pdf.

[70] Wright & Kroese, *supra* note 42, at 128.

the treatment of conditions like Huntington's disease. Clinicians may have difficulty explaining the limitations of the underlying science to patients who hope for crystal balls.

Yet despite these challenges, genomic information is filtering into regular medical practice, in part because multi-SNP gene chips are cheaper and more efficient than single-gene tests.[71] One hospital reduced its diagnostic expenses by replacing the stand-alone tests for two genes with a screen covering 225 genes;[72] to deal with the resulting data, it "obtain[s] consent from patients to withhold results that are not clinically interpretable," and archives those results in case they become useful in light of new research.[73]

Whole-genome sequencing will likely supersede gene chip tests in the next few years. From the Human Genome Project's estimated $3 billion price tag,[74] the cost of whole genome sequencing has fallen to about five thousand dollars, and is expected to dip below the thousand-dollar mark soon.[75] Affordable whole-genome sequencing will enable individuals to obtain their genomic sequence once, file the data away, and efficiently reanalyze those data as new clinical needs arise.[76] But it will also generate collateral information with unknown, evolving clinical significance—the so-called "incidentalome."[77] Health care providers are struggling with guidelines for disclosure and use of that collateral information,[78] recognizing that even highly knowledgeable individuals may not wish to know every detail of their own genetic makeup. When James Watson, co-discoverer of the DNA double helix, released his genome sequence publicly in 2007, he famously withheld one gene—ApoE, linked to Alzheimer's—because he did not want to know his own risk of that disease.[79]

C. *Direct-to-Consumer Genomic Services*

Over the past decade, commercial providers have begun offering genetic and genomic tests directly to curious consumers. Many of these services focus on ancestry; although health-related genomic services have generated the lion's share of media coverage and academic debate, they have historically represented only a portion of the DTC market.[80]

The typical DTC testing process is easy: consumers enroll via the service's website, and receive a saliva collection container by mail.[81] The saliva sample is sent to and

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[71] IOM Integration Workshop Summary 43 ("genotyping can be cheaper, easier, and more effective than testing one gene at a time"); *Id. at* 48 (at the $1,000 price point, "sequencing a person's entire genome will be nearly as inexpensive as a single genetic test").

[72] IOM Integration Workshop Summary 40.

[73] *Id.* (noting "the medical staff would rather not have [patients'] medical record[s] populated with genomic information of uncertain clinical utility").

[74] Stephan, *supra* note 30, at 88.

[75] John Markoff, *Breaking a Gene Barrier*, N.Y. Times B1 (Mar. 8, 2012) (reporting intense competition in the whole-genome sequencing services sector). *See also* Andrew Pollack, *A Genome Deluge*, N.Y. Times B1 (Dec. 1, 2011) ("It costs more to analyze a genome than to sequence a genome.").

[76] Steven L. Salzberg & Mihaela Pertea, *Do-it-yourself Genetic Testing*, 11 Genome Biol. 404 (2010) ("once an individual's genome has been sequenced, it becomes a resource that can be re-tested as new disease-causing mutations are discovered").

[77] *See* I.S. Kohane, D.R. Masys, & R.B. Altman, *The Incidentalome: A Threat to Genomic Medicine*, 296 J. Am. Med. Ass'n 212 (2006).

[78] *See* Am. Coll. Med. Genetics & Genomics, *Policy Statement: Points to Consider in the Clinical Application of Genomic Sequencing* (March 27, 2012), http://www.acmg.net/StaticContent/PPG/Clinical_Application_of_Genomic_Sequencing.pdf ("When interpreting secondary findings, or results that are generated in the course of screening asymptomatic individuals, it is critical . . . to avoid burdening the health care system and consumers with what could be very large numbers of false positive results.").

[79] Nicholas Wade, *Genome of DNA Discoverer Is Deciphered*, N.Y. Times (June 1, 2007).

[80] Heidi Carmen Howard & Pascal Borry, *Is there a doctor in the house? The presence of physicians in the direct-to-consumer genetic testing context*, 3 J. Community Genetics 105, 105 (2012).

[81] *See, e.g.*, Kathy Hudson et al., *ASHG Statement on Direct-to-Consumer Genetic Testing in the United States*, 81 Am. J. Human Genetics 635, 635 (2007).

processed by a clinical laboratory, which genotypes half a million to a million SNPs. The DTC service presents this SNP information to the consumer in the form of a personalized genomic report, which typically includes disease risk estimates, some pharmacogenomic information, carrier status for some heritable diseases, and/or ancestry information. The ethos of these services "is broadly one in which the consumer has direct access to his or her own genome so that they can take charge of their own health," and their advertising rhetoric emphasizes empowerment and informed choices.[82]

The best-known DTC genomic service, 23andMe, reports both ancestry and health-related information "for research, informational, and educational use only."[83] 23andMe and its competitors report variants in metabolic genes involved in drug sensitivity, carrier status for inherited diseases, gene variants linked to ancestry, and relative risk for several dozen diseases. These services also provide additional explanatory material and links to primary literature. They are within the reach of many, though certainly not all, consumers: as of May, 2012, 23andMe's service was priced at $399, while its competitor deCODE Genetics' service was $1,100.[84] Approximately thirty-five other DTC services offer ancestry information without health information,[85] typically for a few hundred dollars.[86] Several services offer social networking tools or "relative finder" applications;[87] some offer additional tests for traits like hair color, baldness, or earwax stickiness.[88] Finally, some DTC services focus on personalized diet (or "nutrigenomic") information,[89] or test for specific diseases, like Alzheimer's.[90]

A few years ago, many more DTC services jostled for a share of the market. In 2009, the Genetics and Public Policy Center identified forty DTC providers just for health-related conditions, including nine "personal genome services."[91] Over the last few years, under the scrutiny of state and federal regulators, many companies "left the market in silence" or switched to a prescriber-mediated model.[92] Today, about twenty DTC providers offer health-related information, including 23andMe and deCODE Genetics.[93] Genomic services Navigenics and Pathway Genomics, which at one point

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[82] Caroline F. Wright & Daniel G. MacArthur, *Direct-to-Consumer Genetic Testing*, *in* MOLECULAR GENETICS AND PERSONALIZED MEDICINE at 215, 215 (D.H. Best & J.J. Swensen, eds. 2012).

[83] *Terms of Service*, 23ANDME, https://www.23andme.com/legal/tos/ (last visited Apr. 29, 2012).

[84] *23andMe Store*, 23ANDME, https://www.23andme.com/store/cart (last visited Apr. 29, 2012); *Our Products*, deCODEme, https://www.decodeme.com/store (last visited Apr. 29, 2012).

[85] Jennifer K. Wagner, Jill D. Cooper, Rene Sterling & Charmaine D. Royal, *Tilting at Windmills no Longer: a Data-Driven Discussion of DTC DNA Ancestry Tests*, GENETICS IN MED. (Mar. 1 2012).

[86] *Id.; see, e.g.*, *Homepage*, FAMILYTREEDNA, http://www.familytreedna.com/ (last visited Apr. 29, 2012).

[87] Wagner et al., *supra* note 85.

[88] FamilyTreeDNA genotypes SNPs associated with physical traits like "earwax," "baldness," "longevity," and "freckling;" it describes these tests as "Factoids" "best used as 'cocktail conversation' starters." *Types of Tests*, FAMILYTREEDNA, http://www.familytreedna.com/faq/answers.aspx?id=8#883 (last visited Apr. 29, 2012).

[89] GAO, GAO-06-977T, NUTRIGENETIC TESTING: TESTS PURCHASED FROM FOUR WEB SITES MISLEAD CONSUMERS (2006) [hereinafter 2006 DTC INVESTIGATION].

[90] Smart Genetics briefly entered the field in 2008 with an Alzheimer's test, but exited after a patent dispute. Erika Check Hayden, *Alzheimer's Tests Under Fire*, 455 NATURE 1155, 1155 (2008). Graceful Earth, which also sells dietary supplements, still offers an Alzheimer's test. Katie Skeehan, Christopher Heaney, & Robert Cook-Deegan, *Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Alzheimer's Disease*, 12 GENETICS IN MED. S71 (2011).

[91] *Direct-to-Consumer Genetic Testing Companies*, GENETICS AND PUBLIC POLICY CENTER (updated May 27, 2009), http://www.dnapolicy.org/resources/DTCcompanieslist.pdf.

[92] Pascal Borry, Martina C. Cornel & Heidi C. Howard, *Where are you going, where have you been: a recent history of the direct-to-consumer genetic testing market*, 1 J. COMMUNITY GENETICS 101 (2010).

[93] *Direct-to-Consumer Genetic Testing Companies*, GENETICS AND PUBLIC POLICY CENTER (updated Aug 11, 2011), http://www.dnapolicy.org/resources/DTCTableAug2011Alphabydisease.pdf.

planned to sell tests through Walgreen's drugstores, now offer their services only through prescribers.[94] Counsyl, which specializes in pre-pregnancy testing,[95] likewise switched to a prescriber-mediated model.[96] Gene chip manufacturer Illumina offers whole genome sequencing, but requires physician approval.[97] Knome, one of the first companies to offer commercial whole-genome sequencing, has shifted its focus to interpreting sequences generated by third-party laboratories.[98]

While the various genomic services use similar test methodologies, their personalized reports vary in format, degree of detail, and presentation of risk estimates.[99] 23andMe, deCODE, and Navigenics agreed in 2008 to use only those SNPs that were clinically validated in two or more studies, and to collaborate on developing consensus risk calculation factors.[100] Nevertheless, risk predictions inevitably vary between providers, as do the diseases reported, and the amount of scientific background material included. Because some services permit consumers to download their raw genotype data, a market niche exists for third parties offering stand-alone (re-) interpretive reports; however, this niche has not yet been filled.[101] Knome, which bills itself as the "human genome interpretation company," offers stand-alone interpretation only for whole genome sequences provided by institutional clients.[102] A free stand-alone SNP interpretation application called Promethease enables DTC service consumers to re-analyze their own SNP data, but its capabilities are rudimentary.[103]

Of the genomic services, 23andMe has the most dynamic business model, bundling personalized reports with a blog, forums, and online community where "consumers with similar genomic profiles" can "congregate in virtual space" and share their genetic data.[104] It also has a research arm, 23andWe, which has secured federal grants[105] and publishes in peer-reviewed journals.[106] 23andMe consumers opt in to 23andWe studies; they are not compensated, and 23andMe retains any intellectual property or commercial

[94] Pathway Genomics, https://www.pathway.com/about-us (last visited Apr. 29, 2012).

[95] *See, e.g.*, Andrew Pollack, *Firm Brings Gene Tests to Masses*, N.Y. Times B1 (Jan. 28, 2010) (describing Counsyl's pre-pregnancy carrier screening service).

[96] *Id.* (quoting Counsyl's CEO as saying "[o]ne of our goals is to make this like the home pregnancy test"). Alberto Gutierrez, Director of OIVD, credited FDA's 2010 letter to Pathway Genomics with prompting Counsyl to "change their business model" and leave the DTC space. Mary Carmichael, *Why the FDA Is Cracking Down on Do-It-Yourself Genetic Tests: An Exclusive Q&A*, Newsweek (June 11, 2010).

[97] *Ordering a Test*, Illumina, http://www.everygenome.com/for_doctors/ordering_a_test.ilmn (last visited Apr. 29, 2012).

[98] *FAQs*, Knome, http://www.knome.com/company/faqs/ (last visited Apr. 29, 2012).

[99] *See* Daniel MacArthur, *deCODEme opens its doors to free data upload from 23andMe customers*, Wired.com (Dec. 17, 2009, 8:45 AM), http://www.wired.com/wiredscience/2009/12/deCODEme-opens-its-doors-to-free-data-upload-from-23andMe-customers ("the value of genome scans is not in the actual generation of the data (this is a straightforward procedure), but in the breadth and quality of the interpretation service."); *see also* Annelien L. Bredenoord & Johannes J. M. van Delden, *Research Ethics in Genomics Research: Feedback of Individual Genetic Data to Research Participants*, in Human Medical Research 127, 133–34 (J. Schildmann et al., eds, 2012) ("Whereas whole genome 'sequencing' results in raw sequencing data, whole genome 'analysis' processes these data into intelligible information.").

[100] PMC, *supra* note 47, at 2–3.

[101] There have been some exceptions; for example, in 2009, deCODE Genetics briefly sought to recruit 23andMe consumers by offering to interpret their raw data for free. *See supra* note 99.

[102] *FAQs*, Knome, http://www.knome.com/company/faqs/ (last visited Apr. 29, 2012).

[103] *Promethease*, SNPedia (updated Apr. 14, 2012), http://www.snpedia.com/index.php/Promethease.

[104] Sandra Soo-Jin Lee & LaVera Crawley, *Research 2.0: Social Networking and Direct-To-Consumer (DTC) Genomics*, 9 Am. J. Bioethics 35, 37 (2009).

[105] Press Release, 23andMe, 23andMe Receives Funding from the National Institutes of Health to Evaluate Web-Based Research on the Genetics of Drug Response (Dec. 16, 2010), *available at* https://www.23andme.com/about/press/20101216/.

[106] *See, e.g.*, Chuong B. Do et al., *Web-Based Genome-Wide Association Study Identifies Two Novel Loci and a Substantial Genetic Component for Parkinson's Disease*, 7 PLOS Genetics e1002141 (June 23, 2011); Nicholas Eriksson et al., *Web-Based, Participant-Driven Studies Yield Novel Genetic Associations*

benefits derived from peer-reviewed research activities.[107] 23andMe, like other providers, also reserves the right to use consumers' personal data for internal research purposes.[108] Despite all these potential sources of revenue, 23andMe CEO Anne Wojcicki stated in January 2012 that her company was not yet profitable.[109] Nevertheless, 23andMe's embrace of participatory research has successfully distinguished it from its competition, and demonstrated that many consumers enjoy taking part in communal, curiosity-driven genomic activities.

D. *Participatory Genomics*

Participatory research is yet another manifestation of "open science,"[110] the open source software movement, "citizen science," and crowdsourcing. It is most apparent in online patient communities such as PatientsLikeMe, where members self-organize to conduct "personalized research" and exchange actionable medical information.[111] For example, a group of amyotrophic lateral sclerosis (ALS) patients conducted an "ad hoc clinical trial" of lithium inspired by an unpublished Italian clinical study: they obtained prescriptions from their physicians, tracked their vital data using PatientsLikeMe's online tools, and shared their results.[112] Such self-guided experimentation elicits fears that PatientsLikeMe "tacitly encourages" risky choices by nonexpert patients, such as using drugs off-label or changing dosages.[113]

Other participatory research initiatives emphasize altruism and scientific advancement. Harvard's Personal Genome Project ("PGP") plans to sequence the genomes of 100,000 volunteers and contribute their genomic and medical record information to a new "public genomics."[114] PGP cites "advanc[ing] medicine and global health," "contribut[ing] directly to a scientific endeavor," and pursuing autonomy-related values like "self-curiosity" as motivations for participation.[115] Sage Bionetworks seeks "common genomic research" volunteers willing to "share [genetic and health] data in order to benefit the common good."[116] Genomera, a startup "platform for group health science" with the motto "heal the world," promises to "enable[e] participants to design and operate open health studies" and plans "crowd-sourced clinical trials"[117] with its

for Common Traits, 6 PLOS GENETICS e1000993 (June 24, 2010) (reporting novel associations for traits like the tendency to sneeze in bright sunlight and the inability to smell asparagus metabolites in urine).

[107] *Consent Document*, 23ANDME, https://www.23andme.com/about/consent/ (last visited Apr. 29, 2012).

[108] *See, e.g.*, *Terms of Service*, 23ANDME, https://www.23andme.com/about/tos/ (warning that consumers will not be compensated for "research or commercial products that may be developed by 23andMe or its collaborating partners") (last visited Apr. 29, 2012).

[109] *See* Anne Wojcicki, *An Update to 23andMe Customers*, The Spittoon (Jan. 8, 2012 12:57 AM), http://spittoon.23andme.com/2012/01/08/an-update-to-23andme-customers/.

[110] *See, e.g.*, Heidi Ledford, *Life Hackers*, 467 NATURE 650, 651 (2010).

[111] Thomas Goetz, *Practicing Patients*, N.Y. TIMES MAGAZINE, 32 (Mar. 23, 2008); Lee & Crawley, *supra* note 104, at 38 (comparing PatientsLikeMe and 23andMe).

[112] Goetz, *supra* note 111.

[113] *Id.*

[114] John M. Conley, Adam K. Doerr, & Daniel B. Vorhaus, *Enabling Responsible Public Genomics*, 20 HEALTH MATRIX 325 (2010).

[115] *Important Considerations*, PERSONAL GENOME PROJECT, (Apr. 22, 2011), http://www.personalgenomes.org/considerations.html. The PGP was founded by Harvard Medical School Professor George Church, who later co-founded Knome.

[116] Sage Bionetworks, *Draft Informed Consent Form, Portable Legal Consent for Public Genomics Research*, available at http://weconsent.us/consentform (last visited Apr. 29, 2012) (differentiating "common genomic research" like the PLC-PGR from "public genomic research" like the Personal Genome Project); *see also* Editorial, *Your Data are not a Product*, 44 NATURE GENETICS 357 (Mar. 28, 2011).

[117] *About Us*, GENOMERA, http://genomera.com/about (last visited Apr. 29, 2012); *see also* Elie Dolgin, *Personalized Investigation*, 16 NATURE MED. 953, 953–56 (2010).

partner, DIYgenomics.[118] The communal research model is also reflected in publicly curated information resources: SNPedia is a Wikipedia-like database of SNP information, and Promethease is a free application for interpreting SNP genotype data.[119]

So far, 23andMe is the only DTC genomic service to have integrated the participatory ethos into its corporate identity. 23andMe effectively rebranded itself in 2008[120] by creating a research arm, 23andWe,[121] which "make[s] meaningful scientific contributions by enabling its customers to participate directly in genetic research."[122] The 23andWe research model is more "top-down" and less "democratic" than Genomera's,[123] and 23andMe has been criticized for failing to make its data publicly available to outside researchers. But by enabling its customers to download and reshare their own raw SNP data, 23andMe indirectly facilitates a variety of third-party research initiatives.[124]

Studies suggest the participatory research consumer-volunteer differs from the traditional patient or the traditional clinical research subject. Richard Tutton and Barbara Prainsack describe 23andMe as targeting those "enterprising" consumers "willing to pay for information about personal genetic risks while, at the same time . . . actively contribute towards new research;" they see this as a significant departure from the traditional view of research subjects as "need[ing] protecting from personal genetic risk information which could have adverse consequences for them."[125] Media accounts indicate that Tutton and Prainsack have aptly captured the mindset of many 23andMe early adopters, so-called "health hackers" in pursuit of scientific knowledge and self-improvement.[126] In a more critical vein, Kaushik Sunder Rajan argues that the American biotechnology industry "configures subjects as *sovereign consumers*"—"valoriz[ing] individuals as agential, biosocial patient-consumers," yet devaluing their non-expert perceptions of health.[127] Sunder Rajan recognizes that sovereign consumers have the liberty to "choose rationally among available options"—a liberty "inherent to the very rationale of personalized medicine as a practice that is, in the first instance, *preventative*"—but he questions the extent to which consumers are actually empowered by the market.[128]

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[118] Melanie Swan, *Scaling Crowdsourced Health Studies: the Emergence of a New Form of Contract Research Organization*, 9 Future Med. 223, 223–24 (2012).

[119] Elie Dolgin, *Personalized Investigation*, 16 Nature Med. 953, 955 (2010).

[120] Howard & Borry, *supra* note 80, at 106–07.

[121] Lee & Crawley, *supra* note 104, at 38–39.

[122] *Consent Document*, 23andMe, https://www.23andme.com/about/consent/ (last visited Apr. 29, 2012).

[123] Dolgin, *supra* note 119, at 955.

[124] *See, e.g.*, Adam Higginbotham, *Secrets of my DNA*, Wired 108, 114–15 (Mar. 2011) (participatory genomics organizers used their 23andMe data in conjunction with blood tests to conduct a small-scale study of vitamin metabolism).

[125] Richard Tutton & Barbara Prainsack, *Enterprising or Altruistic Selves? Making up Research Subjects in Genetic Research*, 33 Sociology of Health & Illness 1081, 1090 (2011) (describing 23andMe's model of the patient as "the 'enterprising self' who is addressed through a discourse of democratisation and empowerment, and who has the right to information as a value in itself"); *accord* Higginbotham, *supra* note 124, at 117 ("Someone need be motivated only by self-interest–"Does Centrum work for me?"–to contribute their valuable genetic data to a study" with public benefit).

[126] Higginbotham, *supra* note 124, at 111; Elie Dolgin, *Personalized Investigation*, 16 Nature Med. 953, 954 (2010). *See also* Brendan Maher, *Nature Readers Flirt with Personal Genomics*, 478 Nature 19 (2011) (of 1,588 survey respondents, mostly scientists, 18% had their genomes analyzed in some way; half of them had used 23andMe to do it).

[127] Kaushik Sunder Rajan, *Two Tales of Genomics, in* Reframing Rights: Bioconstitutionalism in the Genetic Age at 193, 196, 201, 210 (Sheila Jasanoff, ed. 2011).

[128] *Id.* at 201.

To medical researchers, participatory models offer certain benefits: reduced costs, quicker subject recruitment,[129] and more avenues for individuals with rare genetic variations to come forward and bring their information to the attention of the research community.[130] While relatively unstructured crowdsourcing is unlikely to supplant traditional clinical trials, it can complement traditional research by "get[ting] to testable hypotheses faster."[131] But participatory genomics is "relatively unchartered territor[y],"[132] and the heterogeneous varieties of "democratiz[ed] research"[133] flowering at 23andWe, PatientsLikeMe, PGP and Genomera do not fit existing paradigms of human subjects research.[134] To give truly informed consent, participants in open genomic studies must have a working knowledge of basic genetics, understand that risks and benefits cannot be anticipated, and recognize that their privacy cannot be guaranteed.[135] PGP requires that volunteers pass an entrance exam demonstrating their understanding of these risks.[136] "Genetic-information altruists" will likely participate despite the risks,[137] and a "portable consent" permitting their data to be shared across multiple platforms has already been drafted.[138] But researchers are still unsure how to structure studies, obtain institutional review, and comply with statutory and regulatory requirements (if those requirements even apply).[139]

Another area of uncertainty is participant access to study data.[140] Human subjects research guidelines recommend withholding information without clinical utility from study subjects.[141] But withholding participants' data is incompatible with the open genome philosophy espoused by PGP,[142] or the "enterprising self" model used by

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[129] Swan, *supra* note 118, at 223; Eriksson, *supra* note 106.

[130] *See* Higginbotham, *supra* note 124, at 111–12 ("If you found a family that avoided diabetes, despite having all the risk factors, that would be [significant]. It's something that scientists can't just do sitting in a laboratory. This is one of the few things where scientists really need citizen science." (quoting George Church, founder of PGP)).

[131] Victoria Colliver, *Another Look at Avastin and Who it Might Benefit*, S.F. CHRONICLE A1 (Apr. 14, 2012) (quoting Philippe Bishop, vice president of Genentech).

[132] *Personal Genome Project Study Guide, Part VI: Project Literacy, Lesson 11: Participating in the Personal Genome Project*, PERSONAL GENOME PROJECT, http://www.pgpstudy.org/projectlit/participating/participating7.htm (last visited Apr. 29, 2012).

[133] Lee & Crawley, *supra* note 104, at 38; Katherine Wasson, *Direct-to-Consumer Genomics and Research Ethics: Should a More Robust Informed Consent Process Be Included?* 9 AM. J. BIOETHICS 56, 56 (2009).

[134] Swan, *supra* note 118, at 223–5.

[135] John M. Conley, Adam K. Doerr, & Daniel B. Vorhaus, *Enabling Responsible Public Genomics*, 20 HEALTH MATRIX 325 (2010). Several studies over the past few years have indicated that deidentified patient information or genetic study information can be reidentified by filtering it or combining it with other data sources.

[136] Elie Dolgin, *Personalized Investigation*, 16 NATURE MED. 953, 955 (2010).

[137] Isaac S. Kohane & Russ B. Altman, *Health-Information Altruists — A Potentially Critical Resource*, 353 N. E. J. MED. 2075 (2005).

[138] Editorial, *Your Data Are Not a Product*, 44 NATURE GENETICS 357 (MAR. 28, 2011).

[139] *See, e.g.*, Swan, *supra* note 118, at 226.

[140] The Health Insurance Portability and Accountability Act (HIPAA) requires disclosure of personal information to research participants, but only in limited circumstances.

[141] Matthew P. Gordon, *A Legal Duty to Disclose Individual Research Findings to Study Subjects?* 64 FOOD & DRUG L. J. 250–52 (2009) (describing disclosure guidelines from the National Bioethics Advisory Commission and National Heart, Blood, and Lung Institute, both of which "set the bar for disclosure at (or near) clinical utility"). Nondisclosure is conceptually related to "medical paternalism," which authorizes physicians to withhold information from patients in exceptional cases. Id.

[142] *PGP Consent Form* 9, PERSONAL GENOME PROJECT (approved Feb. 21, 2012) *available at* http://www.personalgenomes.org/consent/PGP_Consent_Approved_02212012.pdf ("Once the PGP has completed the analysis of your specimen(s), the PGP will make the data available to you via a password protected area on the PGP website. This information is for research purposes only. You may not use this data for any medical or clinical purpose unless the data are first confirmed by a licensed healthcare professional. . . One month after

23andMe, which draws participants seeking increased access to personal data, forming a "virtuous circle" of research and self-knowledge.[143] Study participants increasingly expect (or demand) access to their data;[144] data return provisions have growing importance in the "social contract" of crowdsourced studies.[145] Yet most commentators still advocate restrictions on data disclosure.[146] Thus, although an informed "genetic information altruist" may be empowered to contribute her tissue, DNA sequence, and/or personal information to advance medical research, it is not always clear that she will have access to the data generated by that research.

E. *Concerns About DTC Genome Services*

All genetic tests implicate ethical, legal, and social issues, including concerns about disclosure, misuse, and the impact of adverse news on a patient's wellbeing. However, DTC genome services prompt especially vociferous objections, summarized briefly below.

1. Misleading DTC Service Advertising. Many critics predict that consumers misled by inaccurate, incomplete, or unclear advertising will misunderstand the service they are buying. Consumers may expect a service to be more comprehensive than it is; for example, they may not realize that 23andMe tests only three SNPs out of dozens associated with breast cancer.[147] And misplaced beliefs in genetic determinism—the idea that one's genes dictate one's identity, to the exclusion of other factors—may foster unrealistic expectations about the utility of test results.

Non-European consumers, in particular, may fail to appreciate the limited relevance some tests have for members of their ethnic groups.[148] Because ninety-six percent of GWAS research subjects are of European descent,[149] study findings may not be generalizable to other populations.[150] Public and private research initiatives are seeking to mitigate this disparity,[151] and 23andMe has offered free testing to African-American consumers to diversify their database.[152] But in the meantime, genomic test results may be less accurate or relevant to non-European consumers, and this limitation is unlikely to be apparent to potential consumers.

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you are notified of your specimen analysis data, or at your option immediately, these will be made available on the PGP's public website and database.").

[143] Tutton & Prainsack, *supra* note 125, at 1090.

[144] Juli Murphy Bollinger et al., *Public Preferences Regarding the Return of Individual Genetic Research Results: Findings From a Qualitative Focus Group Study*, 14 Genetics in Med. 451, 451 (2012).

[145] Swan, *supra* note 118, at 226.

[146] Annelien L. Bredenoord & Johannes J. M. van Delden, *Research Ethics in Genomics Research: Feedback of Individual Genetic Data to Research Participants*, in Human Medical Research 127, 128–29 (J. Schildmann et al., eds., 2012). The debate about disclosing genetic data with uncertain utility parallels the debate about FDA regulation of DTC genome services. Both debates start from the presumption that disclosure/access has benefits and risks, and typically focus on clinical utility as the measure of potential benefits. Id. at 133. Study designers also must consider the potential harms of disclosure to the study protocol itself.

[147] *See infra* Part IV.B.

[148] GAO, 2010 DTC Investigation, *supra* note 3, at 10.

[149] Carlos D. Bustamante, Esteban González Burchard & Francisco M. De La Vega, *Genomics for the World*, 475 Nature 163, 163 (2011); *see also* Mike Bamshad, *Genetic Influences on Health: Does Race Matter?* 294 J. Am. Med. Assoc. 937, 937 (2007) ("[T]he paucity of data on gene-disease associations in individuals of African ancestry is disturbing").

[150] Bustamante at al., *supra* note 149, at 164.

[151] *Id.* at 165.

[152] Daniel MacArthur, *Personal Genomics: No Longer Just For White Folks*, Wired (July 26, 2011 10:26 AM), http://www.wired.com/wiredscience/2011/07/personal-genomics-no-longer-just-for-rich-white-folks/.

2. Lack of Expert Gatekeepers. Some critics contend that DTC genomic services, particularly internet-mediated services, "undermine[] the health professional's role as gatekeeper and mediator of complex health technologies,"[153] and that medical experts should have a mandatory pre-test gatekeeping role.[154] Ideally, medical experts would step in to correct misunderstandings, raise any concerns the consumer may have overlooked, and discourage testing that would not be in the consumer's best interest. However, many physicians have little genetic training, and may lack the very "basic gatekeeping abilities" they are expected to provide.[155] If so, "designating [non-geneticist physicians] as gatekeepers" could be tantamount to "sticking healthcare in a time capsule for a decade or more, until physicians get up to speed."[156]

3. Burdening Health Care Systems. Some critics argue that gene chip tests, while efficient at generating information, will ultimately waste scarce medical resources through "a medical testing 'cascade effect' with unwarranted diagnostic, pharmacologic, and surgical interventions."[157] Demands on clinicians' time are expected to increase as tests become more comprehensive: according to one estimate, it would take a genetic clinician five hours to explain the variants of interest in a typical patient's whole-genome sequence.[158] Apparently healthy patients demanding unwarranted follow-up testing would further burden health care providers, and could place patients themselves in unnecessary risk.[159]

4. Inaccurate Results. Although occasional high-profile mistakes have sparked fears of inaccuracy,[160] a 2009 study by DNA sequencing pioneer J. Craig Venter indicates that DTC companies' raw data are quite accurate.[161] The same may not be true, however, for their estimated risk predictions.[162] GAO's 2010 testimony criticized four DTC services for reporting discordant risk predictions based on the same DNA samples—e.g., reporting "high risk" versus "low risk" for the same disease.[163] GAO deemed the "contradictory" tests useless and misleading. Id. However, such discrepancies are explained by methodological differences (such as using different SNP markers and population risk estimates)[164] and the relative immaturity of genetic testing technology. DTC providers are

[153] Robertson, *supra* note 11, at 242.

[154] *See, e.g.*, James P. Evans & Jonathan S. Berg, *Next-Generation DNA Sequencing, Regulation, and the Limits of Paternalism* 306 J. AM. MED. ASSOC. 2376, 2376 (2011); Am. Coll. Med. Genetics, *ACMG Statement on Direct-to-Consumer Genetic Testing* (Apr. 7, 2008); Eur. Soc. Human Genetics, *Press Release, DTC genetic tests neither accurate in their predictions nor beneficial to individuals* (May 30, 2011), available at http://bit.ly/m88dhf (63% of European clinical geneticists surveyed thought DTC genome services should be banned).

[155] Howard & Borry, *supra* note 80, at 109–10 (arguing that insufficient medical supervision could cause overuse of genetic tests and give patients a false sense of security).

[156] Thomas Goetz, *Is Your DNA Dangerous to Your Health?* HUFFINGTON POST (July 18, 2010 9:00 AM), http://www.huffingtonpost.com/thomas-goetz/dna-test-is-your-dna-dang_b_616568.html.

[157] Khoury et al., *supra* note 42, at 560.

[158] IOM INTEGRATION WORKSHOP SUMMARY 50; *See also* Elaine R. Mardis, *The $1,000 genome, the $100,000 analysis?* 2 Genome Med. 84 (2010), http://genomemedicine.com/content/2/11/84.

[159] Justin P. Annes, Monica A. Giovanni, & Michael F. Murray, *Risks of Presymptomatic Direct-to-Consumer Genetic Testing*, 363 N.E.J. MED. 1100, 1101 (2010).

[160] *See, e.g.*, Rob Stein, *Genetic testing mix-up reignites debate over degree of federal regulation needed*, WASH. POST (July 17, 2010) (describing a laboratory mix-up that resulted in misidentification of eighty-seven consumers' 23andMe data).

[161] Ng et al., *supra* note 47, at 724 (reporting more than 99.7% agreement between 23andMe and Navigenics).

[162] *See, e.g.,* Eur. Soc. Human Genetics, *supra* note 154 (reporting that information supplied by deCODEme predicted risks of greater than 100%—an impossibility, regardless of interpretive variation—for five of eight diseases).

[163] GAO, 2010 DTC INVESTIGATION, *supra* note 3.

[164] Ng et al., *supra* note 47, at 724; *see also* PERSONALIZED MEDICINE COALITION, PERSONAL GENOMICS AND INDUSTRY STANDARDS: SCIENTIFIC VALIDITY (July 2008) (detailing common standards and differences between

aware of these concerns, and have expressed willingness to ameliorate them: 23andMe, deCODE and Navigenics committed in 2008 to collaborate on improving the quality of their predictions,[165] and in 2010, 23andMe requested assistance from FDA and NIH in developing standards and best practices for risk reporting.[166]

5. Misleading Results. Because predictive testing involves complex science and statistics, many critics fear consumers will misunderstand their results.[167] These fears appear well-founded, given that public health literacy is unfortunately low, and even educated consumers have trouble understanding relative risk data.[168] A 2010 study found that most US adults would have trouble reading and using genomic service websites.[169]

6. Collateral Results. Because personal genomic services report risk estimates for hundreds of health conditions, consumers may be exposed to unanticipated or unwanted risk information—the so-called "incidentalome."[170] 23andMe mitigates this concern by "locking" certain results, such as breast cancer, so consumers must affirmatively opt-in to see the information. However, few studies appear to have gathered data on the effects of exposure to unwanted genetic information, much less sought to quantify those effects.

7. Consumer Distress. Many critics warn that the psychological impacts of adverse genetic information can be "extreme," particularly without genetic counseling, and that some consumers will react to "potentially traumatizing genetic test results"[171] with distress, fear, anxiety, or depression.[172] This fear seems plausible with respect to serious conditions like breast cancer or Alzheimer's. However, recent studies have found no evidence to support consumer distress resulting from DTC testing.[173]

8. Harmful Consumer Action. Coupled with fear of consumer distress is another fear: that consumers will make poor choices, with harmful consequences. These fears were heightened by a 2006 GAO report concluding that DTC nutrigenomic companies deceived consumers into buying overpriced nutritional supplements.[174] Critics argue that a "false sense of security" based on predictions of lowered risk could lead to poor

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the predictive methodologies of 23andMe, Navigenics, and deCODE) *available at* http://bit.ly/KpJenC (last visited Apr. 29, 2012).

[165] PMC, *supra* note 47, at 2–3.

[166] *23andMe Letter to Heads of FDA and NIH*, The Spittoon (Jul. 6, 2010, 11:13 PM), http://spittoon.23andme.com/2010/07/06/23andme-letter-to-heads-of-fda-and-nih/.

[167] *See, e.g.*, David Magnus, Mildred K. Cho & Robert Cook-Deegan, *Direct-to-Consumer Genetic Tests: Beyond Medical Regulation?* 1 Genome Med. 17, 17.2 (2009).

[168] *See, e.g.*, Christina R. Lachance et al., *Informational Content, Literacy Demands, and Usability of Websites Offering Health-Related Genetic Tests Directly to Consumers*, 12 Genetics in Med. 304, 304 (2010); *see also supra* note 36 (discussing the confusing relationship of odds ratios and risk ratios).

[169] *Id.*, at 309. *But see* David Kaufman et al., *Direct From Consumers: A Survey of 1,048 Customers of Three Direct-to-Consumer Personal Genomic Testing Companies About Motivations, Attitudes, and Responses to Testing*, Am. Soc. Human Genetics Meeting (2010) ("88% of DTC customers agreed their risk report was easy to understand").

[170] *See generally* Kohane, Masys, & Altman, *supra* note 77.

[171] Robertson, *supra* note 11, at 242.

[172] *See, e.g.,* Solberg, *supra* note 22 at 720–21; Green & Botkin, *supra* note 10, at 573.

[173] Cinnamon S. Bloss, Nicholas J. Schork, & Eric J. Topol, *Effect of Direct-to-Consumer Genomewide Profiling to Assess Disease Risk*, 364 N.E.J. Med. 524, 532 (2011) ("We found no evidence that learning the results of [Navigenics'] genomic risk testing had any short term psychological, behavioral, or clinical effects on the study subjects."); R. C. Green et al., *Disclosure of APOE Genotype for Risk of Alzheimer's Disease*, N. Engl. J. Med. 361, 245–254 (2009) (subjects who tested positive for increased risk of Alzheimer's had negative feelings, but no clinically significant psychological distress); *but see* Howard & Borry, *supra* note 80, at 107 (disputing the relevance of the Green study to DTC testing, because its subjects received medical supervision and counseling).

[174] GAO, 2006 DTC Investigation, *supra* note 89. 23andMe and its peers do not sell personalized nutritional products to consumers, but by juxtaposing DTC genome services with disreputable nutrigenomics companies in its 2010 testimony, GAO unfortunately created the impression that all DTC companies engage in deceptive marketing.

lifestyle decisions[175] or reduced compliance with preventative screening,[176] while predictions of heightened risk could trigger medication switches[177] or unwarranted prophylactic surgery.[178] However, these speculative fears are countered by evidence suggesting that predictive genetic testing motivates individuals to engage in healthy behavior[179] and plan for the future.[180]

9. Lack of Genetic Counseling. The American College of Medical Genetics and Genomics recommends both pre- and post-test counseling for asymptomatic individuals undergoing genetic screening.[181] Genetic counseling could compensate, at least to some extent, for low public health literacy and physicians' inexperience with genetic tests.[182] In the past, FDA has required post-test phone counseling in conjunction with DTC HIV testing;[183] something similar could be implemented for genomic testing, though it would almost certainly increase the cost to consumers.

10. Unanticipated Harms. Finally, the evolving DTC industry elicits relatively novel concerns, ranging from potential exploitation of consumers' genetic data by insurance companies and other entities, to ownership of participatory research results and innovations, to the security of personal data should a DTC company fail.[184] Privacy-related concerns include fears that individuals could be tested without their knowledge or consent, that family members may be exposed to information unwillingly, and that parents may test minor children, rather than letting their children make such choices for themselves.

F. *Heightened Scrutiny of DTC Genomic Services*

Aware of the concerns outlined above, federal agencies and advisory committees have closely monitored the genetic testing industry for over a decade. The Secretary of HHS convened two influential advisory committees to recommend improvements to regulation of genetic testing.[185] As DTC tests entered the market in 2006, FDA, FTC and CDC released a joint consumer alert recommending skepticism, and noting that

[175] SACGHS OVERSIGHT REPORT 131, 137; Krieger, *supra* note 19 (describing bioethicist George Annas' concerns that testing college students for a gene "linked to alcohol metabolism could influence students' alcohol consumption").

[176] *Id.*; Frueh et al., *The Future of Direct-to-Consumer Clinical Genetic Tests* 12 NATURE REVIEWS GENETICS 511, 511 (2011) (women who test negative for breast cancer mutations may stop getting mammograms, and "such an ill-informed action could be fatal").

[177] Carmichael, *supra* note 96.

[178] Andrew Pollack, *F.D.A. Faults Companies on Unapproved Genetic Tests*, N.Y. TIMES (June 11, 2010) ("It is not unknown for women to take out their ovaries if they are at high risk of ovarian cancer" (quoting Alberto Gutierrez, Director of OIVD)); *see also* Solberg, *supra* note 22, at 721 (noting that some women with BRCA mutations will undergo prophylactic double mastectomies, and "[a]n inaccurate test result could therefore be devastating").

[179] *See, e.g.*, J.S. Roberts et al, *Genetic Risk Assessment for Adult Children of People with Alzheimer's Disease: the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study*, 18 J. GERIATRIC PSYCHIATRY & NEUROLOGY 250, 254 (2005) (Alzheimer's risk information motivated engagement in risk-reducing activities like exercise).

[180] *See, e.g.*, Donald H. Taylor et al., *Genetic Testing For Alzheimer's And Long-Term Care Insurance*, 29 HEALTH AFFAIRS 102, 102 (2010) (individuals at increased risk of Alzheimer's are more likely to purchase long-term care insurance); *cf.* Roberts et al., *supra* note 179 at 252–54 (subjects desired Alzheimer's risk information primarily for "reasons related to advance planning and emotional coping with the threat of disease").

[181] Am. Coll. Med. Genetics & Genomics, *supra* note 78.

[182] Frueh et al., *supra* note 176, at 514.

[183] *See infra* notes 376-380 and accompanying text.

[184] deCODE Genetics, an Icelandic company, has already gone bankrupt once.

[185] SACGHS OVERSIGHT REPORT 13–15 (describing the mandates of the Secretary's Advisory Committee on Genetic Testing (SACGT) and its successor, the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS)).

FDA did not approve DTC testing services. Also in 2006, GAO's investigation of the DTC nutrigenomic service industry concluded that "the tests . . . mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information."[186] In 2008, New York and California sent cease-and-desist letters to DTC providers doing business in their states.[187]

In 2010, Congress, GAO, and FDA converged on the DTC genomics issue. FDA began sending untitled letters[188] to DTC companies, notifying them that their services were medical devices subject to FDA oversight. The first letter targeted Pathway Genomics, which had recently announced a marketing partnership with drugstore chain Walgreens; in light of the letter, Walgreens backed out.[189] 23andMe, Navigenics, deCODE Genetics, Knome, and gene chip manufacturer Illumina received untitled letters in June of that year, and FDA sent fourteen more untitled letters in July.[190] An FDA official credited FDA's untitled letter to Pathway Genomics with prompting Pathway Genomics and Counsyl to "change their business model[s]" and leave the DTC industry.[191] Meanwhile, FDA proposed a new approach to diagnostic test regulation, requested public comments, and held a hearing that included a panel on DTC genomic services.[192]

Also in July of 2010, GAO reported the results of its second DTC investigation to Congress, describing DTC services as "misleading and of little or no practical use" and "egregious examples of deceptive marketing."[193] GAO investigators reached these conclusions after four services, later identified as 23andMe, Navigenics, Pathway Genomics and DeCODE Genetics, reported inconsistent disease risk estimates for the same genetic samples.[194] Although the GAO report, like its 2006 predecessor, reflected an overly deterministic, simplified vision of genetics,[195] the House Committee on Energy and Commerce Subcommittee on Oversight and Investigations responded with a hearing that was highly critical of DTC genomic services.[196]

In early 2011, FDA held a public advisory committee meeting on DTC genomic services.[197] FDA has not issued further guidance since that meeting, and the DTC industry

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[186] GAO, 2006 DTC Investigation, *supra* note 89.

[187] Magnus et al., *supra* note 167.

[188] Untitled Letters, formerly known as Information Letters, request that a recipient voluntarily correct a violation without threatening enforcement action. Peter Barton Hutt, Richard A. Merrill, & Lewis A. Grossman, Food and Drug Law: Cases and Materials 1339 (3d ed. 2007).

[189] Rob Stein, *Walgreens Won't Sell Over-the-Counter Genetic Test After FDA Raises Questions*, Wash. Post (May 13, 2010); Letter from James L. Woods, Deputy Director, Patient Safety and Product Quality Office of In Vitro Diagnostic Device Evaluation and Safety, FDA, to James Plante, Founder and CEO, Pathway Genomics Corp., May 10, 2010, *available at* http://www.fda.gov/MedicalDevices/ResourcesforYou/Industry/ucm211866.htm.

[190] Pollack, *supra* note 15.

[191] Carmichael, *Q&A*, *supra* note 96 (quoting Alberto Gutierrez, Director of OIVD).

[192] *See infra* notes 284–286 and accompanying text.

[193] GAO, 2010 DTC Investigation, *supra* note 3.

[194] *Direct-to-Consumer Genetic Testing and the Consequences to the Public Health: Hearing before the Subcommittee on Oversight and Investigations of the House Energy and Commerce Committee*, 112th Cong. (July 22, 2010).

[195] *Cf.* David Castle & Nola M. Ries, *Ethical, Legal and Social Issues in Nutrigenomics: The Challenges of Regulating Service Delivery and Building Health Professional Capacity*, 62 Mutation Res. 138, 140 (2007) ("the [2006] GAO report has some serious methodological flaws that undermine many, if not all of its criticisms. For example, the report is premised on an incorrectly deterministic view of genetics").

[196] Dan Vorhaus, *"From Gulf Oil to Snake Oil": Congress Takes Aim at DTC Genetic Testing*, Genomics L. Rep. (July 22, 2010), http://www.genomicslawreport.com/wp-content/plugins/as-pdf/generate.php?post=4008.

[197] FDA, *March 8-9, 2011: Molecular and Clinical Genetics Meeting Announcement* (updated Apr. 6, 2011), http://www.fda.gov/AdvisoryCommittees/Calendar/ucm242537.htm (announcing a meeting to

is suspended in a regulatory limbo that may be stifling investment and innovation.[198] Federal interest continues, however: in March 2012, the President's Commission on Bioethical Issues solicited public comment on privacy and access in relation to whole-genome sequencing, issues highly relevant to the next wave of whole-genome DTC services.[199]

II. REGULATION OF GENETIC TESTS

As many scholars have noted, FDA is the obvious candidate to regulate DTC genomic services. The agency already exercises jurisdiction over medical devices, including in vitro genetic diagnostic tests, under the Federal Food, Drug, and Cosmetic Act ("FD&C Act"). For a century, FDA has been tasked with protecting the public safety, and although the agency's reputation has become slightly tarnished in recent years, it still enjoys substantial credibility with the public. FDA is involved in HHS' Personalized Health Care Initiative,[200] collaborating "on regulatory and translational science to accelerate the translation of research into medical products and therapies . . . to help make personalized medicine a reality;"[201] FDA's 2011 strategic plan flagged "stimulat[ing] innovation in clinical evaluations and personalized medicine" as a key priority.[202] And certain aspects of the DTC debate find informative parallels in FDA history— challenges the agency was successful in overcoming.[203]

On the other hand, because FDA has historically exercised enforcement discretion over tests conducted in clinical laboratories (so-called "lab-developed tests" or "homebrews"), the vast majority of genetic tests have never been FDA-approved. Regulating those tests will strain the agency's resources, and could overlap with the CLIA regime administered by CMS. FDA's regulatory framework for medical device regulation, which requires evidence of safety and efficacy, is poorly suited to predictive genetic tests or genomic services. Finally, FDA's regulation of information services may implicate First Amendment concerns and larger, long-term questions about how to regulate patients' data and access to medical information.

This Part outlines FDA's statutory and regulatory authority over medical devices and in vitro diagnostics, and identifies other governmental actors with overlapping authority.

A. *Medical Devices*

The Federal Food, Drug, and Cosmetic Act of 1938 ("1938 Act") gave FDA jurisdiction over medical devices, including diagnostic tests.[204] The 1938 Act defined

"discuss and make recommendations on scientific issues concerning direct to consumer (DTC) genetic tests that make medical claims").

[198] ROUNDTABLE ON TRANSLATING GENOME-BASED RESEARCH FOR HEALTH, INSTITUTE OF MEDICINE, GENOME-BASED DIAGNOSTICS: CLARIFYING PATHWAYS TO CLINICAL USE: WORKSHOP REPORT 12–14 (Nat. Acad. Press 2012) [hereinafter IOM PATHWAYS WORKSHOP SUMMARY].

[199] DHHS, Request for Comments on Issues of Privacy and Access With Regard to Human Genome Sequence Data, 77 Fed. Reg. 18247, 18247 (Mar. 27, 2012) (requesting comment on, inter alia, "balancing individual and societal interests with regard to the sharing of and access to large-scale human genomic data. . . who should have access to these data and who should control access; models and mechanisms for governing access to genomic information").

[200] DHHS, PERSONALIZED HEALTH CARE: OPPORTUNITIES, PATHWAYS, RESOURCES, 32–36 (2007).

[201] Margaret A. Hamburg & Francis S. Collins, *The Path to Personalized Medicine,* 363 NEW ENG. J. MED. 301, 304 (2010).

[202] FDA, ADVANCING REGULATORY SCIENCE AT FDA: A STRATEGIC PLAN 10–13 (Aug. 2011), *available at* http://www.fda.gov/regulatoryscience.

[203] *See infra* Part III.A.

[204] Pub. L. No. 75-717, 52 Stat. 1040 (1935).

drugs and devices in "nearly identical terms,"[205] as products "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease," or "intended to affect the structure or any function of the body."[206] The 1938 Act authorized FDA to take action against adulterated or misbranded medical devices, most importantly under section 502, "which declares a drug or device to be misbranded '[i]f its labeling is false or misleading in any particular.'"[207] However, medical devices were not regulated as tightly as drugs, and device manufacturers were not required to obtain premarket clearance or approval from FDA.[208]

FDA sometimes sought to exert additional regulatory authority over medical devices by deeming them "drugs," a strategy upheld by the Supreme Court in *United States v. Bacto-Unidisk*.[209] After *Bacto-Unidisk*, FDA took the position that it could regulate all diagnostic products as drugs, although it refrained from doing so.[210] But the agency's authority over diagnostic products was not completely clear. Just a few years after *Bacto-Unidisk*, *United States v. Article of Drug (Ova II)* held that a pregnancy test was not a "drug" within FDA's jurisdiction.[211] The *Ova II* court distinguished *Bacto-Unidisk* on the grounds that while a test for diagnosing a bacterial infection might be a "drug" under the FD&C Act, a pregnancy test "is not a test for the diagnosis of disease. It is no more than a test for news, which may be either good news or bad news depending on whether pregnancy is wanted or not."[212]

Congress responded by expanding and clarifying FDA's statutory authority over the medical device category.[213] The new, expansive definition of "device" in the 1976 Amendments to the FD&C Act includes, *inter alia*, any

> instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is . . . *intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease*, in man or other animals, or . . . intended to affect the structure or any function of the body of man or other animals.[214]

The 1976 Amendments distinguished devices from drugs by specifying that devices do not "achieve [their] primary intended purposes through chemical action" or metabolism.[215] Congress intended that medical device regulation "should differ from,

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[205] Peter Barton Hutt, *A Brief History of the Regulation of In Vitro Diagnostic Products*, *in* In Vitro Diagnostics: The Complete Regulatory Guide 1, 1 (Scott D. Danzis & Ellen J. Flannery eds., 2010).

[206] *Id.* at 2 (quoting FD&C Act §§ 201(g), (h); 21 U.S.C. §§ 321(g), (h)).

[207] Peter Barton Hutt, Richard A. Merrill, & Lewis A. Grossman, Food and Drug Law: Cases and Materials 969 (3d ed. 2007).

[208] Peter Barton Hutt, *A Brief History of the Regulation of In Vitro Diagnostic Products*, *in* In Vitro Diagnostics: The Complete Regulatory Guide 1, 5 (Scott D. Danzis and Ellen J. Flannery eds., 2010).

[209] 394 U.S. 784 (1969). The Bacto-Unidisk product was a paper disc impregnated with antibiotics, which was exposed to a patient sample. The disc helped clinicians identify the best antibiotic to administer to the patient. The Supreme Court accepted the agency's determination that the disc was a drug, reasoning that "the word 'drug' is a term of art for purposes of the Act, encompassing far more than the strict medical definition of that word," and that the FDCA "is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health."

[210] Hutt, *supra* note 205, at 4.

[211] 414 F. Supp. 660, 664 (D.N.J. 1975), *aff'd mem.*, 535 F.2d 1248 (3d Cir. 1976).

[212] 414 F. Supp. at 664.

[213] Hutt, *supra* note 205, at 4.

[214] FD&C Act § 201(h)–(h)(2) (emphasis added).

[215] FD&C Act § 201(h)(3).

and be less stringent than, [that] designed for drugs."[216] However, Congress also intended that FDA's medical device authority should be broad enough to reach products like the diagnostic test in *Ova II*.[217]

Drugs and medical devices cannot be legally marketed until FDA is satisfied that they are "safe and effective." Though FDA may not always intervene, the agency's absolute premarket approval authority carries with it the "concomitant authority to prohibit distribution of any unapproved product—even for dying patients."[218] FDA cemented this authority in the late 1970s, when it cracked down on Laetrile, a popular but unapproved alternative cancer treatment.[219] Cancer patients and their families sued, arguing that terminally ill patients and their physicians should have the choice to use the drug.[220] But the Supreme Court, approving the agency's cautious approach to safety and efficacy, unanimously upheld the FDA's authority to ban Laetrile.[221]

Today, FDA regulates a wide range of products as medical devices, from wheelchairs to "mobile medical apps."[222] A product's "intended use" is critical to determining whether FDA considers it a medical device under FD&C Act § 201(h). For example, while general-purpose calculator software is not a medical device, FDA will regulate software intended to calculate drug doses based on a patient's height and weight.[223] FDA considers the manufacturer's objective intent, as demonstrated by a device's labeling, advertising, statements, and other factors, to be evidence of intended use.[224]

A device's intended use also determines the scope of premarket review. All medical devices are subject to a three-tier, risk-based system of regulatory oversight. Devices are classified according to "the level of [regulatory] control necessary to assure the safety and effectiveness of the device," when used as intended, taking into account the potential risks to the patient or user.[225] Class I includes devices that pose the lowest risk to the patient or user, such as latex exam gloves.[226] Mercury thermometers,[227] blood

[216] Peter Barton Hutt, Richard A. Merrill, & Alan M. Kirschenbaum, *The Standard of Evidence Required for Premarket Approval Under the Medical Device Amendments of 1976*, 47 FOOD & DRUG L.J. 605, 628 (1992); *see also* Eric R. Claeys, *The Food and Drug Administration and the Command-and-Control Model of Regulation*, 49 St. Louis U. L.J. 105, 115–17 (2004).

[217] *See* Clinical Reference Lab. v. Sullivan, 791 F. Supp. 1499, 1508 (D. Kan. 1992), *aff'd in relevant part sub nom*. United States v. Undetermined Number of Unlabeled Cases, 21 F.3d 1026 (10th Cir. 1994) (deferring to FDA's determination that specimen collection containers sent to and from a clinical laboratory were medical devices under the 1976 Amendments). The district judge explained that Congress disapproved of *Ova II* and intended to correct it in the 1976 Amendments. *Id.* (citing House Comm. on Interstate and Foreign Commerce, Medical Device Amendments of 1976, H.R. Rep. No. 853, 94th Cong., 2d Sess. 9, 14 (1976)).

[218] Gail H. Javitt, *Drugs and Vaccines for the Common Defense: Refining FDA Regulation to Promote the Availability of Products to Counter Biological Attacks*, 19 J. CONTEMP. HEALTH L. & POL'Y 37, 98 (2002).

[219] DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA 414–26 (2010).

[220] *Id.*

[221] United States v. Rutherford, 442 U.S. 544, 555–60 (1979).

[222] FDA, *Draft Guidance for Industry and Food and Drug Administration Staff - Mobile Medical Applications* (July 21, 2011).

[223] FDA, *supra* note 222 ("software that calculates a drug dose based on a patients height, weight, mass, and other patient-specific information [is regulated] as a 'Drug Dose Calculator' under 21 CFR 868.1890").

[224] *See* 45 Fed. Reg. 60576, 60579 (1980) ("The most important factors [FDA] will consider in determining the intended use of a particular product are the labeling, advertising, and other representations accompanying the product."); *Meaning of intended uses*, 21 C.F.R. § 801.4 (2011).

[225] FDA, *Device Classification*, *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default.htm (last visited Apr. 29, 2012). The device classification process is codified in 21 C.F.R. §§ 862–92 (2011).

[226] 21 C.F.R. § 878.4460 (2011).

[227] 21 C.F.R. § 880.2920 (2011).

pressure cuffs,[228] and over-the-counter pregnancy tests[229] are Class II devices. Class III devices, such as extended wear soft contact lenses[230] and test kits for diagnosing HIV infection,[231] are those that FDA has determined pose the greatest risk.[232] Subject to various exemptions, FDA clears Class I and II devices through the 501(k) premarket notification process, which requires the manufacturer to demonstrate that the new device is "substantially equivalent" to a legally marketed device. Class III devices are subject to a more stringent process, which requires a premarket approval application ("PMA") providing "reasonable assurance" that the device is safe and effective.[233]

FDA oversees medical device labeling in two important ways. First, as a condition of allowing a device to be marketed, FDA can impose affirmative labeling requirements, such as usage instructions and disclaimers. These labeling requirements are a key tool in FDA's arsenal.[234] Second, all medical devices are subject to the general regulatory controls of the FD&C Act, including its adulteration and misbranding provisions.[235] A device may be adulterated or misbranded for various reasons, including "[i]f its labeling is false or misleading in any particular."[236] FDA has asserted, and courts have upheld, an expansive definition of "labeling" that reaches virtually all information "accompanying" a device, including posters, tags, pamphlets, circulars, booklets, brochures, instruction books, direction sheets, fillers, and advertising materials;[237] deficiencies in any of the instructional or informational materials relating to a device may be grounds for barring distribution.

FDA may also impose special controls on a device, over and above the FD&C Act's general controls. FDA may restrict a device's sale, distribution or use,[238] and/or require it to be prescribed by a licensed practitioner.[239] FDA may also impose postapproval requirements, such as mandatory postmarketing evaluation and reporting.[240] FDA has

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[228] 21 C.F.R. § 870.1120 (2011).

[229] 21 C.F.R. § 862.1155 (2011).

[230] 21 C.F.R. § 886.5925 (2011).

[231] Bruce Patsner, *New "Home Brew" Predictive Genetic Tests Present Significant Regulatory Problem*s, 9 Hous. J. Health L. & Pol'y 237, 247 (2009).

[232] *Id.*

[233] Hutt, Merrill, & Kirschenbaum, *supra note* 216, at 607–09. The 1976 Amendments allowed certain types of Class III devices already on the market ("preamendment devices") to be cleared through the less stringent 501(k) process, until FDA issues regulations requiring PMAs or reclassifies them. GAO, Medical Devices: FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process, 10 (2009), available at http://www.gao.gov/assets/290/284882.pdf. FDA has been criticized for continuing to allow preamendment devices to be cleared under the less stringent 501(k) process. *Id.*

[234] Peter Barton Hutt, *Turning Points in FDA History*, *in* Perspectives on Risk and Regulation: the FDA at 100, 14–28, at 18 (Arthur Daemmrich & Joanna Radin, eds. 2007).

[235] FDA, *Labeling Requirements–Misbranding, available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLabeling/GeneralDeviceLabelingRequirements/ucm052190.htm, (last visited Apr. 29, 2012). The jurisdictional prerequisite of a connection with interstate commerce is presumed. FD&C Act § 709, 21 U.S.C. § 379a.

[236] FD&C Act § 302.

[237] FD&C Act §§ 201(k), (m); FDA, *Labeling Requirements – Misbranding, supra* note 235.

[238] FD&C Act § 520(e). A device may be restricted "if, because of its potentiality for harmful effect or the collateral measures necessary to its use, the Secretary determines that there cannot otherwise be reasonable assurance of its safety and effectiveness." *Id.*

[239] 21 C.F.R. § 801.109. While most prescription devices are also restricted, the categories are not identical. *See, e.g.,* Becton Dickinson v. FDA, 589 F.2d 1175, 1181 (2d Cir. 1978); Patsner, *supra* note 231.

[240] Peter Barton Hutt, Richard A. Merrill, & Lewis A. Grossman, Food and Drug Law: Cases and Materials 1017 (3d ed. 2007). § 522 postmarket surveillance requirements, as modified by recent legislation, apply only to devices "the failure of which would be reasonably likely to have serious adverse health consequences." *See* FDA, *Postmarket Surveillance Under Section 522 of the Federal Food, Drug and Cosmetic*

not yet implemented a comprehensive system for device postmarket reporting and surveillance, but recent legislation requires the agency to move in that direction.[241]

B. *In Vitro Diagnostics*

In vitro diagnostic products ("IVDs") represent a subset of medical devices including "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."[242] IVDs include products used to collect, prepare, or examine human tissue samples (e.g., blood, saliva, urine).[243] IVDs range from home pregnancy tests marketed directly to consumers, to test kits sold to hospitals and labs.[244] As with all medical devices, "intended use" is key: a general-purpose clinical laboratory instrument may not be a "medical device" for FDA purposes, unless it is intended for diagnostic use.[245]

Like other medical devices, IVDs are subject to the Act's general controls, and additional controls may be imposed under the three-tier classification scheme for medical devices.[246] Most FDA-reviewed IVDs are cleared for marketing via the 501(k) process,[247] which requires a showing that the IVD is "substantially equivalent" in safety and efficacy to a legally marketed "predicate device" that does not require a PMA.[248] Manufacturers of new IVDs not eligible for 501(k) clearance must submit a PMA or request de novo classification.[249]

FDA requires that PMAs supply "valid scientific evidence" supporting a "reasonable assurance that the device is safe and effective" for its intended use.[250] In evaluating safety and efficacy, FDA reviewers engage in cost-benefit analysis. A device is sufficiently safe if, when used as intended, "the probable benefits to health . . . outweigh any probable risks."[251] A device is sufficiently effective if, when used as intended, it "will provide clinically significant results" in a "significant portion of the target population."[252]

If a test's intended use is deemed high-risk, FDA review will be more demanding. For example, a cancer test intended to prompt a patient's referral from a generalist

Act (Apr. 25, 2006), *available at* http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072517.htm.

[241] Peter Barton Hutt, *The State of Science at the Food and Drug Administration*, 60 ADMIN. L. REV. 431, 445 (2008). *See also* Evans, *Seven Pillars*, *supra* note 61, at 419 (2010) (arguing that to cope with genomic technology, FDA must abandon its focus on premarket approval and prioritize postmarket information collection and monitoring).

[242] 21 C.F.R. § 809.3(a) (2011).

[243] FDA, *Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions* 6 (June 25, 2010). IVDs are overseen by the FDA Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD). *Id.*

[244] *See* Gail H. Javitt, Erica Stanley & Kathy Hudson, *Direct-to-Consumer Genetic Tests, Government Oversight, and the First Amendment: What the Government Can (and Can't) Do to Protect the Public's Health*, 57 OKLA. L. REV. 251, 271–72 (2004).

[245] Jeffrey Gibbs, *Regulatory Pathways for Clearance or Approval of IVDs*, *in* IN VITRO DIAGNOSTICS: THE COMPLETE REGULATORY GUIDE 43, 57 (Scott D. Danzis and Ellen J. Flannery eds., 2010).

[246] *See generally* Gibbs, *supra* note 245, at 43–68. *See also* 21 C.F.R. §§ 862, 864, 866 (2011) (existing IVD classifications).

[247] *Id.* at 45 (noting that in 2005, OIVD cleared 434 501(k)s, but approved only nine PMAs).

[248] *Id.* at 51–52. If there is no predicate device suitable on the market, the applicant may request de novo classification. *Id.* at 52–53. While FDA has exempted many Class I and II devices from 501(k), the exemption does not apply to IVDs for "noninvasive testing" and/or "use in screening or diagnosis of familial or acquired genetic disorders," which presumably includes DTC genetic tests. 21 C.F.R. § 880.9 (2011).

[249] Gibbs, *supra* note 245, at 52–53.

[250] 21 C.F.R. § 860.7(c)(1) (2011).

[251] 21 C.F.R. § 860.7(d)(1) (2011).

[252] 21 C.F.R. § 860.7(e)(1) (2011).

to a specialist was perceived as having lower risk than a similar test intended to prompt referral from a specialist to a generalist, and the latter test received additional review.[253] Agency staff "rel[y] on valid scientific evidence in making risk and benefit determinations . . . including the critical issue of identifying 'probable risks' and 'probable benefits' in the first place."[254] A device may be approved even if only a minority of patients would accept the risks, so long as the information required to make an informed decision is provided.[255]

FDA has approved relatively few genetic IVDs, most of which are Class II or III.[256] A pharmacogenomic example is Roche's AmpliChip CYP450 test, a gene chip that screens for polymorphisms in the Cytochrome P450 2D6 (CYP2D6) gene. Variations in CYP2D6, a metabolic gene, influence how quickly a patient processes certain drugs; knowing a patient's CYP2D6 genotype may help a physician avoid under-dosing or over-dosing. FDA approved the CYP450 test via the de novo classification process, as a Class 2 device with special controls.[257]

The ACCE framework, which describes genetic tests in terms of analytical validity, clinical validity, and clinical utility,[258] does not map squarely onto FDA's statutory mandate to evaluate safety and effectiveness.[259] FDA is sometimes described as requiring only evidence of analytical validity and clinical validity.[260] However, clinical utility, which involves balancing the benefits and harms of a test,[261] seems likely to be encompassed by FDA's risk-benefit approach to safety and effectiveness.

FDA will require evidence of clinical utility to support manufacturer claims of clinical utility for a test,[262] and some experts assert that IVDs lacking clinical utility are generally not approved.[263] An FDA official recently explained that while FDA reviews analytic validity and clinical validity, the most important factor in premarket review is intended use; whether that use has a broad or narrow scope determines how useful clinical utility is to the review.[264] Roche's CYP450 test, for example, was approved without prospective evidence of clinical utility.[265] Instead, FDA reviewed research supporting the clinical

[253] Gibbs, *supra* note 245, at 58 (in general, "a test with an intended use claim of 'ruling in' a disease will be reviewed differently than 'ruling out.'").

[254] FDA, *Guidance for Industry and Food and Drug Administration Staff: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications* (Mar. 27, 2012), *available at* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf.

[255] *Id.*

[256] Patsner, *supra* note 231, at 247.

[257] FDA, *510(k) Substantial Equivalence Determination Decision Summary for Roche AmpliChip CYP450 microarray for identifying CYP2D6 genotype (510(k) Number k042259)*, http://www.accessdata.fda.gov/cdrh_docs/reviews/K042259.pdf (last visited Apr. 29, 2012).

[258] *See supra* Part I, notes 38–46, and accompanying text.

[259] SACGHS Oversight Report 97 ("the law and regulations do not define clinical validity as a parameter to be reviewed by FDA. Instead, FDA is charged with assessing the safety and effectiveness of the device or test").

[260] SACGHS Oversight Report 135; IOM Pathways Workshop Summary 8.

[261] SACGHS Oversight Report 115.

[262] *Id.* at 135; IOM Pathways Workshop Summary 35.

[263] Gibbs, *supra* note 245, at 54.

[264] IOM Pathways Workshop Summary 35 (paraphrasing Alberto Gutierrez, Director of OIVD).

[265] Justin P. Annes, Monica A. Giovanni, & Michael F. Murray, *Risks of Presymptomatic Direct-to-Consumer Genetic Testing*, 363 N.E.J. Med. 1100, 1100 (2010) ("The FDA deemed [Roche's test] acceptable for aiding 'clinicians in determining therapeutic strategy and treatment doses,' despite the dearth of prospective data showing clinical utility."); Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group, *Recommendations from the EGAPP Working Group: Testing for Cytochrome P450 Polymorphisms in Adults With Nonpsychotic Depression Treated With Selective Serotonin Reuptake Inhibitors*, 9 Genetics in Med. 819, 820 (2007) ("The FDA extensively reviewed the technical performance of [Roche's] assay; review of clinical validity was limited, and clinical utility was not evaluated.").

validity of CYP450 genotyping in certain circumstances (i.e., before prescribing certain drugs).[266] FDA emphasized the role of the clinician's "professional judgment" in using the test, and warned it should not be used with regard to drugs for which the underlying metabolic process had not been "clearly established."[267]

C. *Laboratory-Developed Tests (LDTs)*

FDA has long refrained from regulating a category of tests offered by clinical laboratories, called laboratory-developed tests ("LDTs") or "home brew" tests.[268] LDTs are developed, validated, and offered within a single laboratory.[269] Because LDTs are not cleared or approved by FDA, developing a diagnostic test as an LDT allows manufacturers "to avoid stringent FDA oversight."[270] However, LDTs cannot be distributed to other laboratories, hospitals or clinics.[271] LDTs were originally used for rare conditions, but the LDT market has "exploded" in recent years.[272] Although FDA has approved a handful of genetic test kits, the vast majority of genetic tests, including the BRCA breast cancer gene tests,[273] are LDTs that FDA has never cleared or approved.[274]

Since at least the early 1990s, FDA has asserted that LDTs are medical devices within its jurisdiction, but that it would nonetheless exercise "enforcement discretion."[275] In 1992, FDA planned to impose premarket requirements on LDTs, but faced with industry resistance, instead opted to regulate the "active ingredients" in LDTs.[276] These "analyte specific reagents" ("ASRs") may be subject to premarket notification or approval requirements, depending on their intended use.[277] Among other things, the ASR rule was meant to ensure that LDTs used quality ingredients, and to clarify that LDTs are not themselves FDA-approved or cleared.[278] FDA has explained that it determined regulation of LDTs was not necessary "due to [FDA's] confidence in high-complexity laboratories' ability to use ASRs."[279]

[266] FDA, *supra* note 257; FDA, *Class II Special Controls Guidance Document: Drug Metabolizing Enzyme Genotyping System - Guidance for Industry and FDA Staff* (Mar. 10, 2005), http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077933.htm ("Prospective clinical testing to determine clinical validity may not be necessary for validation of DME genotyping systems, if there is an established scientific framework and sufficient body of evidence supporting the clinical validity and utility of your device.").

[267] FDA, *supra* note 170.

[268] Hutt, *supra* note 208, at 7.

[269] FDA, *Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments*, 75 Fed. Reg. 34,463, 34,463 (June 17, 2010); Ellen Flannery & Scott Danzis, *FDA Plans to Regulate Laboratory Developed Tests as Devices*, 7 J. Med. Device Reg. 63, 63 (2010).

[270] Gail H. Javitt & Kathy Hudson, *Federal Neglect: Regulation of Genetic Testing*, 22 ISSUES IN SCI. & TECH. 59, 61 (2006).

[271] *Id.*

[272] Patsner, *supra* note 231 at 255, 265 ("an entire industry of diagnostic drug assays and genetic tests has developed outside the penumbra of FDA regulatory oversight").

[273] SACGHS OVERSIGHT REPORT 39 (2008) ("although BRCA tests are widely used to predict patients' future risk of breast and ovarian cancer, no BRCA test has been approved by FDA.").

[274] Evans, *Seven Pillars*, *supra* note 61, at 419, 465 (2010) ("Over 90% of genetic tests currently on the market are lab-developed tests (LDTs) regulated under CLIA and not regulated by FDA.").

[275] Ellen Flannery & Scott Danzis, *FDA Plans to Regulate Laboratory Developed Tests as Devices*, 7 J. MED. DEVICE REG. 63, 63 (2010).

[276] Jeffrey N. Gibbs, *The Past, Present, and Future of ASRs*, IVD TECHNOLOGY (Nov. 1, 2003), available at http://www.ivdtechnology.com/article/past-present-and-future-asrs.

[277] FDA, *Guidance for Industry and FDA Staff. Commercially Distributed Analyte Specific Reagents (ASRs): Frequently Asked Questions.* (2007), *available at* http://www.fda.gov/cdrh/oivd/guidance/1590.pdf. *See generally* 21 C.F.R. § 864.4020 (definition and classification of ASRs), § 809.30 (restrictions on sale, distribution and use), and § 809.10(e) (labeling).

[278] *Id.*

[279] FDA, *Draft Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays* 2 (Sept. 7, 2006). The draft guidance was revised in 2007. FDA, *Draft*

In 2006, FDA issued a draft guidance requiring premarket clearance or approval for a subset of LDTs known as in vitro multivariate index assays ("IVDMIAs").[280] IVDMIAs are more complex than other LDTs, "involv[ing] steps that are not synonymous with the use of ASRs and that are not within the ordinary 'expertise and ability' of laboratories that FDA referred to when it promulgated the ASR rule."[281] The first FDA-cleared IVDMIA was "MammaPrint," a gene expression test used to predict whether early-stage breast cancer would metastasize.[282] However, the IVDMIA guidance was never finalized, and FDA has apparently abandoned that approach.[283]

In June 2010, FDA announced that it would exercise risk-based regulatory oversight over all LDTs, not just IVDMIAs.[284] The agency expressed concern that LDTs, including those "marketed directly to consumers," were becoming more complex and "playing an increasingly important role in clinical decision-making and disease management, particularly in the context of personalized medicine."[285] FDA subsequently requested public comments and held a stakeholder meeting.[286] However, almost two years later, FDA has not yet released further guidance.

It is unclear whether FDA has the resources to implement premarket clearance and approval for thousands of LDTs, even if it wished to do so.[287] Presumably, FDA would focus its attention on high-risk LDTs and continue exercising enforcement discretion for more routine tests. Even under the current system, LDTs are not entirely unregulated; some LDT components, such as ASRs, must be FDA-approved, and FDA occasionally takes enforcement action against tests that fail to qualify as LDTs.[288] In addition, laboratories that conduct LDTs are subject to the Clinical Laboratory Improvement Amendments of 1988 ("CLIA"), overseen by the Centers for Medicare and Medicaid Services ("CMS").[289]

DTC genomic services, which include genotyping by a CLIA-certified laboratory, are often assumed to be LDTs. However, FDA does not seem to see it that way. FDA's 2010 untitled letters to several DTC genome service providers stated that "FDA does not consider your device to be [an LDT] because [it] is not developed by and used in a single laboratory."[290] This distinction seems to emphasize the two-step process used

Guidance for Industry, Clinical Laboratories, and FDA Staff: In Vitro Diagnostic Multivariate Index Assays (July 26, 2007).

[280] *Id.*

[281] *Id.*

[282] FDA, *News Release: FDA Clears Breast Cancer Specific Molecular Prognostic Test* (Feb. 6, 2007) (describing the clearance of the MammaPrint test based on "data from a study using tumor samples and clinical data from 302 patients at five European centers.").

[283] Mya Thomae, *Are Multiplex Assays Approvable?* 3 Bioanalysis 1791, 1791–94 (2011); Ellen Flannery & Scott Danzis, *FDA Plans to Regulate Laboratory Developed Tests as Devices*, 7 J. Med. Device Reg. 63, 66 n.9 (2010).

[284] FDA, *Oversight of Laboratory Developed Tests; Public Meeting; Request for Comments*, 75 Fed. Reg. 34,463, 34,463–64. (June 17, 2010). FDA subsequently reopened the comment period until September 15, 2010. 75 Fed. Reg. 51,280.

[285] *Id.*

[286] *Id.*

[287] SACGHS Oversight Report 107 ("Very few LDTs . . . are reviewed by FDA, and the agency does not currently have sufficient resources to carry out such reviews for all tests if existing review mechanisms are used.").

[288] *See, e.g.*, David Filmore, *LabCorp Pulls OvaSure, But Charges FDA With Overreaching*, The Gray Sheet (Oct. 27, 2008) (describing FDA's 2008 warning letter informing LabCorp that its OvaSure biomarker test was not an LDT, because it was "designed, developed, and validated" by Yale researchers, not the clinical laboratory); Patsner, *supra* note 231 at 267.

[289] *See infra* notes 307-329 and accompanying text.

[290] Letter from Alberto Gutierrez, Director, Office of In Vitro Diagnostic Device Evaluation and Safety, FDA, to Anne Wojcicki, CEO, 23andMe (June 10, 2010) ("FDA does not consider your device to be a laboratory developed test because [it] is not developed by and used in a single laboratory"); Letter

by these services: after the third-party laboratory genotypes a consumer's sample, the information is then transmitted to the DTC company for interpretation.[291] It unclear if FDA will continue to emphasize this distinction, or if its new guidance will treat DTC genome services as LDTs.[292] To complicate things further, under the IVDMIA guidance, DTC genomic services likely would have been IVDMIAs.[293]

FDA also recently issued new guidance on IVD products used for research ("RUO" products),[294] which sometimes make their way into LDTs.[295] Since the 1970s, FDA has allowed unapproved IVD products to be marketed for research use, if the intended testing is not invasive or risky and "is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure."[296] FDA permits RUO instruments and reagents to be used in "discovering and developing novel and fundamental medical knowledge related to human disease and conditions," such as "attempting to isolate a gene linked with a particular disease," as long as they are "not intended to produce results for clinical use."[297] RUO products must be labeled "For Research Use Only. Not for use in diagnostic procedures."[298] An RUO product intended by its manufacturer for clinical diagnostic use will be deemed adulterated under section 501(f) and misbranded under section 502(o).[299]

It is unclear to what extent RUOs are currently used in LDTs.[300] However, RUO gene chips are used by some genomic services, including 23andMe.[301] In 2010, FDA stated that chip manufacturer Illumina was "knowingly providing the HumanHap550 array to 23andMe and deCODE Genetics for clinical diagnostic use without FDA clearance or approval."[302] FDA's 2011 draft RUO guidance characterizes a manufacturer's knowledge that RUO supplies are or might be used for clinical purposes as evidence of intended non-research use,[303] a position manufacturers have criticized as unfair.[304] Manufacturers

from Alberto Gutierrez, Director, Office of In Vitro Diagnostic Device Evaluation and Safety, FDA, to Earl M. Collier, CEO, deCODE Genetics (June 10, 2010) (similar); Letter from Alberto Gutierrez, Director, Office of In Vitro Diagnostic Device Evaluation and Safety, FDA, to Jorge Conde, CEO, Knome, Inc. (June 10, 2010) (similar).

[291] *See, e.g.*, Ericksson et al., *supra* note 106, at 2 (summarizing 23andMe's process).

[292] *See infra* Part III, notes 413–415 and accompanying text.

[293] HS OVERSIGHT REPORT 180-181 (IVDMIAs include "a device that integrates a patient's age, gender, and genotype of multiple genes to predict risk of or diagnose a disease or condition"; however, it is unclear when multiple interpretation tasks are combined in different locations if they constitute an IVDMIA.); Magnus, *supra* note 167 (stating that there is "only a thin line" between IVDMIAs and DTC genomic services).

[294] FDA, *Draft Guidance for Industry and FDA Staff - Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions* (June 1, 2011), *available at* http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm253307.htm.

[295] Gibbs, *Past, Present, and Future*, supra note 276.

[296] Hutt, *supra* note 205, at 8. *See also* 21 C.F.R. § 812.2(c) (2011).

[297] FDA, *supra* note 294.

[298] 21 C.F.R. § 809.10(c)(1)(i) (2011). IVDs in the clinical research stage of product development are exempted for investigational study or testing purposes under the investigational device exemption (IDE) regulation, 21 C.F.R. part 812, or as Investigational Use Only ("IUO") devices under 21 C.F.R. § 812.2(c)(3) (2011).

[299] FDA, *supra* note 294.

[300] Alex Philippidis, *Diagnostic Market Stakeholders Take Aim at FDA's RUO/IUO Draft Guidance*, GENETIC ENG'G & BIOTECHNOLOGY NEWS (July 6, 2011), *available at* http://www.genengnews.com/insight-and-intelligenceand153/diagnostic-market-stakeholders-take-aim-at-fda-s-ruo-iuo-draft-guidance/77899428/.

[301] *Our Technology and Standards*, 23ANDME, https://www.23andme.com/howitworks/ (last visited Apr. 29, 2012) ("We utilize the Illumina OmniExpress Plus Research Use Only Chip which has been customized for use in all of our products and services by 23andMe.").

[302] Letter from Alberto Gutierrez, Director, OIVD, FDA, to Mr. Jay T. Flatley, President and CEO, Illumina, Inc. (June 10, 2010).

[303] *FDA Draft Guidance*, *supra* note 297.

[304] Philippidis, *supra* note 300.

also object that stricter regulation could disrupt the availability of essential laboratory supplies.[305] Several members of Congress are concerned that the draft guidance would extend FDA regulation into the space occupied by CLIA.[306]

D. *CLIA Oversight of Clinical Laboratories*

The Clinical Laboratory Improvement Act of 1967 originally authorized the Centers for Disease Control ("CDC") to develop and implement standards for clinical laboratories conducting diagnostic tests.[307] Pursuant to the Clinical Laboratory Improvement Amendments of 1988 ("CLIA"), responsibility for administration of these requirements currently rests with the Centers for Medicare and Medicaid Services ("CMS").[308]

Approximately 225,000 non-research laboratories in the United States are subject to CLIA.[309] CLIA's requirements vary according to the complexity of a given laboratory's testing ("waived," "moderate-," or "high-complexity").[310] Laboratories performing moderate- and high-complexity testing must be certified; CLIA-certified labs are inspected for personnel requirements, quality control and assurance, proficiency testing, and recordkeeping.[311] In most states, labs are inspected by state survey agencies or nonprofit accrediting organizations using CLIA standards; New York and Washington State operate their own CLIA-exempt programs.[312]

Under CLIA, laboratories that develop LDTs must establish "performance specifications" for accuracy, precision, analytical sensitivity, analytical specificity, result reporting, reference intervals, and "any other performance characteristic required for test performance."[313] CLIA does not specify the procedures or protocols that laboratories will use; rather, the laboratories themselves are responsible for "ensur[ing] that their test results are accurate, reliable, timely, and confidential and do not present the risk of harm to patients."[314] CMS regulations require CLIA laboratories to obtain a "written or electronic request for patient testing from an authorized person," but the regulation does not require that the "authorized person" be a physician.[315]

CMS' oversight of CLIA laboratories has been criticized, with GAO finding in 2006 that "CMS's oversight of clinical lab quality is inadequate to ensure that labs are meeting CLIA requirements," and that CMS failed to sanction labs with "serious, condition-level deficiencies on consecutive surveys."[316]

Although few genetic testing errors causing harm to patients have been documented in CLIA labs,[317] CLIA oversight of genetic testing has received ongoing federal attention. In 1997, the National Institutes of Health ("NIH") and the U.S. Department of Energy

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[305] *Id.*

[306] Letter from Chairman Joseph R. Pitts, House of Representatives Committee on Energy and Commerce Subcommittee on Health, to FDA Commissioner Margaret A. Hamburg (Mar. 19, 2012).

[307] Hutt, *supra* note 205, at 7.

[308] CMS, *Clinical Laboratory Improvement Amendments (CLIA), available at* http://www.cms.hhs.gov/Regulations-and-Guidance/Legislation/CLIA/index.html.

[309] *Id.*

[310] *Id.* FDA makes these complexity determinations. 42 C.F.R. § 493.17(c)(1)(i) (2011).

[311] *Id.*

[312] GAO, Clinical Lab Quality: CMS and Survey Organization Oversight Should Be Strengthened 8–10 (2006). *See also* Ellen Flannery & Scott Danzis, *FDA Plans to Regulate Laboratory Developed Tests as Devices*, 7 J. Med. Device Reg. 63, 63 (2010) ("New York … requires that all LDTs be approved by state authorities before they may be used in testing specimens from state residents."); SACGHS Oversight Report 35 ("New York State has specific standards for genetic testing, but Washington State does not.").

[313] 42 C.F.R. § 493.1253 (2011).

[314] SACGHS Oversight Report 3.

[315] 42 C.F.R. § 493.1241(a) (2011).

[316] GAO, Clinical Lab Quality, *supra* note 312.

[317] SACGHS Oversight Report 32.

("DOE") convened a joint Task Force on Genetic Testing, which recommended "the creation of a specialty of genetics that would encompass all predictive genetic tests" to the Clinical Laboratory Improvement Advisory Committee ("CLIAC").[318] CLIAC endorsed the proposed genetic test specialty, as did CDC and the Secretary's Advisory Committee on Genetic Testing ("SACGT").[319] However, the proposal was not implemented by CMS.[320] CMS currently does not distinguish laboratories performing genetic tests from those performing other tests of similar complexity.[321] Nor does CMS impose special requirements on laboratories providing DTC testing.[322]

In 2007, SACGT's successor, SACGHS, was tasked with investigating "the oversight of laboratory testing through the lens of genetic tests."[323] SACGHS found that "the most rigorous form of performance assessment" under CLIA, proficiency testing, was not required for all labs offering genetic testing, and that "the resources, funding, and means to develop formal [proficiency testing] for all genetic tests are lacking."[324] SACGHS suggested clarifying CLIA's jurisdiction over health-related tests and DTC tests,[325] rectifying gaps in oversight, and providing more enforcement tools,[326] particularly since denying Medicare or Medicaid reimbursement would have little deterrent effect on labs providing DTC testing.[327] Ultimately, however, SACGHS did not recommend the creation of a special CLIA framework for regulating genetic testing,[328] explaining that "the concerns associated with genetic testing generally do not differ from other complex laboratory tests," and "it will be increasingly difficult to distinguish between genetic and other complex laboratory tests" in the future.[329]

E. *Additional Oversight*

1. FTC. The FTC, pursuant to its authority to protect consumers from unfair and deceptive trade practices, shares jurisdiction with FDA over medical device marketing.[330] Under a 1971 liason agreement, FTC has primary responsibility for medical device advertising, while FDA has responsibility for labeling.[331] Although FDA and FTC have been at odds in the past, more recent FTC activities reflect a "guiding principle of harmonizing the FTC's policies with those of FDA," for example, by requiring advertising to be consistent with PMA requirements.[332]

FTC requires that "advertisers must possess and rely upon a reasonable basis for all objective claims - express and implied - that reasonable consumers take from

[318] Neil A. Holtzman, *Promoting Safe and Effective Genetic Tests in the United States: Work of the Task Force on Genetic Testing*, 45 CLINICAL CHEMISTRY 732, 736 (1999). The final report of the Task Force is available at http://www.genome.gov/10001733.

[319] SACGHS OVERSIGHT REPORT 14.

[320] Kathy Hudson et al., *ASHG Statement on Direct-to-Consumer Genetic Testing in the United States*, 81 AM. J. HUMAN GENETICS 635, 636 (2007).

[321] SACGHS OVERSIGHT REPORT 31.

[322] CMS, *Direct Access Testing (DAT) and the Clinical Laboratory Improvement Amendments (CLIA) Regulations*, *available at* http://www.cms.hhs.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/directaccesstesting.pdf (last visited April 14, 2012).

[323] SACGHS OVERSIGHT REPORT 15.

[324] SACGHS OVERSIGHT REPORT 111, 108.

[325] *Id.* at 113–114

[326] *Id.* at 111–113

[327] *Id.* at 113.

[328] *Id.* at 6, 111.

[329] Letter from the Secretary's Advisory Committee on Genetics, Health, and Society to Secretary Michael O. Leavitt (April 30, 2008).

[330] *See* Anne V. Maher & Lesley Fair, *FTC's Regulation of Advertising*, 65 FOOD & DRUG L.J. 589, 602–05 (2010).

[331] *Id.* at 603.

[332] Maher & Fair, *supra* note 330, at 610.

their advertisements."[333] Unlike FDA, FTC does not have pre-approval authority, and in enforcement actions, "[t]he burden is on the Commission to prove that [the challenged] statements are false."[334] To determine whether advertisements are adequately substantiated, FTC has adopted the *Pfizer* six-factor test, which considers, *inter alia*, the consequences of a false claim (such as potential harms to consumers), benefits of a truthful claim, and the amount of substantiation experts in the field believe is reasonable.[335] For health claims, "competent and reliable *scientific* evidence" is generally required.[336] FTC often looks to FDA labeling requirements to clarify the scope of permissible claims for a medical product.[337]

In 2006, FTC, FDA and the Centers for Disease Control ("CDC") jointly issued a consumer alert warning about DTC tests.[338] FTC followed up in 2008 with a second alert.[339] SACGHS has recommended that FTC collaborate with FDA, CMS and CDC to "strengthen monitoring and enforcement efforts against laboratories and companies that make false and misleading claims about laboratory tests, including direct-to-consumer tests."[340]

2. CDC and NIH. CDC and NIH have no regulatory authority over genetic tests. However, CDC reviews and evaluates genetic tests through the Evaluation of Genomic Applications in Practice and Prevention ("EGAPP") program[341] and Genomic Applications Practice and Prevention Network ("GAPPNet"), which has published evidence-based clinical use recommendations for a few genetic variants.[342] Pursuant to a SACGHS recommendation,[343] NIH recently created a voluntary genetic test registry[344] for use by clinicians and researchers.[345] NIH also maintains public-facing genetic resources like the Genetics Home Reference.[346]

3. State Oversight. "As it enlarged the FDA's powers to 'protect the public health' and 'assure the safety, effectiveness, and reliability of drugs,' Congress took care to preserve state law."[347] The use of genetic tests by clinicians remains an area reserved to the states, governed by state laws and regulations relating to the practice of medicine,[348] informed consent, tort liability, and privacy.[349] Under CLIA, state agencies are also involved in

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[333] *Id.* at 590.

[334] FTC v. QT, Inc., 512 F.3d 858, 861 (7th Cir. 2008).

[335] FTC, Federal Trade Commission Substantiation Policy Statement, 104 F.T.C 840 (adopting factors from Pfizer, Inc., 81 F.T.C. 23 (1972)).

[336] Maher & Fair, *supra* note 330, at 607.

[337] Javitt & Hudson, *supra* note 270, at 65.

[338] FTC, *FTC Facts for Consumers: At-Home Genetic Tests: A Healthy Dose of Skepticism May Be the Best Prescription* (July 2006), *available at* http://www.ftc.gov/bcp/edu/pubs/consumer/health/hea02.shtm.

[339] GAO, 2010 Report, *supra* note 3, at 1.

[340] SACGHS Oversight Report 113.

[341] *Id.*

[342] *EGAPP Working Group Recommendations*, EGAPP (updated Feb. 29, 2012), http://www.egappreviews.org/recommendations/index.htm.

[343] SACGHS Oversight Report 112-13.

[344] Press Release, NIH, Confused By Genetic Tests? NIH's New Online Tool May Help (Feb. 29, 2012) (noting that GTR will include "the purpose of each genetic test and its limitations; the name and location of the test provider; whether it is a clinical or research test; what methods are used; and what is measured") *available at* http://www.nih.gov/news/health/feb2012/od-29.htm.

[345] NIH, *NIH Genetic Testing Registry Fact Sheet* (Feb. 29, 2012), http://oba.od.nih.gov/oba/gtr/GTR_Fact_Sheet_2-28-12.pdf.

[346] *Genetics Home Reference: Your Guide to Understanding Genetics Conditions*, NIH (Apr. 16, 2012), http://ghr.nlm.nih.gov/.

[347] Wyeth v. Levine, 555 U.S. 555, 567 (U.S. 2009) (internal quotations and citation omitted).

[348] *See generally* Marietta & McGuire, *supra* note 15.

[349] SACGHS Oversight Report 37.

inspecting clinical laboratories; two states, New York and Washington, have opted out of CLIA in favor of their own laboratory certification programs.[350]

A number of states, such as New York and California, have statutes or regulations that restrict or prohibit DTC testing.[351] In 2008, New York sent cease-and-desist letters to twenty-three DTC companies; California's Department of Public Health ("CDPH") sent cease-and-desist letters to thirteen DTC companies.[352] California subsequently licensed some DTC companies to operate within the state, including 23andMe.[353] In 2010, CDPH blocked the University of California, Berkeley, from genotyping incoming freshmen as part of an educational exercise, "Bring Your Genes to Cal," because the university had not secured prior physician approval.[354] The university had intended to use a campus research lab to genotype three "innocuous" genes relating to the metabolism of milk, alcohol and folic acid.[355] However, CDPH determined that under state law, letting the students have their results would make the university ineligible for regulatory exemptions applicable to research projects.[356]

While some commentators applaud states' willingness to fill the regulatory gap, state legislation imposes a patchwork of inconsistent requirements on the national genetic test providers.[357] As more states pass legislation affecting genetic testing, conflicts between the laws of various states, and between state and federal law, will increase legal and regulatory uncertainty.[358]

III. FAMILIAR TERRITORY OR HOSTILE TERRITORY? FDA AND DTC GENOMIC SERVICES

Discussions of DTC genomic services often simply assume FDA is the agency best-suited to fix any regulatory problems. FDA has scientific expertise, a statutory mandate to protect public health, and experience evaluating and approving genetic test kits using similar technologies. However, because only a few dozen predictive genetic tests are FDA approved or cleared, "for all intents and purposes, the FDA has ceased to be the gatekeeper for public safety in this arena."[359] FDA's prolonged inaction raises questions about how the agency will adapt its approach to services providing genomic information in a context of increasingly decentralized and informal innovation and research.

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[350] *See supra* note 312 (citing examples of state regulation of clinical laboratory tests).

[351] *See* Genetics & Pub. Pol'y Ctr., *Survey of Direct-to-Consumer Testing Statutes and Regulations*, (June 2007), http://www.dnapolicy.org/resources/DTCStateLawChart.pdf (last visited Apr. 29, 2012) (explaining that although federal regulations do not require CLIA laboratories to obtain physician authorization, state law often does); *see also* Conley, *supra* note 114, at 36–41 (describing the impact of state regulation on public genomics research).

[352] Magnus et al., *supra* note 167, at 17.1–17.2 (2009).

[353] Andrew Pollack, *California Licenses 2 Companies to Offer Gene Services*, N. Y. TIMES C3 (Aug. 19, 2008).

[354] Krieger, *supra* note 19.

[355] Robert Sanders, *UC Berkeley alters DNA testing program*, UC BERKELEY NEWSCENTER (Aug. 12, 2010), *available at* http://newscenter.berkeley.edu/2010/08/12/dna_change/.

[356] *Id.*

[357] Magnus et al., *supra* note 167, at 17.2–17.3 (2009).

[358] Dan Vorhaus & Jennifer K. Wagner, *Alabama's "Genetic Information Privacy Act" & the Ongoing Need for Personal Genomics Leadership*, GENOMICS L. REP. (FEB. 16, 2012), http://www.genomicslawreport.com/index.php/2012/02/16/alabamas-genetic-information-privacy-act-the-ongoing-need-for-personal-genomics-leadership.

[359] Patsner, *supra* note 231, at 266.

A. *Familiar Territory: the Libertarian Critique*

Rhetoric about "FDA's genetic paternalism" may be overblown, but it is not completely unfair.[360] Critics of DTC genomic services often invoke "nightmare" hypotheticals about ignorant, panicked consumers harming themselves.[361] By asserting jurisdiction over DTC genomic services, FDA may appear to have given credence to these fears. At the same time, regulators are questioning whether, given the state of the science, genomic services have any cognizable value at all.[362]

The situation is what Timothy Caulfield calls a "policy paradox": "If, as many in the scientific community are now saying, genetic information is not the oracle of our future health as we were once led to believe, and if access does not, for most, cause harm, *why regulate the area*?"[363] If genomic tests have little predictive value, they are at best entertainment and at worst snake oil, to be restricted mainly so consumers are not misled by scientific razzle-dazzle into buying worthless things. But at the same time, critics insist that qualified gatekeepers must watch over consumers, in case the same worthless tests reveal frightening information about consumers' risk of serious, life-changing diseases. And because DTC genomic services test thousands of SNPs, associated with many potential health conditions, both critiques have a grain of truth to them.

Autonomy-based arguments are often invoked in opposition to government restrictions on genomic testing. For example, one could argue that individuals have a fundamental right to obtain their own genetic or health information without government interference. There is limited federal recognition of such a right: entities covered by the Health Insurance Portability and Accountability Act ("HIPAA") must disclose patient records, with some limitations;[364] although some ethicists and clinicians feared HIPAA-mandated disclosure could distress or confuse patients, such concerns have not been substantiated.[365] In a similar vein, a proposed CMS rule would "increase direct patient access rights" by requiring CLIA-regulated labs to give patients their test results.[366] However, HIPAA and the proposed CMS rule only require disclosure of pre-existing health information; they do not confer an affirmative right to be tested. To support an affirmative right, one might make a stronger patient autonomy argument, asserting the right to "possess both the information and the sense of authority" required to control one's own medical care,[367] and to participate in developing that information through research.

For FDA, these libertarian arguments are familiar territory. From its beginnings, the agency fought popular belief in a "right of self-medication" rooted in consumer

[360] Robert VerBruggen, *The FDA's Genetic Paternalism*, National Review (March 23, 2011 4:00 AM), *available at* http://bit.ly/h1zW7t; *see also* Goetz, *supra* note 156. *But see* Evans & Berg, *supra* note 154, at 2377 (arguing that "medicine is, to at least some extent, an inherently paternalistic endeavor simply because of an inevitable asymmetry in knowledge").

[361] *See supra* Part I.F.

[362] *E.g.,* GAO, 2010 Report, *supra* note 3, at 8 (genomic services are "promising for research, but the application is premature").

[363] Timothy Caulfield, *DTC Genetic Testing: Pendulum Swings and Policy Paradoxes*, 81 Clinical Genetics 4 (2012).

[364] *See, e.g.*, Stephen E. Ross & Chen-Tan Lin, *The Effects of Promoting Patient Access to Medical Records: A Review*, 10 J. Am. Med. Informatics Ass'n 129, 129 (2003) (finding that while few patients sought their records, "patient-accessible medical records are unlikely to cause harm in medical patients and have the potential for modest benefits").

[365] *Id.*, 131–36.

[366] Patient Access: Centers for Medicare & Medicaid Services, CLIA Program and HIPAA Privacy Rule; Patients' Access to Test Reports, 76 Fed. Reg. 56,712, 56,714 (Sept. 14, 2011) ("in an effort to increase direct patient access rights. . . upon a patient's request, CLIA regulations would allow laboratories to provide direct patient access to completed test reports").

[367] DHHS, *supra* note 53.

autonomy and independent judgment.[368] Proponents of the right to self-medicate opposed FDA's gatekeeping authority, while mid-century FDA officials distrusted the capacity of "insufficiently informed" patients who were "prone to disregard directions."[369] Daniel Carpenter has described FDA's crackdown on the unapproved cancer drug Laetrile as the ultimate collision of the libertarian right to self-medication with FDA's expert regulation.[370] On the one side, cancer patients and their supporters "linked a populist ethos of self-medication to issues of justice and to more progressive norms of academic and intellectual freedom, the liberty of research and exploration of ideas."[371] On the other side, FDA arrayed its "gatekeeping power and, even more, its power to define and assess the validity and scientific rigor of therapeutic research."[372]

FDA consistently opposed Laetrile, despite the drug's widespread use by as many as seventy-five thousand patients, and (until 1978) a dearth of evidence that it was toxic.[373] State legislatures, activist groups, and newspaper editorials called on FDA to leave terminal cancer patients alone.[374] Yet the Laetrile controversy ended in resounding victory for the agency, with the Supreme Court "rejecting with unanimity the libertarian critique of the FDA."[375] The episode established FDA's expansive ability to control access to regulated products, even for experimental or limited uses. Intuitive arguments about autonomy, paternalism and patient rights—arguments echoed by DTC genetic test advocates—failed despite popular support, sympathetic patients, and doctors willing to prescribe Laetrile to their dying patients. Against this backdrop, any paternalism-based critiques of FDA gatekeeping face an uphill battle.

FDA's regulation of HIV tests in the 1980s offers another historical analogy to genomic service regulation, which is in some ways an even better fit.[376] At the time, FDA's decision to prohibit home HIV tests was supported by AIDS advocates, who feared that if consumers learned they were HIV-positive without clinical support, it would trigger "widespread suicides, panic and a rush to public health clinics."[377] Although advocates of home testing dismissed these arguments as "paternalistic claptrap,"[378] FDA delayed approving home HIV tests for almost a decade. When the first home test was finally approved (as a Class III device requiring anonymous telephone counseling), the agency's fears of adverse reactions were not realized.[379]

Contemporary debates about the DTC genomic testing, with their dire warnings of irrational consumers jumping off buildings, are reminiscent of the HIV home testing debates.[380] Perhaps this is because HIV status and genetic information have both been

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[368] CARPENTER, *supra* note 219, at 79–80.

[369] *Id.* at 215–16.

[370] *Id.*

[371] *Id.* at 414.

[372] *Id*. at 411.

[373] Id. at 418–22.

[374] *Id.* at 417–18.

[375] *Id.* at 423.

[376] Serra Schlanger, *Filling in the Cracks: Improving the Regulation of Direct-to-Consumer Genetic Tests*, 14 J. HEALTH CARE L. & POL'Y S1, S19–24 (2011); Jennifer A. Gniady, *Regulating Direct-to-Consumer Genetic Testing: Protecting the Consumer Without Quashing a Medical Revolution*, 76 Fordham L. Rev. 2429, 2453–54 (2008); Mary Pendergast, *Statement To Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee, March 8-9, 2010 Meeting, FDA-2011-N-0066* (Mar. 1, 2010) (Ms. Pendergast, a former FDA official and medical device consultant, has advised 23andMe).

[377] Gniady, *supra* note 376, at 2454; *see also* Schlanger, *supra* note 376, at S20.

[378] Gary Blonston, *Home HIV Test Wins Support, Opposition—FDA Advisory Committee Wrestles With Proposal*, SEATTLE TIMES (June 23, 1994) (quoting Bruce Decker, president of the Health Policy Research Foundation).

[379] Schlanger, *supra* note 376, at S19–24.

[380] *Id.* at S25; Pendergast, *supra* note 376.

treated as exceptionally sensitive sources of potential stigma, requiring a high level of regulatory vigilance.[381] But while FDA's experience with home HIV tests has been cited as a "viable path" for DTC genetic test regulation,"[382] a former FDA official argues that DTC services make "a far less compelling case for physician intervention" than home HIV tests.[383] In the 1980s and 1990s, stigma, fear, and desperation made verification of HIV infection seem, to many, like a death sentence.[384] The uncertain risk estimates offered by predictive genomic services seem incomparable—even with respect to serious diseases like Alzheimer's.[385]

Whether FDA seems paternalistic or precautionary in closing each of these gates likely depends on whether one thinks consumers are justified in disregarding expert risk assessments.[386] According to Dennis Thompson, FDA did not claim "unqualified paternalistic authority" to ban Laetrile, but rather "sought to show the decision to use Laetrile is usually impaired" by the cancer patient's desperation, disease, and distrust of medical authority.[387] Government regulators cannot avoid paternalism entirely; even the decision not to regulate is a "nudge" in one direction or another.[388] If FDA does nothing at all, its hallowed reputation for protecting public welfare may lead consumers to assume it has approved DTC tests. But it is also hard to justify restricting access to DTC genomic tests when there is no empirical evidence that they cause harm.[389] Caution is understandable, but speculative harms are not the kind of significant evidence FDA should use in its evidence-based regulatory decisions.

B. *FDA's Statutory Jurisdiction over DTC Services as Medical Devices*

Courts will likely defer to FDA's determination that health-related DTC genomic services are medical devices under the FD&C Act. DTC genomic services are predictive, in that they offer estimates of disease risk, and the plain language of section 201(h)(2) covers products for use in disease "prediction."[390] While DTC providers deny their services are diagnostic, the services could reasonably be characterized as diagnostics for a pre-symptomatic health condition (increased risk of disease).[391] Section 201(h)(2)

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[381] Ross, *supra* note 10, at 142-43 (comparing HIV exceptionalism with genetic exceptionalism).

[382] Schlanger, *supra* note 376, at S29 (observing that both tests could cause "dramatic health-related decisions").

[383] Pendergast, *supra* note 376.

[384] Schlanger, *supra* note 376, at S25; Green & Botkin, *supra* note 10, at 573.

[385] *See* Pendergast, *supra* note 376 ("I cannot conceive of any information that a consumer could learn through a genetic test that would be as important as HIV status."). Even if this does not hold true with respect to dominant single-gene disorders like Huntington's disease, predictive SNP chip testing does not typically test for, or report on, single-gene disorders like Huntington's.

[386] *Cf.* Shobita Parthasarathy, *Breaking the Expertise Barrier: Understanding Activist Strategies in Science and Technology Policy Domains*, 37 Sci. Pub. Pol'y, 355, 356–57 (2010) ("proposals to incorporate citizen participation in [science and technology] policy . . . have had limited impact" because "insiders often argue that the average person operates at a knowledge 'deficit' and cannot properly comprehend the complex issues under discussion").

[387] Dennis Thompson, Political Ethics and Public Office 173 (1987).

[388] *See generally* Richard H. Thaler & Cass R. Sunstein, Nudge: Improving Decisions About Health, Wealth, and Happiness (2008).

[389] *See, e.g.*, Bloss, *supra* note 173.

[390] FD&C Act § 201(h)(2).

[391] *Cf.* SACGHS Oversight Report 119 (suggesting that predictive testing may increase "medicalization of previously unknown conditions and risk factors linked to important health conditions"); Marietta & McGuire, *supra* note 15, at 371 ("It could be argued that testing asymptomatic persons for disease risk does not constitute a diagnosis. . . because no disease or pathology exists," but "this 'assumes a limited view of medicine'" (quoting Han, *supra* note 22)).

also covers products for use in diagnosing non-disease "conditions."[392] In close cases, courts have construed the FD&C Act's definition of "device" expansively,[393] and FDA's expertise has earned the agency the judicial deference necessary to "regulate products that fell into the interstices between statutory categories" and make "novel and broad interpretations of its jurisdiction."[394]

FDA has disavowed jurisdiction over DTC services that provide only non-health related information, such as ancestry services,[395] which are not within the plain language of section 201(h)(2). However, there are at least two arguments FDA might make to support jurisdiction over these services as well. First, some ancestry information can predict health outcomes. Certain populations have higher risks of developing or passing on diseases; for example, Tay-Sachs disproportionately afflicts Ashkenazi Jewish individuals. Drug response also varies between populations: African-Americans respond less well, on average, to beta-blockers.[396] Thus, clinicians often use self-reported race in drawing inferences about patients' risks.[397] However, racial identity is a complex social concept that does not necessarily correlate with geographic ancestry.[398] Not all health disparities between racial groups have a genetic basis, but for conditions with a significant genetic component, markers of ancestry may be better risk indicators than traditional self-reported racial categories.[399]

Second, the genotype data generated by DTC ancestry services are functionally identical to the data generated by DTC health services. The same genetic sequence, or set of SNPs, can support inferences about either ancestry or health.[400] Thus, raw genetic data returned to a consumer by an ancestry service could be used to estimate disease risk (or vice versa).[401] FDA therefore argue that effective gatekeeping of health risk information would be circumvented, if non-health services were permitted to operate without oversight—an argument somewhat analogous to justification for prohibitions on off-label promotion of FDA-approved drugs. However, the pharmaceutical manufacturers subject to off-label restrictions are clearly subject to FDA's jurisdiction, because they

[392] *Id.*

[393] *See, e.g.,* United States of America v. 25 Cases, More or Less, of an Article of Device. . . "Sensor Pad for Breast Self-Examination," 942 F.2d 1179 (7th Cir. 1991) (rejecting as "untenable" a "screening/diagnosing distinction" that would mean a breast exam pad "used *before* actual diagnosis" was not a device); *cf.* U.S. v. Undetermined Number of Unlabeled Cases, 21 F.3d 1026 (10th Cir. 1994) (holding that sample containers for HIV testing were devices, even when used for insurance risk assessment rather than medical treatment).

[394] James T. O'Reilly, *Losing Deference in the FDA's Second Century: Judicial Review, Politics, and a Diminished Legacy of Expertise*, 93 CORNELL L. REV. 939, 947–48 (2008).

[395] *E.g.*, FDA, *Executive Summary, Molecular and Clinical Genetics Panel*, 5 (Mar. 8–9, 2011), *available at* http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MolecularandClinicalGeneticsPanel/UCM245660.pdf.

[396] Bamshad, *supra* note 149, at 937.

[397] *Id.*

[398] *Id.* at 937, 940 (explaining the difference between race and ancestry); *see also generally* Rick A. Kittles & Kenneth M. Weiss, *Race, Ancestry and Genes: Implications for Defining Disease Risk*, 4 ANNUAL REV. GENOMICS & HUMAN GENETICS 33 (2003) ("race reflects deeply confounded cultural as well as biological factors, and a careful distinction must be made between race as a statistical risk factor and causal genetic variables").

[399] Bamshad, *supra* note 149, at 944–45.

[400] 23andMe, offers both ancestry and health services, and apparently sequences the same SNPs for both. *Our Technology and Standards,* 23ANDME, https://www.23andme.com/howitworks/ ("We utilize the Illumina OmniExpress Plus Research Use Only Chip which has been customized for use in all of our products and services. . . ") (last visited April 29, 2012).

[401] It is unclear how many of the DTC ancestry companies permit consumers to download raw SNP data, but interestingly, only one quarter of them expressly limit the "intended use" of their services to "recreational, educational, or entertainment purposes." Wagner et al., *supra* note 85.

must secure premarket approval to market their drugs at all. Imposing FDA authority on an ancestry service that does not sell any FDA-regulated drugs or medical devices might be harder to justify.

Whether or not DTC genome services fall under the LDT umbrella,[402] they are administered by CLIA laboratories. Thus, past challenges to FDA's jurisdiction over CLIA-administered LDTs[403] may recur here. One challenge is based on the enactment of distinct statutory regimes for medical devices and clinical laboratory services. When Congress expanded the definition of "medical device" in the 1976 Amendments, the Clinical Laboratories Improvement Act of 1967 already provided for regulation of laboratory services—including then-existing LDTs.[404] The failure of the 1976 Amendments to mention CLIA, coupled with the minor role given to FDA in the 1988 Clinical Laboratories Improvement Amendments, support the inference that Congress did not intend to give FDA jurisdiction over laboratory services.[405]

While a device/service distinction is a fair inference from the statutory scheme, it seems outdated in application.[406] Laboratory services are far more complex and numerous than they were in 1976. Laboratory-developed genetic tests are advertised and marketed nationally,[407] just like FDA-approved test kits; FDA already exercises jurisdiction over some, though not all, components of DTC tests.[408] Under the circumstances, it seems unlikely that a court would question a construction of the FD&C Act reaching DTC genomic services.

Alternatively, one could argue that the Administrative Procedure Act requires FDA to promulgate a rule in order to reverse a longstanding exercise of "enforcement discretion."[409] This has not yet happened with respect to LDTs: the ASR rule excluded LDTs from regulation,[410] and FDA's IVDMIA guidance was never promulgated as a rule. Although it is not unusual for FDA to make policy through informal guidances, courts may be suspicious when established enforcement practices are informally reversed.[411] For example, a district court recently rejected FDA's assertion of authority over bulk compounding of animal drugs, in light of FDA's "decades of inaction" in that area.[412] However, FDA has not been similarly inactive toward LDTs. The ASR rule placed clinical laboratories on notice that FDA saw LDTs as medical devices, and FDA has

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[402] *See supra* notes 290–291, and accompanying text.

[403] *See* FDA Docket No. 2006-P-0402, Citizen Petition of Washington Legal Foundation (Sept. 28, 2006) (challenging FDA authority over LDTs, with the express exclusion of DTC tests); FDA Docket 1992-P-0405, Citizen Petition of Hyman, Phelps & McNamara, P.C. (Oct. 22, 1992).

[404] *See* Comments of Hyman, Phelps & McNamara, P.C., in Support of Wash. Legal Found. Citizen Petition 2–9 (Mar. 23, 2007); FDA Docket No. 2006-P-0402, Citizen Petition of Wash. Legal Found. 8–11 (Sept. 28, 2006).

[405] *Accord* Richard A. Merrill, *Genetic Testing? A Role for FDA*, 41 Jurimetrics 63, 64 (2000) ("A prescription for a genetic test, to be performed by a laboratory that brews its own assays . . . surely falls near the outer periphery of FDA's historical authority.").

[406] *See* Han, *supra* note 22, at 431–32.

[407] *See, e.g.*, Shobita Parthasarathy, Building Genetic Medicine: Breast Cancer, Technology, and the Comparative Politics of Health Care 129–32 (2007) (describing Myriad Genetics' national advertising campaign for its BRACAnalysis breast cancer risk tests).

[408] *See supra* notes 276–278 and accompanying text (discussing the ASR rule).

[409] *See* Comments of Hyman, Phelps and McNamara, P.C., in Support of Washington Legal Foundation Citizen Petition 9-25 (March 23, 2007); FDA Docket No. 2006-P-0402, Citizen Petition of Washington Legal Foundation 15-17 (Sept. 28, 2006).

[410] Ellen Flannery & Scott Danzis, *FDA Plans to Regulate Laboratory Developed Tests as Devices*, 7 J. Med. Device Reg. 63, 63 (2010).

[411] *See generally* K.M. Lewis, *Informal Guidance and the FDA*, 66 Food & Drug L.J. 507, 520, 540–41 (2011).

[412] United States v. Franck's Lab, Inc., 816 F. Supp. 2d 1209, 1253 (M.D. Fla. 2011). An appeal to the was pending at the time this paper was submitted. 11th Cir. No.11-15350-BB.

subsequently moved (in fits and starts) toward LDT regulation. If DTC services are LDTs, FDA's assertion of authority should warrant judicial deference. If DTC services are not LDTs, FDA never promised to exercise enforcement discretion toward them. And either way, FDA could easily overcome this argument by promulgating a rule.

C. *Unfamiliar Territory: Regulating Information*

Both the speculative harms and the potential benefits of DTC genomic services are derived from greater self-knowledge. Genomic services are essentially information services, providing consumers with raw genomic data, and interpreting those data in light of a corpus of scientific scholarship. While all medical diagnostics could be described as information services, predictive genome services are set apart by their indeterminacy: the information provided does not clearly instruct or advise action. Instead, it invites further exploration, creates uncertainty, and may challenge the authority of the medical practitioner.

1. Generation and Interpretation. While DTC services are often assumed to be LDTs, FDA's 2010 untitled letters indicate that DTC genomics services may not be LDTs if they are "not developed by and used in a single laboratory."[413] This statement may offer a clue to FDA's forthcoming DTC genomic service policies.[414] Considered alone, the stand-alone *generation* of genotype data by a CLIA-certified laboratory would fit comfortably within the LDT category. But FDA seems to view the DTC company's subsequent *interpretation* of those data, which is computational and does not take place in the laboratory, to be part of the "medical device." While this is somewhat counterintuitive, it is consistent with FDA practice: FDA regulates interpretive medical software together with the underlying diagnostic tests, and the agency has shown increasing concern about complex tests, like IVDMIAs, that cannot be understood by clinicians without a layer of interpretive processes.[415]

Suppose, then, that a consumer obtains her raw genotype data from a clinical laboratory. Assuming the data are generated for non-health purposes (such as ancestry research), the test is not a "medical device." She then sends her data to two DTC interpretive services, and each generates a personalized report. Ancestry Company's report uses a database of SNP associations based on ethnographic studies of human genealogy, while Health Company's report uses a database of SNP associations based on GWAS studies of common diseases. The interpretive step involves no genetic test, no laboratory, and no human tissue sample. Neither company offers medical advice; they provide a report with hyperlinks to relevant scientific and medical research literature. FDA has disavowed authority over Ancestry Company's service. But would Health Company's service be a "medical device"—even decoupled from the genetic test itself?

It appears likely, based on currently available evidence, that FDA would consider Health Company's service a medical device. Consider Knome, a developer of genome interpretation software tools.[416] At one point, Knome offered DNA sequencing,

[413] *E.g.*, Letter from Alberto Gutierrez, Director, OIVD, FDA, to Jorge Conde, CEO, Knome, Inc. (June 10, 2010).

[414] Beyond its untitled letters, FDA has not clarified why DTC services are not LDTs. FDA may also have concerns about other aspects of DTC services, such as mailing sample containers directly to consumers, reporting results directly to consumers, or using gene chips meant for research use only. *Cf.* Stein, *supra* note 189 (citing an unnamed FDA official, explaining that Pathway Genomics' service required approval because "it involved consumers collecting their own DNA").

[415] *See, e.g.*, Statement of Jeff Shuren, *supra* note 8 (noting that LDTs "often require complex software and may incorporate automated interpretation in lieu of expert interpretation"); Magnus et al., *supra* note 167.

[416] *Technology Overview*, KNOME, http://www.knome.com/technology/ (last visited Apr. 29, 2012) (describing Knome's "genome informatics engine" kGAP).

including a whole-genome service called KnomeCOMPLETE.[417] Knome later partnered with SeqWright, a CLIA-certified sequencing lab,[418] and Knome now states that it "outsources" sequencing. In 2010, FDA informed Knome that KnomeCOMPLETE was a medical device.[419] FDA's untitled letter emphasized KnomeCOMPLETE's interpretive and explanatory functions: "[KnomeCOMPLETE] describes the genetic basis of specific disease traits or conditions. Consumers may make medical decisions in reliance on this information."[420] When asked in an interview why Knome was targeted, even though its product was more like a "service" than a test, an FDA official explained that "[s]oftware is a medical device, and [Knome is] making medical claims. They're taking results and making medical claims that come out of those results."[421] Asked whether "pointing people to medical research papers" would also constitute a "medical claim," he answered, "It depends."[422]

FDA has historically walked a fine line between regulating medical products and regulating medical information. Medical texts and reference materials are not medical devices (although they may constitute device labeling or advertising). But when these resources are coupled with software providing personalized results tailored to a user, FDA treats them as medical devices.[423] Accordingly, FDA has asserted jurisdiction over health-related smartphone apps,[424] including "mobile apps that allow the user to input patient-specific information along with reference material to automatically diagnose a disease or condition."[425]

The problem is that personalization is ubiquitous in the informational ecosystem. If software that generates a report based on personal information is a medical device, then the medical device definition should likewise apply to Promethease,[426] the free program which consumers can download and use to process their raw SNP data at home,[427] or an open source BRCA diagnostic tool for comparing a user's genetic sequence to known mutations in the BRCA1/2 breast cancer genes.[428] It could apply to Interpretome, a web-based educational tool created by Stanford University that evaluates raw SNP data and makes drug dosing recommendations using genetic and non-genetic information.[429] Any software integrating information from multiple online databases in response to

[417] Mallorye Allison, *Illumina's Cut-Price Genome Scan*, 27 Nature Biotechnology 685 (Aug. 8, 2009) ("Knome . . . the only other company currently marketing whole-genome scans to consumers, charges $99,500 for KnomeCOMPLETE"); Andrew Pollack, *F.D.A. Faults Companies on Unapproved Genetic Tests*, N.Y. Times (June 11, 2010) ("Knome [] offers consumers a complete sequence of their DNA").

[418] Press Release, *Knome and SeqWright to Offer Personal Genomics Services Through CLIA-Certified Laboratory* BusinessWire (June 10, 2009, 04:55) *available at* http://bit.ly/KgZORv.

[419] Letter from Alberto Gutierrez to Jorge Conde, *supra* note 413 ("[Knome] described KnomeCOMPLETE™ as consisting of a software program that analyzes genetic test results that are generated by an external laboratory in order to generate a patient specific test report. Thus, the KnomeCOMPLETE™ is a diagnostic device and subject to all applicable requirements of the Act.").

[420] *Id.*

[421] Carmichael, *Q&A*, *supra* note 96 (quoting Alberto Gutierrez).

[422] Mary Carmichael, *DNA Dilemma: The Full Interview With the FDA on DTC Genetic Tests*, Newsweek (Aug 5, 2010)

[423] *See* FDA *supra* note 222.

[424] *Id*.

[425] *Id.* (FDA considers such software "mobile medical apps," but intends to exercise enforcement discretion over software that can "automate common medical knowledge available in the medical literature" or "allow individuals to self-manage their disease or condition," even if that software is a medical device.).

[426] *Promethease*, SNPedia (updated Apr. 14, 2012), http://www.snpedia.com/index.php/Promethease.

[427] *Cf.* Donald H. Taylor et al., *Genetic Testing For Alzheimer's And Long-Term Care Insurance*, 29 Health Affairs 102, 106 (2010) (if "Alzheimer's disease risk is not reported directly" by a DTC service, "it can be inferred" with "freely available Internet resources such as SNPedia.").

[428] Salzberg & Pertea, *supra* note 76, at 404.

[429] *Interpretome*, Stanford University, http://esquilax.stanford.edu/ (last visited Apr. 29, 2012).

user queries could raise similar issues.[430] It seems doubtful FDA wants the burden of regulating freeware like Promethease, much less search engines—but on the other hand, armed with her medical records and an open source online algorithm, a patient could approximate the type of complex analysis FDA sought to regulate in its IVDMIA guidance.[431] While this scenario may be farfetched, the only way to shut down DIY diagnostic activity would be to restrict access to certain categories of health data, like associations between SNPs and disease risk—a step that seems impractical and unwise.

2. Medical Claims. FDA asserts that DTC genetic tests come within the ambit of the FD&C Act—and are therefore medical devices—"when they make medical claims."[432] However, FDA's conception of "medical claims" appears elastic, encompassing the "genetic basis of specific disease traits or conditions on which consumers may base medical decisions," "personalized information" on medications, "genetic predispositions for important health conditions and medication sensitivities,"[433] and perhaps even "pointing people to medical research papers."[434] Note that while FDA has disclaimed statutory authority over *ancestry* tests, it is still unclear whether it considers *research* tests to be medical devices; a crowdsourced study of a relatively innocuous trait, like the genetics of Vitamin E response, would certainly involve "medical claims" under the expansive description above.[435]

FDA's "medical claims" approach reflects the agency's general practice of relying on manufacturer representations as evidence of a device's "intended use."[436] However, in the genomic context there has been some slippage. Consider a hypothetical statement by a manufacturer of crib mattresses, that his product "…helps reduce 'sinkhole' effects linked to SIDS" or "reduces the risk of SIDS." These are clearly medical claims.[437] But it is less obvious that a tool for identifying whether a crib mattress has such a "sinkhole" should be a medical device, even if it is sold with the claim "find out if your crib mattress has a 'sinkhole' linked to SIDS!" The discovery of a sinkhole is valuable information, and it suggests an obvious health-related action (replace the mattress). But what if the remedy were nonobvious, or the information were valuable for non-health related purposes? FDA's evaluation of medical claims seems to depend, at least implicitly, on whether consumers' hypothetical responses to the information they obtain are likely to include health-related decisions. But if that's enough, wouldn't a *cookbook* be a medical device?

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[430] *See, e.g.*, Benjamin M. Good, Salvatore Loguercio & Andrew I. Su, *Linking Genes to Diseases With a SNPedia-Gene Wiki Mashup*, BIO-ONTOLOGIES SIG (July 19, 2011) *available at* http://bio-ontologies.knowledgeblog.org/250 (describing a software tool for answering the question "Based on what we know now, what genes are linked to which diseases?").

[431] Salzberg & Pertea, *supra* note 76, at 404, 406 ("In creating this software, we are not violating the BRCA patents directly but any user would be…"). Interestingly, Salzberg & Pertea's paper openly criticized "restrictive" gene patents because "any individual should be allowed to interrogate his or her genome for all mutations of interest," but never mentioned FDA.

[432] Carmichael, *DNA Dilemma*, *supra* note 422 ("The question with 23andMe has been whether their claims were medical claims or not. . . Now clearly [they] are medical claims." (quoting OIVD Director Alberto Gutierrez)); Statement of Jeff Shuren, *supra* note 8 (DTC tests "meet the statutory definition of a medical device on the basis of the manufacturers' claims about the test results").

[433] Statement of Jeff Shuren, *supra* note 8.

[434] Carmichael, *DNA Dilemma*, *supra* note 422.

[435] *See* FDA, *Executive Summary, Molecular and Clinical Genetics Panel*, 5 (Mar. 8–9, 2011), *available at* http://1.usa.gov/hqk1lo (identifying three types of genetic tests: clinical tests for the purpose of 'diagnosis, prevention, or treatment'; tests for research; and tests 'that do not carry medical claims, such as ancestry or forensic tests.' FDA disclaimed authority over the third category only).

[436] *See supra* notes 224-245, and accompanying text.

[437] Adapted from FDA, *Medical Claims on Labeling and Promotional Materials of Infant Mattresses and Infant Positioners Distributed in the United States* (March 13, 2000).

3. The First Amendment. When information is regulated, First Amendment concerns are inevitably implicated.[438] A complete First Amendment analysis is far beyond the scope of this Article. However, a few key points arise in light of the Supreme Court's recent decision in *Sorrell v. IMS Health*.

Commercial speech regulations are generally evaluated under the *Central Hudson* test, which allows lawful commercial speech to be regulated if doing so "directly advances" a "substantial" government interest in a manner that "is not more extensive than is necessary."[439] Courts have traditionally given the government additional leeway for laws and regulations safeguarding public health.[440] However, recent cases may have shifted this balance. For example, FDA's authority to regulate supplement health claims has been curtailed.[441] Although that authority is not directly applicable to medical devices, courts may be giving manufacturers more breathing room to express opinions differing from FDA's. One extensive analysis of the constitutionality of governmental restrictions on DTC genomic advertising concluded that any "attempt to categorically prohibit such advertising [would likely be found] unconstitutional if challenged in court."[442]

Last year, in *Sorrell v. IMS Health*, the Court applied heightened scrutiny to strike down a Vermont regulation prohibiting the sale of aggregate drug prescription data.[443] Justice Breyer, dissenting, warned that the opinion would place the constitutionality of FDA regulations in doubt.[444] Nonetheless, the majority opinion, penned by Justice Kennedy, extended First Amendment protection to information not typically thought of as "speech": prescriber-identifying information used for data-mining by pharmaceutical marketers. Rejecting the First Circuit's characterization of such information as a mere "commodity," Justice Kennedy stated that "the creation and dissemination of information are speech within the meaning of the First Amendment . . . Facts, after all, are the beginning point for much of the speech that is most essential to advance human knowledge."[445]

Sorrell casts an intriguing light on DTC genetic data. If a file of automatically collected prescriber data is "speech," not a "commodity," then a file of SNP genotypes, or a whole genome sequence, could likewise be speech. The *Sorrell* Court rejected Vermont's argument that the statute regulated not the act of speech, but rather access to information.[446] If "creating and disseminating" prescriber data (or genomic data) is within the purview of the First Amendment, and conveying a file of prescriber data (or genomic data) to a paying customer is "speech," then barring parties from completing

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[438] For an insightful general discussion of First Amendment doctrine with relation to expert knowledge, including medical knowledge, *see* Robert C. Post, Democracy, Expertise, and Academic Freedom: A First Amendment Jurisprudence for the Modern State (2012).

[439] *See, e.g.*, Kevin Ouetterson, *Higher First Amendment Hurdles for Public Health Regulation*, N. E. J. Med. e131 (Apr. 23, 2012).

[440] *See generally* David Orentlicher, *The Commercial Speech Doctrine in Health Regulation: The Clash Between the Public Interest in a Robust First Amendment and the Public Interest in Effective Protection From Harm*, 37 Am. J. L. Med. 299 (2011).

[441] *See, e.g.,* Pearson v. Shalala, 164 F.3d 650 (D.C. Cir. 1999).

[442] Javitt, Stanley & Hudson, *supra* note, at 254.

[443] Sorrell v. IMS Health Inc., 131 S. Ct. 2653, 2666–67 (U.S. 2011) (internal quotations and citations omitted).

[444] *Id.* at 2676.

[445] *Id.*

[446] *Id.; see also* Orentlicher, *supra* note 440, at 310 (asserting that "[t]he data mining laws [at issue in *Sorrell*] regulate economic transactions between data mining companies and their customers, not the content of their expression.").

such a (presumably lawful) transaction might—at least under certain circumstances—be subject to heightened scrutiny.[447]

Special judicial solicitude for access to one's own genomic data would dovetail nicely with characterizations of the commercial speech doctrine as "oriented to the rights of audiences to receive information" and intended to "protect the flow of information so as to enhance the quality of public decision-making."[448] Of course, the First Amendment does not require that the public be exposed to inaccurate or misleading information—particularly if they are not qualified to evaluate it. Robert Post explains that courts turn to "the disciplinary methods by which expert knowledge is created and certified" to determine if the speech contributes to democratic competence and should therefore be covered by the First Amendment.[449] And the passage from *Sorrell v. IMS Health* that opens this Article must be read in light of the sentence immediately following in, which explains that First Amendment precepts "apply with full force when the audience, in this case prescribing physicians, consists of 'sophisticated and experienced' consumers."[450] Thus, while rejecting a paternalist approach to regulating information exchange, *Sorrell* left the door open for stricter restrictions where the audience is composed of *non-experts*, because unsophisticated consumers require greater regulatory protection. It is unclear whether that significantly mitigates Justice Breyer's concern about weakening FDA authority, since much of the speech FDA seeks to regulate is directed to expert audiences, like prescribers. But it does clarify that *Sorrell* leaves the door open to FDA regulation of DTC genomic services (or advertising thereof).

Even so, it is difficult to characterize regulations limiting access to genetic information as protecting consumers from misleading information. The DTC companies' data are accurate, and their interpretations are evidence-based. It would be unreasonable to require that scientific information attain perfect certainty before it is protected by the First Amendment or valued for its contributions to democracy. Even if citizen science and participatory research do not yet produce expert knowledge as accurate as traditional research, DTC genomic test regulation would restrict access not to the fruits of those efforts, but to the predicate genetic data—an informational infrastructure[451] essential to public participation in genetic science.

D. *Hostile Territory: Personal Utility, Speculative Harms, and Risk-Based Regulation*

FDA's safety and efficacy framework is a poor fit for predictive genomic tests. Clinical evidence is often lacking, important benefits may be intangible, risks may be overstated, and preapproval would be prohibitively resource-intense. Under FDA's current framework, it is unclear whether the agency would have the capacity to pre-approve the current incarnation of DTC genomic services, even using a risk-based model to allocate its resources.

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[447] Among the many differences between these situations, it is especially important to note that patient privacy was not an issue in *Sorrell*. Had the "speech" implicated privacy concerns, the Court's analysis might have turned out differently.

[448] POST, *supra* note 438, at 43. For an interesting discussion of the "right to receive" aspect of First Amendment doctrine in the context of gene patents, *see* Krysta Kauble, *Patenting Everything Under the Sun*, 58 U.C.L.A. L. REV. 1123 (2011).

[449] POST, *supra* note 438, at 55–60.

[450] Sorrell v. IMS Health Inc., 131 S. Ct. at 2671.

[451] For an in-depth analysis of the intellectual property infrastructures undergirding innovation, *see* BRETT M. FRISCHMANN, INFRASTRUCTURE: THE SOCIAL VALUE OF SHARED RESOURCES 253–314 (2012).

By statute, FDA is charged with assessing the safety and effectiveness of a given test, not its analytic validity, clinical validity, or clinical utility.[452] However, FDA has considered the ACCE factors in the past, and will likely continue to do so. Various commentators have suggested that gatekeepers (whether FDA or physicians) should handle genetic tests differentially on the basis of particular criteria.[453] FDA likely does not have discretion to suspend safety or efficacy, but it can modify its approach in light of the product's intended use.

1. Clinical utility. Clinical utility represents "a balance between health-related benefits and the harms that can ensue from a genetic test."[454] It is contextual; a test with adequate utility in one situation may lack utility in another.[455] Even advocates of closer FDA attention to clinical utility admit that "clinical utility still is somewhat like art: 'I don't know what it is, but I know it when I see it.'"[456]

Clinical utility is problematic as applied to genomic services, because diagnostic tests, standing alone, lack clinical utility. Clinical benefits only accrue when therapeutic or preventive interventions are informed by the use of the diagnostic;[457] for example, the test for human epidermal growth factor receptor 2 (HER2) has clinical utility because HER2-positive patients will respond better to the drug Herceptin.[458] Predictive genomic tests, which are generally unable to inform treatment, lack clinical utility if it is defined in this way.[459] Thus the evidence of significant clinical utility required for safety and effectiveness is generally unattainable.

The clinical utility problem has already been acknowledged in human subjects research. Guidelines issued by two advisory organizations set "the bar for disclosure at (or near) clinical utility"[460]—that is, where the information would be medically actionable. But an HHS working group was criticized this standard because "individuals have differing personal perspectives about whether information has 'significant implications' for their own health."[461] The HHS group reasoned that "even if there is no prevention or treatment measure that the researcher or IRB judges to be effective," the information could help the subject make "certain life choices" or seek an intervention that the subject (though not the researchers) believes may be helpful.[462] These intangible elements are captured by a different dimension: personal utility.

2. Personal utility. Many individuals "passionately believe that consumers should not be prevented from accessing their own personal genetic information, even in the absence

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[452] SACGHS Oversight Report 97; *see also id.,* at 120 (noting subtle differences between FDA's use of the term "effectiveness" and the use of "effectiveness" in studies of clinical utility).

[453] *See, e.g.,* Robertson, *supra* note 11; Han, *supra* note 22 at 438–41 (arguing that FDA should not regulate a genetic test's "predictive value" to patients); Green & Botkin, *supra* note 10, at 573 ("Tests that should be handled with caution include those that identify stigmatizing diseases, substantially affect family members, lack acceptable and effective treatments, and have results that are difficult for clinicians to interpret.").

[454] SACGHS Oversight Report 115.

[455] *Id.* at 117.

[456] IOM Pathways Workshop Summary 8 (quoting Daniel Hayes of the University of Michigan Comprehensive Cancer Center).

[457] Marietta & McGuire, *supra* note 15 at 373.

[458] SACGHS Oversight Report 127.

[459] *See, e.g.*, Bogardus, *supra* note 68, at 210 ("[T]here is not likely to be clinical utility of the GWAS results (for BMI and type 2 diabetes at least) in the foreseeable future in populations of European descent.")

[460] Gordon, *supra* note 141, at 252.

[461] Gordon, *supra* note 141, at 252 (quoting HHS, *Response of the Department of Health and Human Services to NBAC's Report Research Involving Human Biological Materials: Ethical Issues and Policy Guidance*, at 23 (2001), available at http://aspe.hhs.gov/sp/hbm/hbm.pdf).

[462] *Id.*

of proven [clinical] utility."[463] The existence of consumer demand for DTC genomic services, and continuing participation in "research communities" like 23andWe, illustrate that individuals desire genomic information even if it is not medically actionable: some value knowledge, some seek to advance a research goal, some pursue identity, autonomy, or recreational satisfaction.[464] One 23andMe consumer was "elated" to verify that, despite some physical differences, he and his twin brother were genetically identical.[465] Patients may find satisfaction, closure or control in "ending a diagnostic odyssey," even if no treatment is available,[466] and predictive testing for serious diseases like Alzheimer's can enable life planning and end stressful uncertainty.[467] A common anecdotal benefit ascribed to DTC services is that genomic information can provide a much-needed stimulus to implement healthy lifestyle changes, like improved diet or exercise.

In 2011, FDA's Molecular and Clinical Genetics Advisory Panel discussed whether FDA should consider personal utility when evaluating safety and effectiveness (assuming the agency has the statutory authority to do so). The results were mixed.[468] Because individuals react differently to the prospect of risk prediction, the "personal utility" of information is hard to assess. Obtaining quantifiable evidence of it would be a tall order. But accounting for personal utility could be the only way to demonstrate benefits derived from purely informational, non-diagnostic, yet health-related applications of DTC genomic services.

3. Speculative harms. FDA has stated that it intends to apply risk-based oversight to genome services. However, it is not at all clear what that will entail, since the alleged harms of genomic testing[469] are highly speculative, and little empirical data support their existence.[470] Time and money are obvious costs; it is also plausible (though as yet empirically unproven) that patients may change medications or skip mammograms.[471] But concerns about prophylactic ovary removal[472] or mastectomies[473] seem farfetched: for one thing, women could not unilaterally take those actions without a physician, so a gatekeeper would be involved regardless. FDA does not yet seem to have resolved which speculative harms would be considered in its risk-based framework. When FDA's Molecular and Clinical Genetics Panel considered whether evidence of anxiety should be part of the safety determination, the panel's nonbinding consensus was that "legitimate data" about anxiety should be neither required nor ignored.[474] Regardless, it is unclear how this would impact genomic services, because thus far, studies suggest they do not cause undue anxiety.

It seems likely that the projected harms of DTC genomic services have been magnified through the lens of genetic exceptionalism, and genetic information that

[463] Wright & MacArthur, *supra* note 82, at 230.

[464] *See, e.g.*, *supra* note 126 (summarizing reasons NATURE READERS OBTAINED DTC TESTING).

[465] Michael Convente, *Our Genome Decoded: How Companies Like 23andMe Are Advancing the Field of Personal Genomics*, DAILY KOS (Mar. 30, 2011), http://www.dailykos.com/story/2011/03/30/961626/-Our-Genome-Decoded-How-Companies-Like-23andMe-Are-Advancing-the-Field-of-Personal-Genomics.

[466] SACGHS OVERSIGHT REPORT 122; IOM INTEGRATION WORKSHOP SUMMARY 5 (attributed to Leslie Biesecker of NHGRI).

[467] *But see* Evans & Berg, *supra* note 154 (observing that over "80% of individuals who are intimately familiar with Huntington disease choose not to pursue presymptomatic testing").

[468] Transcript, March 8, 2011 Meeting of the Molecular and Clinical Genetics Panel, Medical Devices Advisory Committee, CDRH, FDA, 290-98.

[469] *See supra* Part I.F.

[470] SACGHS OVERSIGHT REPORT 187.

[471] Frueh et al., *supra* note 176.

[472] Pollack, *supra* note 178.

[473] Solberg, *supra* note 22.

[474] Transcript, March 8, 2011 Meeting of the Molecular and Clinical Genetics Panel, Medical Devices Advisory Committee, CDRH, FDA, 298-303.

might induce people to harm themselves will turn out to be rare. But if the typical consumer's misconceptions about genomic services are magnified by misconceptions about genetics, taking that into account is fair. DTC genome services provide detailed explanatory materials and disclaimers to defuse such misconceptions,[475] however, and while they could no doubt be improved upon, it is troubling that FDA seems unwilling to credit those disclaimers as mitigating the risk of poor health decisions.

4. Expert gatekeepers and genetic counseling. There seems to be little consensus about the safety of genetic tests marketed without expert gatekeepers.[476] James Evans and Jonathan Berg argue that "[t]he most compelling arbiters of whether the acquisition of medical information should require a relationship with a health care professional are its complexity, ability to mislead, and potential for harm."[477] If so, the importance placed by FDA on clinician expertise in interpreting metabolic genetic tests, the increased complexity of genetic tests as noted in the IVDMIA draft guidance, and the confusing nature of relative risk argue in favor of an expert gatekeeper. On the other hand, for many people, insurance will not cover the test. It seems unfair to make a healthy, asymptomatic individual spend the time and money to visit a health care provider, in order to obtain nondiagnostic information not covered by a health plan. For most consumers, access to a health care provider or genetic counselor may be more beneficial *after* the test, when the results have prompted specific questions. If prescriptions are ultimately required, as they are in some states, the requirement will lack force if DTC companies' in-house physicians can approve consumers' orders. Regulations would need to be crafted so that, if a gatekeeper is imposed, she will act in the best interests of the consumer, have no conflicts of interest, and be qualified to discuss the results of the test—quite a challenge.

5. Resources. FDA currently evaluates the analytic validity and clinical validity of diagnostics in premarket review. While these can be demonstrated for gene chip based genomic tests, and thus pose less of a conceptual problem than clinical utility, clinical validity is "is perhaps the most complex part of the [ACCE] evaluation process, and requires significant expertise and resources."[478] Clinical validity represents the test's accuracy in detecting the presence of, or predicting the risk for, a health condition or phenotype."[479] But because SNPs are only proxies for nearby genes, even a well-validated SNP-disease association may not hold true for every person.[480] Both the scientific validity of the supporting studies and the test's expected performance in a specific patient population would have to be considered. The strength of genetic associations varies with ethnicity, environmental risk factors, and behaviors; given the lack of minorities in GWAS,[481] some associations may not be supported in non-Europeans, and the tests would be ineffective for those groups.

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[475] *See, e.g., Terms of Service*, 23andMe, https://www.23andme.com/about/tos/ (last visited Apr. 29, 2012):

"You should not change your health behaviors solely on the basis of information from 23andMe. Make sure to discuss your Genetic Information with a physician or other health care provider before you act upon the Genetic Information resulting from 23andMe Services. For most common diseases, the genes we know about are only responsible for a small fraction of the risk. There may be unknown genes, environmental factors, or lifestyle choices that are far more important predictors. If your data indicate that you are not at elevated genetic risk for a particular disease or condition, you should not feel that you are protected."

[476] Kirell Lakhman, *Should Clinical Labs Rejoice Over FDA Panel's DTC Genetic-Test Recommendations?* GenomeWeb (Mar. 11, 2011) http://www.genomeweb.com/blog/should-clinical-labs-rejoice-over-fda-panels-dtc-genetic-test-recommendations (split FDA advisory panel recommended that DTC tests should only be accessible through doctors).

[477] Evans & Berg, *supra* note 154.

[478] Wright & Kroese, *supra* note 42, at 129-130

[479] SACGHS Oversight Report 85.

[480] Wright & Kroese, *supra* note 42, at 130.

[481] Bustamante et al., *supra* note 66.

It would be very difficult for FDA to muster the resources to evaluate even a single genomic test in a reasonable amount of time.[482] CDC's EGAPP completed only four ACCE-based gene test associations between 2004-09,[483] and none of those involved a complex common disease, much less a million-SNP gene chip. While FDA's staffing and resources are much greater, it would be beyond any agency's resources to monitor the scientific and medical literature in order to dynamically re-evaluate the clinical significance of each SNP in the human genome in real time. Realistically, premarket processing of the tests would be delayed.[484]

Adding to the difficulty, DTC genomic services are bundles of individual SNP-disease associations. FDA could leave all genomic services on the market pending a risk-prioritized review. Alternatively, it could pull the highest-risk services off the market. A third option would involve identifying disease associations FDA deems most likely to cause harm (such as BRCA1/2, Alzheimer's, etc.), and barring DTC services from reporting those associations, pending review. Although the third option is best tailored to FDA's concerns, it would be messy to implement because of the informational nature of genomic services.[485] A DTC service could remove a high-risk SNP-disease association from its reports, or block the raw genotype data for that association, or alter the laboratory process so that the SNPs were never genotyped, but regardless, such a piecemeal system of approval seems highly problematic for FDA, for the regulated industry, and for the consumer.

IV. CHOOSING GATEKEEPERS

Even if it were possible to tailor an exceptional regulatory scheme just for DTC genomic services, the rapid turnover and evolution in the DTC market, coupled with the imminence of whole-genome testing, will soon supersede a regulatory framework tailored to current SNP technology. Nevertheless, it is essential to lay a groundwork that can adapt to a complex and information-rich future.[486] Currently, of FDA, CMS, and FTC, FDA is the most actively engaged in the regulatory space. Yet FTC is the agency tasked with addressing consumer confusion and exploitation. Why not keep all three agencies involved, but reverse their relative commitments, so FTC and CMS take the lead—a strategy that could be facilitated by statutory adjustments to CMS' authority, and discretionary forbearance by FDA?

A. *CMS*

CMS already regulates clinical laboratories, and is in the right position to regulate DTC genomic services conducted by those laboratories. However, CMS has limited authority. CLIA does not give CMS authority to regulate clinical validity or clinical

[482] Accelerated review, coupled with insufficient resources, time, and evidence, has caused problems for FDA before. When FDA contracted review of "old" drugs under the 1962 Kefauver-Harris Amendments to the National Academy of Sciences, the process was flawed by insufficient documentation of efficacy, time constraints, and procedural inconsistencies, leading to "findings [that] were more in the nature of educated opinions than of definitive scientific facts." SHEILA JASANOFF, FIFTH BRANCH: SCIENCE ADVISERS AS POLICYMAKERS 217-19 (1990). These deficiencies elicited misgivings from panelists about "being in a position to adjudicate for the country, with all its varied opinions and patterns for practice." *Id.* Industry challenged the findings, but as usual, courts deferred to FDA's expertise. *Id.*

[483] Wright & Kroese, *supra* note 42, at 127.

[484] An abbreviated version of ACCE is used in the UK; if FDA were able to streamline and standardize an ACCE module for use in safety and efficacy review, premarket approval of genomic tests might be more feasible.

[485] *See supra*, Part III.C.

[486] *Cf.* von Eschenbach, *supra* note 18.

utility,[487] and analytic validity is generally a lesser concern for genomic services.[488] To the extent premarket approval is desired, CLIA does not give CMS premarket gatekeeping authority.[489] Perhaps because of these limitations, SACGHS recommended that CLIA's scope be expanded "to encompass the full range of health-related tests, including those offered directly to consumers."[490] SACGHS envisioned complementary roles for CMS and FDA, but did not specify the details;[491] however, SACGHS noted that CMS believed Congress "did not expect CLIA to ensure the clinical validity of the tests" because "it would have created duplicative roles for FDA and CLIA."[492]

Various statutory fixes have been proposed to the CLIA regime. Recently, the Modernizing Laboratory Test Standards for Patients Act of 2011, H.R. 3207, would have extended CMS' authority to regulate LDTs, to require documentation of clinical validity from labs, and to review clinical validity for new and existing DTC tests.[493] The bill would have required labs to notify CMS before introducing a new DTC test, and created a databank for LDT and DTC tests. While the bill authorized additional inspectors to assess clinical validity, it could have been improved by addressing the deficiencies in inspection and enforcement criticized by GAO and SACGHS.[494] H.R. 3207 is unlikely to pass; it was referred to committee in Fall 2011, and as of this writing it had not reported out.[495] However, it represents a sensible compromise between unilateral FDA regulation and the current, inadequate system of CMS oversight.

B. *FTC*

For its part, FTC should take an active role in regulating DTC advertising, and ensuring that DTC genomic services neither oversimplify nor overstate their tests' capabilities. For example, some information on 23andMe's website is likely to confuse potential consumers: visitors are invited to "find out if you may pass on risk genes for 40+ Inheritable Conditions (including Cystic Fibrosis, Breast Cancer, and Tay-Sachs). *…23andMe will tell you if you have any of these risk genes*."[496] But 23andMe does not genotype all genetic variants associated with these diseases, or sequence the complete disease genes. With respect to breast cancer risk, it genotypes only the three BRCA1/2 mutations found predominantly in women of Ashkenazi Jewish ancestry.[497] By contrast, Myriad Genetics' Comprehensive BRACAnalysis Test sequences the complete coding regions of both BRCA1 and BRCA2 genes.[498]

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[487] Solberg, *supra* note 22, at 738–39.

[488] *See, e.g.*, Khoury et al., *supra* note 42, at 561–62.

[489] Javitt & Hudson, *supra* note 270, at 61.

[490] SACGHS Oversight Report 113; *see also id.* at 30-31, 111-114.

[491] *Id.* ("FDA's risk-based regulatory authority and regulatory processes[] should be expanded").

[492] SACGHS Oversight Report at 94 (citing Judy Yost, CMS, personal communication).

[493] *See Side-by-Side Comparison of CLIA and HR 3207, Modernizing Laboratory Test Standards for Patients Act*, *available at* http://acla.com/sites/default/files/CLIA%20v%20Burgess%20side-by-side%20FINAL.pdf (last visited Apr. 29, 2012).

[494] *See supra* notes 316-329 and accompanying text.

[495] H.R. 3207: Modernizing Laboratory Test Standards for Patients Act of 2011, available at http://www.govtrack.us/congress/bills/112/hr3207 (last visited Apr. 29, 2012).

[496] 23andMe, https://www.23andme.com/health/ (last visited Apr. 29, 2012) (emphasis added) (small type underneath indicates that "risk genes" "refers to specific genetic risk variants.").

[497] *BRCA Cancer Mutations (Selected)*, 23andMe, https://www.23andme.com/health/BRCA-Cancer/ (last visited Apr. 29, 2012) (the three mutations are 185delAG in BRCA1, 5382insC in BRCA1, and 6174delT in BRCA2).

[498] *BRACAnalysis Technical Specifications*, Myriad Genetic Labs (Feb. 2012), http://www.myriad.com/lib/technical-specifications/BRACAnalysis-Technical-Specifications.pdf.

23andMe discloses in multiple locations on its website that it screens only three of the hundreds of BRCA1/2 genetic variants.[499] However, because users must click several links to find this information, it could well be overlooked prior to (or after) purchase. Similarly, 23andMe's invitation to "estimate[] your genetic chances of getting Type 2 Diabetes" may confuse prospective consumers unaware that the "genetic chance" of getting diabetes is far outweighed by non-genetic factors, like diet and exercise. This is disclosed by 23andMe, but again, it may be overlooked by potential customers.[500] 23andMe also discloses in a less-than-salient location whether the genetic associations it reports are clinically supported in European, East Asian, or African populations.[501] This information is essential to prospective consumers' ability to evaluate the service's benefits, and should be highly visible before purchase without exhaustively touring the site.

Policing DTC service websites and advertising is squarely within FTC's mandate. However, FTC will need to partner with FDA to build the subject matter expertise required to police misstatements about genetic risk. Since FTC already relies on FDA's expertise in other contexts, this should be straightforward. And both agencies should take an active role in the development of best practices and standards for reporting genomic data.

C. *FDA*

1. Facilitating Autonomy and Participatory Research. Predictive genetic tests are still in their infancy, and will probably never become the "crystal balls" many hoped for. But giving healthy, curious individuals access to their genomic data has yielded at least one benefit: a vibrant, innovative culture of "health hackers" creating participatory research frameworks to supplement the traditional clinical research model, and generating an innovation infrastructure with unknown potential.

FDA can and should regulate medical devices within its statutory mandate, as Congress intended, to protect the public from unsafe or ineffective products. For complex LDTs requiring greater expertise than usual, FDA clearance or approval may be a good thing complement to CMS regulation; FDA's approach does not have to be one-size-fits-all.[502] But for predictive tests generally, FDA should consider developing a less cumbersome form of ACCE analysis (accounting for personal utility) more clearly matched to its evaluation of device safety and effectiveness.

FDA has a tradition of exercising enforcement discretion when its rigorous system of premarket oversight would be excessive; it should invoke that tradition here. FDA should abandon its reliance on the limitless "medical claims" standard as applied to DTC genomic services, and instead exercise autonomy-based enforcement discretion as to tests (including but not limited to DTC genomic services) for generating and/or interpreting *objective information about a person,* as opposed to *medical recommendations,*

[499] *See, e.g., Get Tested to See What Your Genetics Say About Breast Cancer*, 23ANDME, https://www.23andme.com/health/Breast-Cancer/ (last visited Apr. 29, 2012); *BRCA Cancer Mutations (Selected)*, 23ANDME, https://www.23andme.com/health/BRCA-Cancer/ (last visited Apr. 29, 2012) ("the BRCA mutations covered by this report are only three of hundreds . . . their absence does not rule out the possibility that you may carry another cancer-causing variation"); *BRCA Cancer Mutations (Selected) Technical Report*, 23ANDME, https://www.23andme.com/health/BRCA-Cancer/techreport/BRCA (last visited Apr. 29, 2012) ("Hundreds of mutations have been reported in the BRCA1 and BRCA2 genes. 23andMe provides data for only three…").

[500] *Get tested to learn what your genetics say about: Type 2 Diabetes*, 23ANDME, https://www.23andme.com/health/Type-2-Diabetes/ (last visited Apr. 29, 2012) ("The heritability of type 2 diabetes is estimated to be 26%.").

[501] *Health Reports: By Ethnicity*, 23ANDME, https://www.23andme.com/health/ethnicity/ (last visited Apr. 29, 2012).

[502] Hudson et al., *supra* note 81, at 635.

decisions, or advice. This policy would not turn on genetic exceptionalism; genomics, metabolomics, proteomics, and other health datasets should be treated consistently. FDA should also ensure that in the research context, personal information can be disclosed to participants without jeopardizing the RUO status of IVD manufacturers.[503]

Most DTC consumers don't want government gatekeepers limiting access to genomic services. Since those services show no sign of harming consumers, there should be no reason to impose a gatekeeper.[504] But if a gatekeeper becomes necessary, a pre-test physician gatekeeper would be much less burdensome than a pre-market FDA gatekeeper.[505] If FDA deems it necessary to impose a uniform national prescribing standard for DTC tests, it should regulate DTC tests as Class II, and allow tests lacking traditional clinical benefits to be approved on the basis of benefits cognizable under "personal utility" (or its equivalent).

2. Reporting Standards and Best Practices. Several years ago, DTC genomic services acknowledged the need for reporting standards and best practices to clarify their communications with consumers.[506] Two years later, 23andMe requested help from NIH and FDA in developing reporting guidelines.[507] FDA, CDC, NIH, and any other agencies with relevant expertise should answer this call, and collaborate to create a common vocabulary and set of parameters for genomic information reporting. An interagency working group should also develop a plan, in collaboration with professional groups, to train health care providers in genetics and statistics.

3. Postmarket surveillance and adverse event reporting. In 2008, SACGHS reported a deficit of studies documenting the harms of genetic testing. In subsequent years, that deficit has not been remedied. As a result, FDA may be compelled to base premarket review of genetic tests on hypothetical risks. Although there is currently no indication that DTC genomic services are harmful, as the DTC consumer profile shifts away from knowledgeable early adopters, or as more time passes, projected harms may materialize. If they do materialize, it is essential for regulators to know and take action.

The Food and Drug Administration Amendments Act of 2007 required FDA to establish postmarket surveillance capacities for medical products.[508] In response, FDA is developing a national postmarket risk assessment database called the Sentinel System.[509] As part of this system, FDA should consider establishing a longitudinal project following DTC genomic service users and obtaining feedback on their experience.

[503] *Cf.* 21 C.F.R. 812.2(c)(3) (2011). *See also* FDA, *Guidance for Industry and FDA Staff: In Vitro Diagnostic (IVD) Device Studies - Frequently Asked Questions* 11 (June 25, 2010) (allowing research use of diagnostic only insofar as it does not "influence patient treatment or clinical management decisions before the diagnosis is established by a medically established product or procedure.").

[504] *See, e.g.*, Kaufman, *supra* note 169 (66% of DTC consumers felt the services should be available without government oversight, but wanted an organization like FTC to monitor companies' claims for accuracy).

[505] Because the practice of medicine exception only applies to legally marketed products, even physicians can't use an FDA-prohibited drug or device off-label. *See* FD&C Act § 906 (21 U.S.C. § 396) ("Nothing in this [Act] shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. . . ."); *cf.* Gonzales v. Raich, 545 U.S. 1, 28 (2005) ("the dispensing of new drugs, even when doctors approve their use, must await federal approval"). *See also* R.S. Stafford, *Off-Label Use of Drugs and Medical Devices: A Review of Policy Implications*, Clinical Pharmacology & Therapeutics (Apr. 4, 2012).

[506] Personalized Medicine Coalition, Personal Genomics and Industry Standards: Scientific Validity (July 2008) *available at* http://bit.ly/KpJenC (last visited Apr. 29, 2012).

[507] *23andMe Letter to Heads of FDA and NIH*, The Spittoon (Jul. 6, 2010, 11:13 PM), http://spittoon.23andme.com/2010/07/06/23andme-letter-to-heads-of-fda-and-nih/.

[508] *See generally* Evans, *Seven Pillars, supra* note 61.

[509] FDA, The Sentinel Initiative: A National Strategy for Monitoring Medical Product Safety (2008).

Such a system could potentially yield more than adverse event reports: FDA could also leverage participatory research networks to collect long-term, post-test information. It is notoriously difficult to evaluate the effectiveness of prophylactic treatments meant to prevent long-term health problems,[510] and currently, most studies of genetic tests are "conducted in the premarket approval phase" with little postmarket evidence.[511] DTC genomic services' pre-existing customer networks could facilitate the crowdsourcing of longitudinal research projects.[512] While a collaboration between FDA and DTC services may seem unlikely, it would signal a new openness on the agency's part to nontraditional research models.

V. CONCLUSION

In the 1970s, FDA rejected Laetrile users' case histories as lacking evidentiary value, and declined to approve research studies on the drug. Today, Laetrile users would join PatientsLikeMe. In the 1980s, FDA refused to approve home HIV tests. Today, synthetic biology enthusiasts can sequence genes in their garage, and order whole-genome sequences online, for good or bad.[513] The genomic genie is out of the bottle; the gate has already been flung open. It may be prudent to close that gate a little—but that decision should be based on something more than speculative hyperbole, and the bugaboos of genetic exceptionalism.

FDA's century of expertise and authority is not called into serious question by genomic information services, or by participatory research. But FDA would be best served by admitting that it can't regulate every DNA base pair, and not straining its limited resources to try. It is not necessary to resolve at this point whether there is a "right" to access one's own genetic data that trumps FDA regulation, or whether predictive genetic testing will ultimately live up to its promise. It is only necessary to recognize that risk-based regulatory systems must adapt to accommodate information of uncertain and contingent value—particularly where that information supplies not only autonomy-related personal benefits, but also the infrastructure for a highly democratic, innovative movement like participatory research.

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[510] Evans, *Seven Pillars, supra* note 61, at 462.

[511] SACGHS OVERSIGHT REPORT 121.

[512] *Cf.* Randall S. Stafford, *Regulating Off-Label Drug Use — Rethinking the Role of the FDA*, 358 N.E.J. MED. 1427 (2008) (arguing that FDA should consider "systematically collecting postmarketing data to quantify the harms and benefits of common off-label uses").

[513] *See, e.g.*, Ted Greenwald, *DNA Sequencing For Fun And Profit: A Low-Cost Platform For Garage Biotech,* FORBES (DEC. 31, 2011).