Northwestern Journal of Technology and Intellectual Property

Volume 11 | Issue 1 Article 1

2012

Gatekeepers and Goalposts: The Need for a New Regulatory Paradigm for Whole Genome Sequence Results

Trevor Woodage
Fish & Richardson, P.C.

N O R T H W E S T E R N
JOURNAL OF TECHNOLOGY
AND
INTELLECTUAL PROPERTY

Gatekeepers and Goalposts: The Need for a New Regulatory Paradigm for Whole Genome Sequence Results

Trevor Woodage

October 2012 VOL. 11, NO. 1

Northwestern Journal of Technology and Intellectual Property
Volume 11, Number 1 (October 2012)

Gatekeepers and Goalposts: The Need for a New Regulatory Paradigm for Whole Genome Sequence Results

By Trevor Woodage*

I. INTRODUCTION

¶1 The ability to obtain a person's whole genome sequence for a cost of one thousand dollars is nearly here. Many clinicians expect that this will usher in an era of personalized medicine by allowing the development of individualized disease-risk profiles, preventive medicine strategies, and treatment options. However, it is not clear that the regulatory strategy that currently controls the approval and availability of more limited genetic tests—typically meant to investigate one or a small number of disease or other traits—provides a satisfactory framework for whole genome sequence testing.

¶2 This Perspective takes the position that the generation of whole genome sequence testing information needs to be treated differently than the tests and results associated with more traditional diagnostic assays. Part I considers the current regulatory environment and efforts to reform the oversight of genetic tests, in particular, the solution to the question of whether consumers should be permitted to order whole genome sequence tests without the guidance of a health-care professional. Part II discusses how whole genome sequence tests differ from conventional genetic tests both in the vastly greater amount of information that is generated and in the ways the information can be interpreted and reinterpreted for different purposes at different times. Part III suggests that rather than using the current regulatory approach of concentrating on technical attributes of the whole genome sequence testing process, regulatory approaches should be directed to the tools needed to analyze and apply deoxyribonucleic acid (DNA) sequence information. Such efforts will safeguard patients from adverse outcomes associated with unreliable disease-risk prediction, while improving access to the perceived benefits of whole genome sequence testing.

II. BACKGROUND

¶3 In April 2003, scientists working on the Human Genome Project (HGP) finished a thirteen-year effort to sequence the approximately three billion nucleotides that make up the human genome.[1] This haploid genome (representing only one of the two copies that each person inherits from his or her parents) was a consensus sequence cobbled together

* Attorney, Fish & Richardson, P.C.; Ph.D., University of Sydney; J.D., University of Minnesota Law School. Thanks to Susan M. Wolf and Mark S. Ellinger for thoughtful comments.

[1] *See International Consortium Completes Human Genome Project*, NAT'L INST. OF HUMAN GENOME RESEARCH (Apr. 14, 2003), http://www.genome.gov/11006929.

with sequences from DNA samples obtained from several individuals.[2] The HGP's sequencing cost alone was at least $500 million.[3] The first individual human genomes were sequenced in 2007[4] at costs ranging from $1.5 million to $100 million.[5] By mid-2009, eight people had been sequenced, costing as little as $50,000 per person.[6] By the end of 2010, one company announced that it had sequenced over 800 genomes,[7] with sequencing costs under $10,000 per genome.[8] In 2011, whole genome sequencing costs dropped below $5000,[9] and consumers could sign up to have all protein-coding regions of their genomes sequenced for under $1000.[10]

¶4 In the face of these dramatic trends, it is not surprising that scientists and businessmen propound the widespread availability of the "thousand-dollar genome" and claim that personal genome sequencing will herald revolutionary advances in medicine and biology.[11] Much of the excitement about the widespread availability of relatively inexpensive whole genome sequence (WGS) data comes from the prospect that the sequence information will allow people to create individualized disease-risk profiles and take preventative lifestyle measures for improved health.[12]

¶5 Scientists have used DNA sequence information to diagnose and predict the risk of developing disease for decades.[13] However, they have increasingly applied DNA sequence information to understanding common, multifactorial conditions rather than rare, single-gene conditions, making risk estimates more often probabilistic than

---

[2] *See Facts About Genome Sequencing*, U.S. DEP'T OF ENERGY, OFFICE OF SCI., http://www.ornl.gov/sci/techresources/Human_Genome/faq/seqfacts.shtml#whose (last updated Sept. 19, 2008).

[3] Nicholas Wade, *Technology Lowers Cost of Decoding a Genome to $50,000*, N.Y. TIMES, Aug. 11, 2009, at D3, *available at* 2009 WLNR 15505816.

[4] KEVIN DAVIES, THE $1,000 GENOME: THE REVOLUTION IN DNA SEQUENCING AND THE NEW ERA OF PERSONALIZED MEDICINE 27–28 (2010) (noting that diploid sequences were produced in 2007 for both J. Craig Venter and James Watson, two pioneer scientists involved in DNA sequencing).

[5] JULIA E. RICHARDS & R. SCOTT HAWLEY, THE HUMAN GENOME: A USER'S GUIDE 443 (3d ed. 2011). Individual genome sequencing requires characterization of twice as much DNA as the human reference sequence produced by the HGP because a diploid genome—containing the chromosomal DNA inherited from each parent—must be sequenced. *See* Jon Cohen, *Venter's Genome Sheds New Light on Human Variation*, 317 SCI. 1311, 1311 (2007).

[6] Wade, *supra* note 3.

[7] Press Release, Complete Genomics, Complete Genomics Reports Results for Fourth Quarter and Fiscal Year 2010 (Mar. 10, 2011), http://ir.completegenomics.com/releasedetail.cfm/ReleaseID=556147.

[8] Kevin Davies, *The $10,000 Genome and Counting: The Complete Picture for 2011*, BIO-IT WORLD (Feb. 7, 2011) http://www.bio-itworld.com/news/02/07/11/10000-dollar-genome-Complete-picture-2011.html.

[9] *Illumina Drops Cost of Whole-Genome Sequencing Services*, GENOMEWEB DAILY NEWS (May 9, 2011), http://www.genomeweb.com/sequencing/illumina-lowers-cost-whole-genome-sequencing-services.

[10] *Exome 80x Pilot Program*, 23ANDME.COM, https://www.23andme.com/exome/ (last visited May 27, 2012); Matthew Herper, *The Future Is Now: 23andMe Now Offers All Your Genes for $999*, FORBES (Sept. 27, 2011, 4:55 PM), http://www.forbes.com/sites/matthewherper/2011/09/27/the-future-is-now-23andme-now-offers-all-your-genes-for-999/.

[11] *See* DAVIES, *supra* note 4, at 9–13.

[12] *See* FRANCIS S. COLLINS, THE LANGUAGE OF LIFE: DNA AND THE REVOLUTION IN PERSONALIZED MEDICINE 15–17 (2010).

[13] *See generally* Stylianos E. Antonarakis, *Mutations in Human Diseases: Nature and Consequences*, in 1 EMERY AND RIMOIN'S PRINCIPLES AND PRACTICE OF MEDICAL GENETICS 53–63 (David L. Rimoin ET AL. Eds., Pearson Prof'l Ltd 3d ed. 1997) (1983) (discussing a wide variety of mutations that cause disease and how genetic variation (genotype) can correlate with clinical outcome (phenotype)).

absolute.[14] Concerns about how to interpret the results of these new applications fuel a hotly contested debate underway concerning the role of government oversight in controlling the availability and use of genetic tests.[15]

III. REGULATORY OVERSIGHT OF GENETIC TESTS

¶6 Genetic tests can be regulated either as products or services. The Food and Drug Administration (FDA) regulates products, however, services are concurrently regulated by branches of the U.S. Department of Health and Human Services, including the FDA, the Centers for Disease Control and Prevention (CDC), and the Centers for Medicare and Medicaid Services (CMS), and sometimes state agencies.[16] In addition, non-government actors including professional and industry organizations can impose other controls on genetic testing services.[17] Also, even if not considered a source of regulations, health insurers play a major role in controlling availability and widespread access to genetic testing services.[18] Like health insurance companies, CMS can control access to genetic tests through its reimbursement policies.[19] Understanding the regulatory landscape as it relates to WGS testing requires consideration of the authority that agencies have exerted over genetic testing to date and recent moves to increase that authority over direct-to-consumer (DTC) genetic testing.

A. Federal Agencies and Ambiguity in the Exercise of Agency Authority Over Genetic Tests

¶7 Responding to concerns about the quality of clinical laboratory testing, Congress passed the Clinical Laboratory Improvements Amendments of 1988 (CLIA).[20] CLIA

---

[14] David Botstein & Neil Risch, *Discovering Genotypes Underlying Human Phenotypes: Past Successes for Mendelian Disease, Future Approaches for Complex Disease*, 33 NATURE GENETICS 228, 232 (2010).

[15] *Compare* Letter from Michael D. Maves, Exec. Vice-President & Chief Exec. Officer, Am. Med. Ass'n, to Food & Drug Admin. 1 (Feb. 23, 2011), *available at* http://www.ama-assn.org/ama1/pub/upload/mm/399/consumer-genetic-testing-letter.pdf [hereinafter AMA letter] (requesting that the FDA impose strong oversight measures on genetic tests such that they could not be made available to consumers without physician involvement), *with* Daniel MacArthur, *Last Chance: Let the FDA Know Why You Want Direct Access to Your Own Genome*, WIRED SCIENCE (Apr. 29, 2011, 4:55 PM), http://www.wired.com/wiredscience/ 2011/04/last-chance-let-the-fda-know-why-you-want-direct-access-to-your-own-genome/ (arguing for minimal regulation of genetic tests).

[16] LORI B. ANDREWS ET AL., GENETICS: ETHICS, LAW AND POLICY 310 (3d ed.). This Perspective will only consider oversight of genetic testing services. At least in the near-term there is no evidence that stand-alone WGS products are being developed. Further, even if it was possible to produce a "black box" that could completely automate WGS testing, data interpretation issues would remain because of their heterogeneous nature. For state controls over genetic testing, *see* SURVEY OF DIRECT-TO-CONSUMER TESTING STATUTES AND REGULATIONS, GENETICS & PUBLIC POLICY CENTER (2007), *available at* http://www.dnapolicy.org/resources/DTCStateLawChart.pdf. This Paper will not discuss state regulation of genetic tests.

[17] *See id*., at 310.

[18] *See* Michelle Andrews, *Genetic Tests Abound. Why Won't Insurers Pay?*, N.Y. TIMES, May 19, 2002, § 3, at 39, *available at* 2002 WLNR 4064237.

[19] *See, e.g.*, Norm Alster, *Diagnostic Testing Firm Carves out Territory Between Behemoths*, INVESTORS BUS. DAILY, June 24, 2009, *available at* 2009 WLNR 12002504; Bernadette Tansey, *Diagnostic Test Could Pinpoint Origin of Cancers*, S.F. CHRON., May 8, 2008, at C1, *available at* 2008 WLNR 8612425.

[20] Clinical Laboratory Improvements Amendments of 1988, 42 U.S.C. § 263(a) (2006); *see also* Morton K. Schwartz, *Genetic Testing and the Clinical Laboratory Improvement Amendments of 1988: Present and*

allowed the CMS and CDC to implement standards for laboratory certification, focusing on intra-laboratory quality control and quality assurance mechanisms rather than on the clinical uses of test results.[21]

¶8 Under CLIA, genetic testing must meet general testing standards, but there is no requirement that genetic tests meet any particular specialty standards, despite their high complexity.[22] Several groups, including the Secretary's Advisory Committee on Genetic Testing;[23] the Genetic Alliance, a patient advocacy group;[24] and the American Society of Human Genetics,[25] identified a need and called for the creation of a genetic testing specialty under CLIA. However, CMS chose not to create a genetics specialty under CLIA, determining that the "slow and painstaking" development of proficiency standards would not be able to keep up with the rapid development of new genetic tests.[26] Given CMS's failure to act, it appeared that any substantive federal regulatory oversight of genetic tests would have to come from another agency, such as the FDA.

¶9 The FDA has statutory authority to regulate drugs and medical devices.[27] Medical devices include any "instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article", which is "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease."[28] Courts grant the FDA broad discretion in deciding regulatory classifications[29] and the FDA has indicated that it will regulate at least some genetic tests as devices.[30]

¶10 Diagnostic tests sold to hospitals and commercial laboratories are classified as devices by the FDA and must undergo pre-market approval.[31] But a broad exception has been exploited to allow many genetic tests to escape the requirement for that FDA pre-

---

Future, 45 CLINICAL CHEMISTRY 739, 739 (1999).

[21] *See* SEC'Y'S ADVISORY COMM. ON GENETIC TESTING, ENHANCING THE OVERSIGHT OF GENETIC TESTS: RECOMMENDATIONS OF THE SACGT 9 (2000) [hereinafter SACGT RECOMMENDATIONS], *available at* http://oba.od.nih.gov/oba/sacgt/reports/oversight_report.pdf.The Healthcare Financing Administration (HCFA) was renamed as the CMS in 2001. Press Release, Dep't of Health and Human Servs., The New Centers for Medicare & Medicaid Services (CMS) (June 14, 2001), *available at* http://archive.hhs.gov/news/press/2001pres/20010614a.html.

[22] *See* Rebecca Antar Novick, Note, *One Step at a Time: Ethical Barriers to Home Genetic Testing and Why the U.S. Health System Is Not Ready*, 11 N.Y.U. J. LEGIS. & PUB. POL'Y 621,627–28 (2008).

[23] *See* SACGT RECOMMENDATIONS, *supra* note 21, at 25–28.

[24] Press Release, Genetic Alliance, Genetic Alliance Calls for Genetic Testing Specialty Under CLIA (Mar. 2, 2006), *available at* http://www.geneticalliance.org/policy.clia.release.

[25] Kathy Hudson et al., *ASHG Statement on Direct-to-Consumer Genetic Testing in the United States*, 81 AM. J. HUM. GENETICS 635, 637 (2007).

[26] Novick, *supra* note 22, at 628 (citing Letter from Dennis G. Smith, Dir., Ctr. for Medicaid & State Operations, to Kathy Hudson, Dir., Genetics & Pub. Policy Ctr. (Aug. 15, 2007)).

[27] PETER BARTON HUTT ET AL., FOOD AND DRUG LAW: CASES AND MATERIALS 29 (3d ed. 2007).

[28] Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321(h) (2006); *see also* Juliana Han, Note, *The Optimal Scope of FDA Regulation of Genetic Tests: Meeting Challenges and Keeping Promises*, 20 HARV. J.L. & TECH. 423, 430–34 (2007) (discussing the sources of FDA jurisdiction over genetic tests).

[29] *See United States v. An Article of Drug . . . Bacto-Unidisk . . .*, 394 U.S. 784, 798 (1969) (holding that the FDA had the authority to determine whether an article should be classified as a drug or a device and stating that "remedial legislation such as the Food, Drug, and Cosmetic Act is to be given a liberal construction consistent with the Act's overriding purpose to protect the public health").

[30] Gregorio M. Garcia, *The FDA and Regulation of Genetic Tests: Building Confidence and Promoting Safety*, 48 JURIMETRICS J. 217, 218 (2008).

[31] Douglas A. Grimm, *FDA, CLIA, or a "Reasonable Combination of Both": Toward Increased Regulatory Oversight of Genetic Testing*, 41 U.S.F. L. REV. 107, 118 (2006).

market approval.[32] "Home brew" tests use analyte-specific reagents (test reagents developed from basic ingredients by the laboratories themselves) that only must comply with general controls.[33] Companies can then avoid the need for pre-market approval by allowing end-users to employ home-brew testing.[34] In July 2007 the FDA moved to restrict the breadth of this loophole by issuing a draft guidance document indicating that it would regulate complex genetic tests known as *In Vitro* Diagnostic Multivariate Assays (IVDMIAs).[35]

¶11 Although the subject has not explicitly been addressed, it is likely that WGS testing would fall squarely within the IVDMIA category. The FDA noted that IVDMIAs are tests that are "developed based on observed correlations between multivariate data and clinical outcome, such that the clinical validity of the claims is not transparent to patients, laboratorians, and clinicians who order these tests."[36] Because it comes from so many different genes, WGS information is a prototypic example of multivariate data. Further, the clinical validity on which correlations between genotype and phenotype rely is definitely not transparent.[37] The FDA's rationale for imposing pre-market approval requirements in the guidance would also apply to WGS testing: "IVDMIAs frequently have a high risk intended use. FDA is concerned that patients and healthcare practitioners are relying upon IVDMIAs with high risk intended uses to make critical healthcare decisions without any independent assurance that the IVDMIA has been properly clinically validated."[38]

¶12 If the draft guidance had been implemented, the FDA likely would have regulatory authority over WGS testing. But, facing industry resistance, the guidance has not yet been adopted.[39] Instead, the FDA has decided to address DTC genetic testing concerns by developing guidance for the broader set of laboratory-developed tests and moving to regulate in a risk-based manner rather than just by the class of test involved.[40]

---

[32] *Id.* at 118–19.

[33] *Id.* at 119; *see also General Controls for Medical Devices*, FOOD & DRUG ADMIN., http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm (last visited May 28, 2012).

[34] Andrew Pollack, *F.D.A. Asks If a Genetic Test Is Sold Without Approval*, N.Y. TIMES, July 18, 2003, at C2, *available at* http://www.nytimes.com/2003/07/18/business/fda-asks-if-a-genetic-test-is-sold-without-approval.html?pagewanted=all&src=pm ("Companies that develop tests they want to sell to many laboratories can take advantage of the home-brew system. Instead of selling a complete test requiring F.D.A. approval, they sell the basic ingredients of a test to clinical laboratories. The labs then use the ingredients to make home-brew tests. The ingredients, usually chemicals or pieces of DNA, are called analyte-specific reagents and are only lightly regulated.").

[35] Draft Guidance for Industry and Food and Drug Administration Staff; In Vitro Diagnostic Multivariate Index Assays; Availability, 72 Fed. Reg. 41,081 (July 26, 2007).

[36] *Id.* at 41,082.

[37] *See infra* notes 80-86 and accompanying text.

[38] 72 Fed. Reg. at 41,082.

[39] *See FDA Shelves IVDMIA Regulatory Initiative; Will Focus on Laboratory Developed Tests*, LAB SOFT NEWS (June 25, 2010, 8:47 AM), http://labsoftnews.typepad.com/lab_soft_news/2010/ 06/fda-shelves-ivdmia-initiative-will-focus-on-laboratory-developed-tests.html.

[40] *See id.*

B. The FDA Addresses Direct-to-Consumer Genetic Testing: Is a Gatekeeper Necessary?

¶13 The confluence of the success of the HGP and the rise of the internet as a source of information and presence as a commercial marketplace have undoubtedly contributed to the proliferation of companies that market and advertise genetic tests directly to consumers.[41] Concerns about DTC genetic testing address two goals that are potentially in conflict: personal empowerment[42] and consumer-protection interests including patient safety, accuracy of test results, and freedom from misleading information.[43] Even strong proponents of consumer access to genetic information concede that some government oversight is appropriate, including regulations ensuring the accuracy of DNA sequence results and the prevention of false claims and unethical advertising.[44] However, there is a substantial amount of disagreement as to whether a healthcare professional should serve as an intermediary between the consumer and the genetic test provider.[45]

¶14 As argued in the previous section, the FDA likely has statutory authority to regulate complex genetic tests that are "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease."[46] One of the central issues in disputes over DTC genetic testing is whether it is *intended* to diagnose or prevent disease.[47] There is no single answer to this question because DTC genetic testing has been offered for a remarkably large variety of applications. These include paternity testing;[48] "recreational genomics,"[49] which includes genealogy[50] or matchmaking[51] tests; assessment of traits not directly related to disease, such as genetic variants associated

---

[41] *See Direct-to-Consumer Genetic Testing Companies*, GENETICS & PUB. POLICY CTR., http://www.dnapolicy.org/resources/DTCcompanieslist.pdf (last visited May 28, 2012) (listing thirty-seven DTC genetic testing companies as of May 2009); Andrew Polack, *A Genetic Test that Very Few Need, Marketed to the Masses*, N.Y. TIMES, Sept. 11, 2007, at C3, *available at* http://www.nytimes.com/2007/09/11/business/media/11genetics.html (noting concerns that advertising of genetic tests for breast cancer mutation screening direct to consumers could result in inappropriate test utilization).

[42] Novick, *supra* note 22, at 641.

[43] Sivan Tamir, *Direct-to-Consumer Genetic Testing: Ethical-Legal Perspectives and Practical Considerations*, 18 MED. L. REV. 213, 214 (2010).

[44] *See* MacArthur, *supra* note 15.

[45] *See supra* note 15; *see also* Gaia Bernstein, *Direct-to-Consumer Genetic Testing: Gatekeeping the Production of Genetic Information*, 79 UMKC L. REV. 283, 287–91 (2010); Cynthia Marietta & Amy L. McGuire, *Direct-to-Consumer Genetic Testing: Is It the Practice of Medicine?*, 37 J.L. MED. & ETHICS 369, 373 (2009).

[46] Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 321(h) (2006); *see also supra* notes 27–35 and accompanying text of this Perspective.

[47] *See* Marietta & McGuire, *supra* note 45, at 369 (arguing that for multiplex genetic tests "[t]he variety of genetic information tested for complicates the issue of whether [DTC genetic testing] companies are providing information for recreational purposes only or whether they are also providing medical diagnostic information").

[48] *See, e.g.*, *DNA Testing and Home DNA Test Services*, EASY-DNA.COM, http://www.easy-dna.com (last visited July 15, 2012); *Home DNA and Paternity Tests*, THE GENETIC TESTING LABORATORIES, INC., http://www.gtldna.com (last visited July 15, 2012).

[49] Andrea Mechanick Braverman, *How the Internet Is Reshaping Assisted Reproduction: From Donor Offspring Registries to Direct-to-Consumer Genetic Testing*, 11 MINN. J.L. SCI. & TECH. 477, 494 (2010).

[50] *See, e.g.*, ANCESTRYBYDNA, http://www.ancestrybydna.com (last visited July 15, 2012); FAMILYTREEDNA, http://www.familytreedna.com (last visited May 28, 2012).

[51] *See, e.g.*, GENEPARTNER, http://www.genepartner.com (last visited July 15, 2012).

with responses to nutrients (nutrigenomics);[52] drug response;[53] athletic performance;[54] and those directed at assessment of disease risk.[55] Whatever the quality of the science underlying these commercial offerings, at least some of the tests, including those for genealogical typing and paternity testing, would not seem to fall under FDA jurisdiction, unlike tests intended for the diagnosis or prevention of disease.

¶15 Consistent with the likelihood that not all genetic tests would fall under the FDA's jurisdiction, the FDA may be moving toward a risk-based classification of genetic tests, requiring higher standards of oversight for tests that pose higher risks to consumers.[56] During a March 2011 meeting, the FDA's Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee planned to discuss "the benefits and risks of direct access for different tests or categories of tests that would support differences in the regulatory approach."[57]

¶16 While it might be feasible to determine the FDA's jurisdiction over assays involving specific genes or DNA sequence variants and particular intended uses, it is more difficult to know if the FDA can regulate tests that analyze a large number of genetic variants for various purposes. Several companies now offer DTC genetic testing of panels of up to one million or more sequence variants.[58] For example, 23andMe analyzes its test results to return information relating to ancestry and health.[59] The company's website sends conflicting messages about whether the results have medical significance: "Your 23andMe results can help you and your doctor make more informed decisions about your healthcare,"[60] and "[t]he information on this page is intended for research and educational purposes only, and is not for diagnostic use."[61] In fact, the FDA has a settled definition for the term "intended use." The FDA seeks to determine the "objective intent" of the manufacturer by examining labeling claims or advertising matter

---

[52] *See, e.g.*, INHERENT HEALTH, http://www.inherenthealth.com (last visited July 15, 2012).

[53] *See, e.g., Drug Response: Genetic Differences Often Determine Drug Benefits—and Adverse Events!*, MATRIX GENOMICS, http://www.matrixgenomics.com/drug-response.php (last visited July 15, 2012).

[54] *See, e.g., Optimum Athletic Performance DNA Analysis—Athletic Analysis & Sports Genetic Test*, CYGENEDIRECT, http://cygene.infinityarts.com/browse-10873/Optimum-Athletic-Performance-Dna-Analysis.html (last visited July 15, 2012).

[55] *See, e.g.*, ENTEROLAB, https://www.enterolab.com (last visited July 15, 2012); *Inherited Level of Risk: DNA-Based Evaluations for Common Disorders*, MATRIXGENOMICS, http://matrixgenomics.com/inherited-predisposition.php (last visited July 15, 2012).

[56] *See FDA Panel Gets Varied Opinions on DTC Genomics*, GENOMEWEB DAILY NEWS (Mar. 10, 2011), http://www.genomeweb.com/dxpgx/fda-panel-gets-varied-opinions-dtc-genomics ("FDA has been considering the possibility of regulating tests in different categories based on risk and benefits, including categories such as genetic carrier screening for hereditary diseases, tests which predict risk of future diseases, and pharmacogenomic tests that predicting patient response to specific drugs.").

[57] Molecular & Clinical Genetics Panel of the Med. Devices Advisory Comm., Meeting Notice, 76 Fed. Reg. 6623, 6624 (Feb. 7, 2011).

[58] *See, e.g.*, 23ANDME, https://www.23andme.com (last visited July 18, 2012); DECODEME, http://www.decodeme.com (last visited July 18, 2012); NAVIGENICS, http://www.navigenics.com (last visited July 18, 2012).

[59] *See* 23ANDME, *supra* note 58.

[60] *Why Should You Know Your Genetic Risk*, 23ANDME, https://www.23andme.com/health/risks/ (last visited July 18, 2012).

[61] *Abdominal Aortic Aneurysm—Sample Report*, 23ANDME, https://www.23andme.com/health/Abdominal-Aortic-Aneurysm/ (last visited July 18, 2012).

and may even use circumstantial evidence to show that something is being "used for a purpose for which it is neither labeled nor advertised."[62]

¶17 Certainly, the FDA seems to regard many DTC genetic tests as falling within the medical device classification because it has sent warning letters to at least twenty companies offering genetic testing services, including companies analyzing large numbers of sequence variants.[63] This also suggests that, if the FDA is using a "regulate to risk" approach, then the FDA treats multivariate genetic tests with several possible applications as belonging to higher-risk classifications.

¶18 At its March 2011 meeting, the Molecular and Clinical Genetics Panel was receptive to the notion that tests imparting clinical information should only be made available to consumers if a medical professional was acting as a gatekeeper.[64] Both academics[65] and professional societies[66] have supported this position, arguing that orders for and interpretation of disease-related genetic tests need professional guidance because of the complexity of the tests and the potential vulnerability of patients concerned about the specter of serious illnesses.[67] Critics attack this position for several reasons. Daniel MacArthur, a United Kingdom-based geneticist, suggests that the American Medical Association's recommendation that medical professionals act as gatekeepers to the interpretation of genetic information arises from self-interest rather than an ability to add value for patients.[68] He notes that the AMA even implicitly admits this by putting

---

[62] 21 C.F.R. § 801.4 (2010); *see also* HUTT, *supra* note 27, at 41–42.

[63] *See In Vitro Diagnostics*, FOOD & DRUG ADMIN., http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/default.htm (last visited July 18, 2012) (listing warning letters to six genetic testing companies); *Letters to Manufacturers Concerning Genetic Tests*, FOOD & DRUG ADMIN., http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm219582.htm (last visited July 18, 2012) (listing warning letters to a further fourteen genetic testing companies); *see also FDA Warns Consumer Genomics Firms, Illumina on Selling Unapproved Dx Products*, GENOMEWEB DAILY NEWS (June 11, 2010), http://www.genomeweb.com/dxpgx/fda-warns-consumer-genomics-firms-illumina-selling-unapproved-dx-products; *More Genetic Test Firms Receive FDA Warnings*, GENOMEWEB DAILY NEWS (July 22, 2010), http://www.genomeweb.com/dxpgx/ more-genetic-test-firms-receive-fda-warnings.

[64] *See* Andrew Zajac, *FDA Panel Advises Caution on Personal Genetic Testing*, L.A. TIMES, Mar. 9, 2011, http://articles.latimes.com/2011/mar/09/nation/la-na-genetic-testing-20110309; *see also* Alex Phillippidis, *FDA Panel Hearing Suggests Medical Professionals May Play Role in Direct-to-Consumer Genetic Testing*, GENETIC ENGINEERING & BIOTECHNOLOGY NEWS (Mar. 22, 2011), http://www.genengnews .com/analysis-and-insight/fda-panel-hearing-suggests-medical-professionals-may-play-role-in-direct-to-consumer-testing/77899379/ ("[I]t has become clear that the agency will enact regulations under which professionals of some sort will play a role in administering at least the riskier consumer DTC tests.").

[65] *See, e.g.*, James P. Evans & Jonathan S. Berg, *Next-Generation DNA Sequencing, Regulation, and the Limits of Paternalism*, 306 J. AM. MED. ASS'N 2376, 2377 (2011) ("[W]hole-genome and whole-exome sequencing represent an extraordinarily complex amalgam of multiple medical tests that can be at once useful, pointless, confusing, or overtly harmful. . . . Harm from casual testing of consumers could be attenuated by prudent FDA regulation requiring a professional relationship between a tested individual and a qualified ordering clinician not in the employ of the testing laboratory."); *see also* Bernstein, *supra* note 45, at 283; Marietta & McGuire, *supra* note 45, at 373.

[66] *See, e.g.*, AMA letter, *supra* note 15, at 1; AM. COLL. OF MED. GENETICS, ACMG STATEMENT ON DIRECT-TO-CONSUMER GENETIC TESTING 1 (2008), *available at* http://www.acmg.net/StaticContent/StaticPages/DTC_Statement.pdf.

[67] *See* Bernstein, *supra* note 45, at 288–89; *see also* Evans & Berg, *supra* note 65, at 2377 ("[M]edicine is, to at least some extent, an inherently paternalistic endeavor simply because of an inevitable asymmetry in knowledge and because those who practice medicine are pledged to avoid causing harm.").

[68] *See* Daniel MacArthur, *American Medical Association: You Can't Look at Your Own Genome Without Our Supervision*, WIRED (Feb. 24, 2011, 6:43 PM),

forward an internally inconsistent position, stating: "Without the guidance of a physician, genetic counselor, or other genetics specialist, test results could be misinterpreted, risks miscalculated, and incorrect health and lifestyle changes pursued,"[69] while at the same time conceding that, "[t]he number of genetic tests available directly to consumers has proliferated rapidly, and several studies have reported that physicians find it difficult to keep up with the pace of genetic technology."[70] There is substantial support for the position that there is a shortage of medical professionals that have the experience and training to interpret complex genetic tests.[71] Other opponents of the medical-professional-as-gatekeeper model maintain that individuals have "property rights" to their genetic information and should not be denied access.[72]

¶19 Despite the argument that consumers should have access to their genetic test results without medical professionals acting as intermediaries, the above analysis suggests that the FDA has the statutory authority to regulate multivariate genetic tests that yield clinical information. Thus, the FDA seems ready to exert that power and require medical gatekeepers. However, the FDA does not appear to have considered whether it is appropriate to extend that control to the different realm of WGS testing.

IV. WHOLE GENOME SEQUENCING IS DIFFERENT THAN CONVENTIONAL GENETIC TESTING

¶20 There are differences between WGS tests and conventional genetic tests. These differences go beyond mere quantitative changes in the number of nucleotides being analyzed and instead move WGS testing into a qualitatively distinct class. One difference is that the data set produced by a WGS test is so much larger than the data set produced in the analysis of a single gene or genetic variant. In addition to the challenges related to the sheer scale of the data collected, WGS information is inherently more complex than limited, single-gene, data sets because of the need to account for interactions between sequence variants in different parts of the genome. Another difference is that a WGS serves as a "universal" genetic test. Sequencing the genome once yields a complete set of DNA sequence information.73 That means that different parties can make completely

---

http://www.wired.com/wiredscience/2011/02/american-medical-association-you-cant-look-at-your-genome-without-our-supervision.

[69] AMA letter, *supra* note 15, at 1.

[70] *Id.* at 3.

[71] *See* Catherine Wicklund, GENETICS EDUCATION PIPELINE AND WORKFORCE 25(2008), *available at* http://www.iom.edu/~/media/Files/Activity%20Files/Research/ GenomicBasedResearch/Wicklund.pdf (noting the inadequate number of genetic counselors); *Shortage of Physician-Geneticists in the United States*, THE PERSONAL GENOME (Dec. 28, 2007), http://thepersonalgenome.com/2007/12/shortage-of-geneticists-in-the-united-states/ (noting that there are almost as many astronauts in the world as there are certified geneticists that see patients in the United States).

[72] *See* Thomas Goetz, *Attention California Health Dept.: My DNA Is My Data*, WIRED SCIENCE (June 17, 2008, 9:57 AM), http://www.wired.com/wiredscience/2008/06/attention-calif/ ("This is *my* data, not a doctor's. . . . Regulation should protect me from bodily harm and injury, not from information that's mine to begin with."); *Cf.* Dan Vorhaus, *Is the Genetics Right Movement Picking up Steam?*, GENOMICS LAW REPORT (Mar. 16, 2011), http://www.genomicslawreport.com/index.php/2011/03/16/is-the-genetic-rights-movement-picking-up-steam/ (discussing bills introduced in the Massachusetts and Vermont state legislatures that would codify personal property interests in genetic information); For a more general discussion of the debate surrounding genetic information as property, *see* Margaret Everett, *The Social Life of Genes: Privacy, Property and the New Genetics*, 56 SOC. SCI. & MED. 53, 53–55 (2003).

[73] At least for normal (non-cancerous) cells.*See What Is a Genome?*, NAT'L CTR. FOR BIOTECHNOLOGY INFO., http://www.ncbi.nlm.nih.gov/About/primer/genetics_genome.html (last visited July 18, 2012).

divergent interpretations, and types of interpretations, at different times. Policymakers should carefully consider the distinctions between conventional genetic testing and WGS testing before trying to fit both types of tests into the same regulatory model.

A. The Scale and Complexity of WGS Information Creates Substantial Interpretive Challenges

¶21 At present, it is impossible for one individual to examine and assess the full significance of the entire sequence of a person's genome without assistance.[74] Apart from the enormous number of nucleotides that need to be examined, it is a major challenge to understand the meaning of a DNA sequence. Genome annotation, the process of identifying and mapping the functional elements of the genome to particular nucleotide sequences, requires the coordinated efforts of many scientists assisted by sophisticated computational methods.[75] Comprehensive genome annotation involves locating and identifying the function of a variety of features of a genome including genes,[76] control elements that can influence whether a gene is expressed by a cell,[77] and regions of genome instability.[78] Importantly, genome annotation has not been a one-time procedure; identification of elements has evolved significantly since the production of the first draft versions of the human genome sequence.[79]

¶22 Annotating the genome with disease associations[80] is perhaps even more clinically important than just identifying the location and nature of functional elements in the genome. The identification of genomic sequences associated with disease risk or other clinically-relevant phenotypes is a work-in-progress.[81] Despite considerable progress in identifying specific genetic variants that are associated with human disease and other clinical phenotypes, most of the underlying heritable factors have not yet been identified.[82] For example, at least seventy-one genetic variants are known to contribute to

[74] If an observer tried to do nothing more than scan the results of a WGS test, at one nucleotide per second, it would take approximately 190 years to examine the approximately six billion nucleotides of a diploid genome.

[75] *See, e.g.*, JAMES SHREEVE, THE GENOME WAR: HOW CRAIG VENTER TRIED TO CAPTURE THE CODE OF LIFE AND SAVE THE WORLD 298–302 (2004) (describing the process of annotating the fruit fly genome).

[76] *See* THE GENE ONTOLOGY, http://www.geneontology.org/ (last visited July 18, 2012)(describing the Gene Ontology project, a major bioinformatics initiative).

[77] The ENCODE Project Consortium, *Identification and Analysis of Functional Elements in 1% of the Human Genome by the ENCODE Pilot Project*, 447 NATURE 799, 804(2007).

[78] Angela Re et al., *Correlated Fragile Site Expression Allows the Identification of Candidate Fragile Genes Involved in Immunity and Associated with Carcinogenesis*, 7 BMC BIOINFORMATICS 413, at 414-15, (2006), *available at* http://www.biomedcentral.com/content/pdf/1471-2105-7-413.pdf.

[79] Michael R. Brent, *Steady Progress and Recent Breakthroughs in the Accuracy of Automated Genome Annotation*, 9 NATURE REVS. GENETICS 62, 62 (2008).

[80] John D. Osborne et al., *Annotating the Human Genome with Disease Ontology*, 10 BMC GENETICS (SUPPL. 1) S6, at S7 (2009), *available at* http://www.biomedcentral.com/content/pdf/1471-2164-10-S1-S6.pdf.

[81] *See generally* Kalliope Panoutsopoulou & Eleftheria Zeggini, *Finding Common Susceptibility Variants for Complex Disease: Past, Present and Future*, 8 BRIEFINGS IN FUNCTIONAL GENOMICS AND PROTEOMICS 345 (2009) (describing progress in the varied techniques used to identify sequence variants associated with common clinical outcomes).

[82] Teri A. Manolio et al., *Finding the Missing Heritability of Complex Diseases*, 461 NATURE 747, 747–48 & tbl.1 (2009) (discussing the so-called "missing heritability" of complex disease—that portion of population variance in disease frequency that can be attributed to genetic factors—and listing the proportion of heritability that has been accounted for to date in several common disease conditions).

Crohn's disease, an inflammatory bowel disease that, at the genetic level, is one of the best understood complex diseases.[83] Even this large number of genetic variants accounts for only 23.2% of the known heritability of Crohn's disease.[84] The situation becomes even more complex when taking into account interactions between genes or other DNA sequences that control gene expression[85] and the effects of different genetic backgrounds associated with ethno-geographic ancestry.[86]

¶23 Genome scientists and bioinformaticians recognize the daunting scale of the challenge being posed by the enormous amounts of data being generated by whole genome sequencing efforts.[87] Between July 2007 and July 2011, genome sequencing costs declined by a factor of more than 800 while computing costs merely decreased four-fold.[88] At present, genome sequence analysis is labor-intensive and requires input from a range of fields, including bioinformatics, statistics, and medical genetics. By one estimate, the current cost of a comprehensive interpretation of one human genome sequence is $285,000.[89] Other scientists correctly recognize that genome analysis must become increasingly automated if we are to avoid being in the position of "$1000 genome, $1M interpretation," regardless of whether such estimates are exaggerations.[90]

¶24 Given the large volume of information generated during a WGS test, the number of factors that need to be considered when analyzing that information, and the costs associated with that analysis, it is not surprising that sophisticated statistical approaches and a range of other computational tools will be needed to interpret WGS results.[91] A number of geneticists are working on algorithms that can be used to predict clinically-relevant outcomes from WGS results.[92] With the complexity of analysis needed to interpret WGS data, it is reasonable to conclude that even the most experienced medical geneticist or genetic counselor, let alone a healthcare professional with no special training

---

[83] Andre Franke et al., *Genome-Wide Meta-Analysis Increases to 71 the Number of Confirmed Crohn's Disease Susceptibility Loci*, 42 NATURE GENETICS 1118, 1118 (2010).

[84] *Id.* at 1122.

[85] *See, e.g.*, Lorenzo Beretta, et al., *Ability of Epistatic Interactions of Cytokine Single-Nucleotide Polymorphisms to Predict Susceptibility to Disease Subsets in Systemic Sclerosis Patients*, 59 ARTHRITIS & RHEUMATISM 974, 974–75 (2008) (discussing the role of gene-gene interactions in an autoimmune disease).

[86] *See, e.g.*, H.-S. Lee & S.-C. Bae, *What Can We Learn from Genetic Studies of Systemic Lupus Erythematosis? Implications of Genetic Heterogeneity Among Populations in SLE*, 19 LUPUS 1452, 1455–58 (2010) (discussing the effects of genetic background in Caucasian and Asian patients with lupus).

[87] *See* Andrew Polack, *DNA Sequencing Caught in Deluge of Data*, N.Y. TIMES, Nov. 30, 2011, http://www.nytimes.com/2011/12/01/business/dna-sequencing-caught-in-deluge-of-data.html?pagewanted=all.

[88] *Id.*

[89] Aabha Khemani & Gauri Jaju, *Contracting Sequencing Costs Could Mean Ballooning Informatics Prices*, GENETIC ENG'G & BIOTECHNOLOGY NEWS (May 9, 2012), http://www.genengnews.com/blog-biotech/contracting-sequencing-costs-could-mean-ballooning-informatics-prices/690/.

[90] Daniel MacArthur, *Genome Interpretation Costs Will Not Spiral Out of Control*, GENOMES UNZIPPED (May 14, 2012), http://www.genomesunzipped.org/2012/05/genome-interpretation-costs-will-not-spiral-out-of-control.php.

[91] *Recovery Act Limited Competition for NIH Grants: Research and Research Infrastructure "Grand Opportunities" (RC2)*, NAT'L HUMAN GENOME RESEARCH INST., http://www.genome.gov/27530674#al-2 (last visited May 28, 2012) (stating that the NIH will fund the development of a range of statistical and computational data analysis methods needed to interpret large-scale sequence data).

[92] *See* Euan A. Ashley et al., *Clinical Assessment Incorporating a Personal Genome*, 375 LANCET 1525, 1526 (2010) (outlining some of the computational approaches being used to identify disease-risk and other clinical information based on analysis of WGS data).

in genetics, will need computational assistance to be able to interpret WGS data and make sound clinical predictions.

B. Fixed Results and Moving Goalposts: Interpreting and Reinterpreting WGS Data

¶25 Except for rare, mutations that occur during cell division (and can be the basis for cancer) and various sequence rearrangements that may occur during immune system responses and brain development, a person's genomic sequence is fixed from the time of conception.[93] Thus, assuming the WGS test has acceptable technical accuracy, there should be no need to sequence a person's genome more than once. In essence, WGS testing is a "universal" test. This conclusion raises questions about who maintains control over the genome sequence produced from the WGS test.

¶26 There are many good reasons why a person would need to have his genomic sequence examined more than once in his life. One might be to reanalyze the sequence for the same reason that the WGS test was originally performed, but in the light of new molecular or clinical information as to the importance of specific genetic variants and disease risk. As discussed in the previous section, the amount of information about correlations between genotype and phenotype continues to grow,[94] and it would seem prudent to periodically update WGS interpretations in light of that increasing knowledge base.[95] Because the same clinical question would be involved for both the initial interpretation and any reinterpretation of the WGS data, it would be reasonable for access to and interpretation of that data to be subject to similar regulatory controls. Thus, if the FDA decreed that a patient could initially gain access to information regarding clinical associations only through a medical professional, then any reinterpretations, too, would only be available through a medical professional. It is true that such a requirement could pose practical difficulties, such as ensuring that different healthcare professionals had access to the WGS data, allowing patients to obtain second opinions and maintain continuity of care should they decide to consult different doctors or genetic counselors.

¶27 A more problematic circumstance would be if, for example, a woman had her genome sequenced to help determine whether she was at an elevated risk of developing recurring breast cancer and later wanted to examine her genome for clues as to her ancestral origin. Would she have to consult her oncologist to gain access to her genomic sequence so that she could perform a genealogical analysis? Even though the FDA has not shown any interest in trying to regulate genealogy tests, it is possible that the woman would have to choose between allowing her healthcare provider to continue acting as a genomic gatekeeper or to wastefully order a repeat WGS test.

¶28 Perhaps still more complex from a regulatory perspective, would be the case of a man who first had WGS testing performed for a low-risk indication and subsequently decided that he wanted to know if he was at risk for a serious medical condition, such as Alzheimer's disease.[96] If the regulators decide to place restrictions on ordering a low-risk

---

[93] *See* KENNETH M. WEISS, GENETIC VARIATION AND HUMAN DISEASE: PRINCIPLES AND EVOLUTIONARY APPROACHES 7-10 (1993).

[94] *See supra* notes 80-86 and accompanying text.

[95] In fact, this practice has already been proposed. Ashley et al., *supra* note 92, at 1534 ("Since risk estimates change as studies are completed, a continually updated pipeline is necessary.").

[96] Under this framework, a low-risk indication would be one without serious consequences, such as a genetic test to predict hair curliness, while a high-risk indication would be one associated with a serious

test and accessing WGS information, then once permission had been granted, it might be difficult to prevent access for the later higher-risk indication, which might require a genetic gatekeeper. In theory, this scenario could be avoided if the FDA chose to regulate WGS testing based on the greatest possible harm that could come to test users through misinterpretation,[97] requiring a medical professional to vet all requests to perform and interpret WGS tests, thereby treating all indications for carrying out WGS tests as high-risk. Regulating all WGS tests as if they were high-risk could lead to undesirable outcomes. For one thing, it could impede genetic research. For example, research-oriented WGS tests could be placed into a high-risk category, simply because clinically-actionable results might be returned to a study participant.[98] This could entangle researchers in additional regulatory requirements such as mandating the necessity of an independent medical professional to order and interpret WGS testing for study subjects. However, it is unlikely that the FDA might elect to regulate WGS tests as if they were all being performed for high-risk indications. The FDA does not have statutory authority to regulate all genetic tests, just those "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease."[99]

¶29 Thus, there are appropriate and desirable reasons to allow reinterpretation of WGS data for the same or different purposes. But if the primary regulatory focus is on the conditions under which the WGS test itself can be performed, there may be difficulties either from constraints on access to the genomic sequence by genetic gatekeepers or statutory impediments to the FDA exerting control over the WGS testing process.

V. OVERSIGHT OF CLINICAL WGS TESTING SHOULD PRIMARILY FOCUS ON TOOLS USED TO INTERPRET WGS DATA

¶30 Rapid changes in genetic technologies and the understanding of genetics raise the risk that regulatory agencies may feel forced to choose between adhering to outdated policies and abandoning oversight in the belief that regulatory targets are changing too quickly for effective response. This Perspective suggests that this dilemma could be avoided by breaking the issue of regulating WGS testing into more tractable parts. In particular, regulatory authorities should separate oversight of technical aspects of WGS test performance from the oversight of data interpretation and presentation.

A. WGS Testing Systems and Services Should be Required to Meet Analytical Validity Standards

¶31 Even opponents of strict regulatory oversight of genetic testing accept that steps should be taken to certify the integrity of raw sequencing data.[100] Ensuring that a test

illness such as Alzheimer's disease or cancer.

[97] For instance, underestimating or overestimating disease risk, failing to recognize a disease-causing DNA sequence variant, or even arriving at an incorrect diagnosis.

[98] *See* Susan M. Wolf et al., *Managing Incidental Findings in Human Subjects Research: Analysis and Recommendations*, 36 J.L. MED. & ETHICS 219,232–36 (2008) (recognizing that there are circumstances when it may be appropriate to return incidental findings to research study participants).

[99] 21 U.S.C. § 321(h) (2006); *see also supra* notes 27-30 and accompanying text.

[100] *E.g.*, Daniel MacArthur, *My Submission to the FDA on the Regulation of Personal Genomics*, GENETIC FUTURE (May 3, 2011, 8:46 PM), http://www.wired.com/wiredscience/2011/05/my-submission-to-the-fda-on-the-regulation-of-personal-genomics/.

actually measures the characteristic it purports to measure and that it does so accurately and reliably is known as analytical validity.[101] Setting analytical validity standards for WGS testing would require consideration of several parts of the data generation process. While a detailed consideration of standards for each step of WGS testing is beyond the scope of this Perspective, attention would need to be given to both the laboratory and informatics procedures employed in the production of WGS data.

¶32 The types of factors considered in the validation of other genetic testing methodologies are well established.[102] The FDA has already granted regulatory approval to DNA sequencing systems for use as diagnostic tests.[103] While sequencing an entire genome is significantly more complex than sequencing a single gene, scientists are developing quality metrics to measure the accuracy of sequence calls made by the high-throughput sequencing techniques used in WGS testing.[104] The human genome sequencing community has a long tradition of paying close attention to quantifying error rates and producing sequence data that minimize errors.[105] Because these error metrics can be used to produce error rates for each nucleotide that is sequenced,[106] error metrics are well-suited to estimating the accuracy of clinical sequencing tests that may need to be assessed for specific genomic locations.

¶33 In addition to setting base-calling standards that can help ensure the accurate reading of each nucleotide, safeguarding the accuracy of WGS testing will also require consideration of the computational algorithms that assemble fragmentary sequence reads into continuous genomic sequence.[107] Computer scientists have put a great deal of work into validating genome assembly algorithms.[108] These efforts could also be leveraged to help develop regulatory standards to ensure the analytical validity of the genome assembly process.

¶34 As well as setting technical standards to judge the analytical validity of WGS testing, some thought needs to be given to the optimal administrative structure to provide

---

[101] SACGT RECOMMENDATIONS, *supra* note 21 at 15.

[102] Jennifer A. Isler et al., *Analytical Validation of Genotyping Assays in the Biomarker Laboratory*, 8 PHARMACOGENOMICS 353, 362 (2007).

[103] Letter from Jay S. Epstein, Dir., Office of Blood Research & Rev., Ctr. for Biologics Evaluation & Research, Food & Drug Admin., to Gillian Morgan, Visible Genetics, Inc. (Sept. 26, 2001), *available at* http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/SubstantiallyEquivalent510kDeviceInformation/ucm088966.htm.

[104] Héctor Corrado Bravo & Rafael Irizarry, *Model-Based Quality Assessment and Base-Calling for Second-Generation Sequencing Data*, 66 BIOMETRICS 665, 672–74 (2010) ("Our ultimate motivation for this work is to allow downstream analysis in clinical and biological research using second-generation sequencing that appropriately quantifies and captures the uncertainty inherent in the sequencing process.").

[105] Brent Ewing & Phil Green, *Base-Calling of Automated Sequencer Traces Using Phred. II. Error Probabilities*, 8 GENOME RES. 186, 186, 193 (1998) (noting the ability to achieve error rates of one nucleotide in 10,000).

[106] *Id.* at 186.

[107] Current WGS generation involves determination of the sequence of many millions of short sequence reads (typically thirty-five to 400 nucleotides long, depending upon the sequencing technology being used). The sequence of the whole genome is "assembled" by sophisticated algorithms that identify overlaps between the short sequence reads and computationally stitching the entire sequence together much like assembling a jigsaw puzzle. Michael C. Schatz et al., *Assembly of Large-Genomes Using Second-Generation Sequencing*, 20 GENOME RES. 1165, 1165 (2010).

[108] Christie Rizk, *To Assess Genome Assemblers Steven Salzburg Organizes a Bake-Off*, GENOME TECHNOLOGY, March 2011, http://www.genomeweb.com/ informatics/assess-genome-assemblers-steven-salzberg-organizes-bake.

this oversight. A reasonable approach would be to have the FDA regulate WGS instruments as medical devices, and to regulate laboratories that perform sequencing services under CLIA. The FDA has already given marketing approval to DNA sequencing machines for more limited genetic testing,[109] and WGS testing instruments should fit within a similar paradigm.[110] Appropriate oversight of laboratories that perform WGS testing services would generally fall under the auspices of CLIA, and many laboratories that perform genetic testing already hold themselves out to be CLIA-certified.[111] However, CLIA certification currently offers only the most rudimentary assurance as to process quality in a WGS-testing laboratory. Because CLIA lacks a genetic testing specialty,[112] it only requires general quality control standards, such as the creation of manuals to document laboratory and quality control processes, as well as calibration and validation of laboratory instruments.[113] CLIA has not yet created a genetic testing specialty, perhaps because it could not determine how to deal with issues relating to clinical interpretation of genetic test results.[114] Under the system proposed in this Perspective, these issues would not be dealt with under CLIA. Instead, a genetic testing specialty under CLIA would need only to certify WGS-testing laboratories for attributes related to analytical validity, a much more tractable goal.

B. Computational Tools Used to Clinically Interpret and Present WGS Information Should be Validated

¶35 Assuming issues of analytical validity can be dealt with by the FDA and CLIA as proposed above,[115] the ability to assess WGS test results for clinical validity (i.e., accuracy of the test in diagnosing or predicting risk for a health condition)[116] and clinical utility (i.e., identification of outcomes associated with positive and negative test results)[117] will still be necessary. It remains too early to tell whether WGS tests will have substantial clinical utility, such as providing information that will spur action to prevent illness, reduce morbidity from inappropriate therapeutic interventions, save healthcare

---

[109] *E.g.*, Press Release, Life Technologies, FDA Grants Clearance for Celera Diagnostics' ViroSeq HIV-1 Genotyping System (Dec. 11, 2002), *available at* http://ir.lifetechnologies.com/releasedetail.cfm?ReleaseID=541494 (noting that FDA approval had been given to an automated DNA sequencer as part of an HIV molecular diagnostic system).

[110] In fact, Jay Flatley, the CEO of Illumina, a manufacturer of high-throughput DNA sequencing instruments, is reported to have begun discussions with the FDA to have next-generation sequencing instruments approved for medical purposes. Matthew Herper, *Can a DNA Sequencer Get FDA Approval?*, THE MEDICINE SHOW (Feb. 11, 2011, 1:32 PM), http://blogs.forbes.com/matthewherper/2011/02/11/can-a-dna-sequencer-get-fda-approval/.

[111] *See, e.g.*, *Perlegen's California Lab Gains CLIA Certification*, GENOMEWEB DAILY NEWS (June 5, 2009), http://www.genomeweb.com/dxpgx/perlegens-california-lab-gains-clia-certification; *Reputable CLIA Certified Laboratory*, EXISTENCE GENETICS, http://www.existencegenetics.com/certifiedlab.html (last visited July 19, 2012).

[112] *See supra* notes 21-26 and accompanying text.

[113] Grimm, *supra* note 31, at 121. Even general controls over laboratory procedures are, of course, very important. In June 2010, 23andMe, a leading DTC genetics company admitted that it had sent incorrect results to 96 subjects because a tray containing DNA was mishandled. DAVIES, *supra* note 4, at 190–91.

[114] Grimm, *supra* note 31, at 122–27.

[115] *See supra* Part III.A.

[116] SACGT RECOMMENDATIONS, *supra* note 21 at 16.

[117] *Id.*

costs, and so on. Long-term studies that objectively measure the costs and benefits of WGS testing will be needed; the CDC has such a program to evaluate genetic tests.[118]

¶36 Before clinical utility can even be addressed, there must be assurances that WGS tests produce clinically valid results. Genetic sequence variants, or sets of sequence variants, must be reliably associated with clinical phenotypes. As discussed previously, genotype-phenotype associations continue to be discovered and refined.[119] This evolving process will likely continue for decades.[120]

¶37 The more immediate need is for a WGS test-result user to know whether to pay attention to a putative genotype-phenotype correlation. For example, the association between increased risk for Alzheimer's disease and the ε4 variant of the APOE gene has been repeatedly confirmed by epidemiological studies[121] and supported by laboratory studies that show how the variant could lead to dementia.[122] In contrast, follow-up studies could not confirm the proposed correlation between several genetic variants and response to an expensive recombinant-DNA-based therapy for rheumatoid arthritis.[123] Indeed, there is evidence that the majority of published genetic associations are false positive results that do not hold up on replication.[124] One way to determine which published genetic associations are likely to prove reliable is to manually curate them. Some genetic testing companies and academic groups have already adopted this approach.[125] Although the FDA or other regulatory agencies may not have the in-house expertise to assess the validity of the large number of genetic associations that could be analyzed in WGS information,[126] one solution would be to call on a federal agency with that expertise, such as the National Institutes of Health (NIH), to maintain a central, curated database of

---

[118] *Genomic Testing*, CTRS. FOR DISEASE CONTROL & PREVENTION, http://www.cdc.gov/genomics/gtesting/ACCE/index.htm (last visited July 26, 2012).

[119] *See supra* notes 80-86 and accompanying text.

[120] *Cf.* Michael Snyder et al., *Personal Phenotypes to Go with Personal Genomes*, 5 MOLECULAR SYSTEMS BIOLOGY 273, 273-74 (outlining some of the complexities involved in correlating WGS with clinical outcomes).

[121] Lindsay A. Farrer et al., *Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: A Meta-Analysis*, 278 J. AM. MED. ASS'N 1349, 1349 (1997).

[122] *See* Ning Zhong & Karl H. Weisgraber, *Understanding the Basis for the Association of ApoE4 with Alzheimer's Disease: Opening the Door for Therapeutic Approaches*, 6 CURRENT ALZHEIMER RES. 415, 415–18 (2009).

[123] Marian Suarez-Gestal et al., *Lack of Replication of Genetic Predictors for the Rheumatoid Arthritis Response to Anti-TNF Treatments: A Prospective Case-Only Study* 12 ARTHRITIS & RHEUMATISM RES. R72, at R72 (2010).

[124] Ramal Moonesinghe et al., *Most Published Research Findings Are False—But a Little Replication Goes a Long Way* 4 PLOS MED. 218, 218 (2007).

[125] *See, e.g.*, ANDRO HSU ET AL., *Guidelines on Vetting Genetic Associations* 3–10 (23andMe, White Paper 23-03, 2010), *available at* https://23andme.https.internapcdn.net/res/pdf/trmm3vmfI1BU5d3Qw_qlGg_23-03_Vetting_Genetic_Associations_2010_06.pdf (discussing approach to assessing the validity of genetic associations and then grading the presumed validity of the associations with a one to four star rating); *Genetic Association Database*, NAT'L INST. ON AGING, http://geneticassociationdb.nih.gov/ (last visited May 28, 2012). The Gene Association Database contains records of genetic associations from over 23,000 publications. Yonqing Zhang et al., *Systematic Analysis, Comparison, and Integration of Disease Based Human Genetic Association Data and Mouse Genetic Phenotypic Information*, 3 BMC MED. GENOMICS , January 2010, at 2 (2010).

[126] Nevertheless, the FDA has been known to refuse approval of genetic tests because of lack of clinical utility. *See, e.g.*, *FDA Tells Celera KIF6 Test Unapprovable Without Changes*, GENOMEWEB DAILY NEWS (Apr. 21, 2011), http://www.genomeweb.com/dxpgx/fda-tells-celera-kif6-test-unapprovable-without-changes.

genetic associations. In fact, the NIH has created a registry of genetic tests[127] so that a wide range of users may "access information about the availability, validity, and usefulness of genetic tests."[128] It should be possible to extend this initiative so that it also reports on the validity of published genetic associations.

¶38 Not only should the validity of specific genetic associations be assessed, but also it is important that WGS test-result users know which genetic associations produced a clinical-outcome prediction. Commentators have noticed that disease-risk predictions from different DTC genetic testing companies can offer differing risk scores.[129] The explanation for these different predictions partly appears to be that each company based its risk scores on different sets of underlying genetic associations.[130] This problem suggests that it is not enough merely to vet the reliability of genetic associations in order to assure the clinical validity of WGS interpretation. Rather, it will also be necessary to assess the tools used to arrive at risk-prediction scores as well as the underlying data. Current approaches to the interpretation of WGS information tend to be very labor intensive, requiring extensive human review.[131] Computational algorithms are already being developed to make risk predictions,[132] and these algorithms will likely be the dominant analytical approach in the near future.

¶39 In addition to algorithms that produce risk scores, there is a need for computational tools to present WGS test results in comprehensible formats. These presentation tools will need to be able to communicate answers to specific questions (e.g., "what is this person's risk of developing colorectal cancer?"), or prioritize clinically significant findings when WGS testing has been performed as a screening test. Because methods will be needed to present clinical interpretations to anyone querying genomic sequence, there is no reason why display interfaces could not be developed for audiences with varying levels of expertise. DTC genetic testing companies already attempt to do this to a certain extent by allowing access to several interpretive layers, ranging from graphical representations of a person's disease risk to numerical risk estimates alongside genotype data.[133] Particularly with the increased attention being paid to innovative ways to present

---

[127] *GTR: Genetic Testing Registry*, NAT'L CTR. FOR BIOTECHNOLOGY INFO., http://www.ncbi.nlm.nih.gov/gtr/ (last visited May 26, 2012).

[128] Press Release, Nat'l Inst. of Health, NIH Announces Genetic Testing Registry: Database to Fill Information Gaps and Serve as Research Resource (Mar. 18, 2010), *available at* http://www.nih.gov/news/health/mar2010/od-18.htm.

[129] *See* COLLINS, *supra* note 12, at xxi (describing the discrepant risk scores for prostate cancer the author received from three DTC genetic testing companies); DAVIES, *supra* note 4, at 149 (describing a similar outcome for type 2 diabetes and prostate cancer risk scores).

[130] *See* COLLINS, *supra* note 12, at xxi; DAVIES, *supra* note 4, at 189.

[131] *See* DAVIES, *supra* note 4, at 223 (stating that in order to understand a subject's disease risk "[a] small army of Stanford physicians exhaustively pored over [his] sequence").

[132] *See, e.g.*, *Doctor in a Box*, CARNEGIE MELLON UNIV., http://www.cmu.edu/homepage/health/2012/winter/doctor-in-a-box.shtml (last visited May 26, 2012); *Find and Classify Phenotypic Correlations for Variations in Whole Genomes*, TRAIT-O-MATIC, http://snp.med.harvard.edu/ (last visited May 28, 2012); *Promethease*, SNPEDIA, http://www.snpedia.com/index.php/Promethease(last visited May 28, 2012

[133] *Compare Colorectal Cancer—Sample Report: Example Data*, 23ANDME, https://www.23andme.com/health/Colorectal-Cancer (last visited May 28, 2012) *with Colorectal Cancer—Sample Report: Technical Report*, 23ANDME,https://www.23andme.com/health/Colorectal-Cancer/techreport (May 28, 2012).

complex data,[134] it should be possible to develop interfaces that can present WGS results in ways that are comprehensible to both expert and lay audiences.

¶40 Shifting attention applied to WGS testing to concentrate on interpretive tools would allow regulatory authorities to address questions related to clinical validity of WGS test findings. However, there is an issue of how strictly such regulatory oversight could be applied. The FDA has statutory authority to regulate computer software intended for use in clinical diagnosis.[135] Even when that software performs independently of an approved medical device (in this case the instrument that generates WGS data), the FDA generally considers software an accessory when it takes data from that medical device and transforms it for presentation to a user.[136] But the FDA is also prohibited from interfering with the practice of medicine,[137] and the use of genetic test information can be part of medical practice.[138] Once the FDA has granted approval to a drug or device, physicians are free to use that drug or device for unapproved purposes when they feel there is a medical justification for doing so.[139] Thus, if the FDA approves software for use in interpreting WGS data under some circumstances, it could not interfere with physicians using the software in other circumstances. This limitation effectively emasculates regulatory control over software, at least so far as use by licensed medical practitioners is concerned.

¶41 Even though the FDA has to date shown little evidence of readiness to embrace innovative approaches to regulating WGS data analysis, it did recently unveil an initiative to advance regulatory science.[140] As part of this initiative, the FDA pledged that a priority would be to "Stimulate Innovation in Clinical Evaluations & Personalized Medicine to Improve Product Development and Patient Outcomes."[141] While the report generally foresees the need to validate new tools and approaches for personalized medicine,[142] the FDA has not provided any detailed guidance about changes in its regulatory approach.[143]

¶42 Whichever route it chooses to adopt, another practical and potentially far-reaching limitation to the FDA's jurisdiction over WGS testing is that there is little the Agency

---

[134] *See* Natasha Singer, *When the Data Struts Its Stuff*, N.Y. TIMES, Apr. 2, 2011, http://www.nytimes.com/2011/04/03/business/03stream.html.

[135] E. Stewart Crumpler & Harvey Rudolph, *FDA Software Policy and Regulation of Medical Device Software*, 52 FOOD & DRUG L.J. 511, 511 (1997).

[136] *Id.* at 512.

[137] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 396 (2006).

[138] Han, *supra* note 28 at 435.

[139] *See "Off-Label" and Investigational Use of Marketed Drugs, Biologicals, and Medical Devices*, FOOD & DRUG. ADMIN., http://www.fda.gov/ RegulatoryInformation/Guidances/ucm126486.htm. (last visited May 28, 2012).

[140] *See* Press Release, U.S. Food & Drug Admin., NIH and FDA Announce Collaborative Initiative to Fast-Track Innovations to the Public (Feb. 24, 2010), *available at* http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2010/ucm201706.htm.

[141] U.S. FOOD & DRUG ADMIN., ADVANCING REGULATORY SCIENCE AT THE FDA 3 (2011), *available at* http://www.fda.gov/downloads/ScienceResearch/SpecialTopics /RegulatoryScience/UCM268225.pdf.

[142] *See id.* at 10-13.

[143] Perhaps the FDA recognizes the complexity of the underlying problem and promises to seek input from other stakeholders before settling on plans to regulate personalized medicine tools. *See id.* at 11 ("Because the scale of data and effort needed to develop, validate or qualify clinical evaluation tools is enormous, intramural efforts are and should be supplemented by collaborative projects involving an array of external partners including academia, industry, and global regulatory agencies.").

could do to prevent people from sending their DNA to off-shore WGS testing companies.[144] Similarly, it would be difficult to stop people from using WGS information analysis tools hosted on servers in other countries.[145]

¶43 The FDA likely has a restricted regulatory scope over WGS interpretive tools because of its inability to interfere with the practice of medicine and its lack of jurisdiction over off-shore testing and analysis. Therefore, it might be more appropriate for the FDA to attempt to encourage the safe and effective use of WGS tests and information using a carrot rather than a stick. One way to do this would be to encourage improved understanding of genetics among medical professionals and the general public.[146] Another would be to support best practices by giving a "seal-of-approval" to WGS data interpretation tools that make responsible use of clinically-validated genetic associations, as well as assessing the limits to which users should rely on interpretations when making important health-related decisions. Ultimately, both healthcare professionals and consumers would benefit if WGS could be integrated with other forms of health information so that genetic information could contribute to medical decision-making. Medical records incorporating genomic information are being introduced into clinical practice,[147] but as of yet no federal agencies have set standards for WGS data-interpreting tools. Although a full discussion of data repositories for WGS information, especially as they might relate to electronic health records, is beyond the scope of this Perspective,[148] entities that regulate and set standards for the storage of WGS information will have a powerful influence over how computational tools are used to interpret and communicate genomic sequence.

VI. CONCLUSION

¶44 It is virtually certain that WGS information soon will become an important and useful tool in both clinical diagnosis and preventive healthcare. What is less certain is how access to this technology will be controlled and how the clinical utility of WGS information will be ensured. This Perspective has argued that individuals will have a lifetime interest in the use, interpretation, and reinterpretation of WGS information. It also posits that it does not make sense to limit access to that data by imposing a

---

[144] Jennifer A. Gniady, Note, *Regulating Direct-to-Consumer Genetic Testing: Protecting the Consumer Without Quashing a Medical Revolution*, 76 FORDHAM L. REV. 2429, 2470 (2008).

[145] U.S. government agency jurisdiction over services offered by international providers is, to say the least, subject to uncertainty. Michael A. Geist, *The Reality of Bytes: Regulating Economic Activity in the Age of the Internet*, 73 WASH. L. REV. 521, 561 (1998).

[146] *See* SEC'Y'S ADVISORY COMM. ON GENETICS, HEALTH, & SOC'Y, GENETICS EDUC. AND TRAINING 1–4 (2011), *available at* http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_ education_report_2011.pdf.

[147] *See Million-Veteran Genetics Program to Expand*, GENOMEWEB DAILY NEWS (May 5, 2011), http://www.genomeweb.com/million-veteran-genetics-program-expand.

[148] For example, the Presidential Commission for the Study of Bioethical Issues met in February 2012 to discuss matters relating to WGS data, in particular, to issues relating to the protection of individual privacy. *Meeting Eight: Feb. 2–3, 2012, in San Francisco, Cal.*, PRESIDENTIAL COMM'N FOR THE STUDY OF BIOETHICAL ISSUES (last visited May 27, 2012); *see also White House Bioethics Commission Tackles Genomic Data*, GENOMEWEB DAILY NEWS (Feb. 3, 2012), http://www.genomeweb.com/white-house-bioethics-commission-tackles-genomic-data. In another context, I have argued that efforts designed to protect genetic privacy may be ineffective and consumer protections should focus on preventing genetic discrimination. Trevor Woodage, Note, *Relative Futility: Limits to Genetic Privacy Protection Because of the Inability to Prevent Disclosure of Genetic Information by Relatives*, 95 MINN. L. REV. 682 (2010).

requirement that healthcare professionals serve as sole gatekeepers controlling whether WGS testing can be procured and how and when WGS data can be correlated with clinically-important outcomes.

¶45 The storehouse of knowledge regarding the correlation of DNA sequence variation with health-related outcomes will continue to grow for decades. With these moving goalposts, people will need to be able to periodically reanalyze their WGS information to keep up to date. No one individual, either geneticist or layperson, could analyze the results of a WGS test by himself. The implicit requirement for computational algorithms to help a user understand WGS information has two important implications. First, these algorithms should be tailored to produce results suitable for audiences with varying levels of sophistication about genetic information. Healthcare professionals will continue to play essential roles in medical decision-making, but there is no need for them to have a monopoly over evaluating and appreciating the significance of WGS information. Second, federal agencies should pay special attention to maximizing the clinical utility of WGS test interpretation. It is important that the FDA continue to regulate instruments and kits used in the generation of WGS data and that CLIA provide qualified oversight over WGS testing services. But, it is also essential that the FDA and other federal agencies make efforts to maximize the safety and efficacy of WGS test interpretation by providing guidance as to which interpretive algorithms and underlying genotype-phenotype associations are reliable. Whether federal agencies try to control WGS testing by regulation or support intelligent application and understanding of WGS test interpretations, devoting resources to the consideration of the clinical validity of WGS testing will help maximize the expected benefits of whole genome sequencing.