Designing a standard of proof: the case for professional standards in next-generation sequencing laboratory-developed tests

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KEYWORDS: genetics, FDA, regulation, laboratory-developed tests, next-generation sequencing

INTRODUCTION

Laboratory-developed tests (LDTs), defined by the Food and Drug Administration (FDA) as ‘in vitro diagnostic tests that are designed, manufactured, and used in a single laboratory’, have become dramatically more sophisticated and accurate in recent years. Some provide genetic information about increased medical risks, diseases an individual might have, and diseases that people could unknowingly pass onto their children. The tests are currently overseen by a federal agency, the Centers for Medicare and Medicaid Services (CMS). But policymakers and professional groups disagree about how to regulate labs performing these advanced, highly specific tests that have implications for clinical care. In particular, federal agencies point to marketing abuses and

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1 US Food and Drug Administration, Laboratory Developed Tests, http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407296.htm (accessed Nov. 30, 2016).

2 Patricia M. Jones, FDA Regulation of LDTs An Update, 47 MED. LAB. OBS. 18 (2015), http://www.mlo-online.com/fda-regulation-of-ldts-an-update.php.

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inconsistency among LDTs to justify greater control over their specificity and clinical validity.3

‘Next-Generation Sequencing’ (NGS), or advanced genetic testing technology, is one type of LDT that FDA has singled out for oversight. NGS has revolutionized genetics, allowing an increase in speed and the number of genetic sequences processed, at minimal cost.4 In July of 2016, FDA issued draft guidance for regulatory oversight of NGS devices used to diagnose genetic variants, as well as draft guidance on public databases used to determine the meaning of genetic variants.5,6 More recently, the agency announced that it was tabling these guidances indefinitely, due to comments from the laboratory community and indications following the recent election that the legislative and executive branches would oppose further regulation in the area.7 Some delay and re-working may be warranted, as the draft guidances fail to protect incentives for economic investment or anticipate problems with FDA regulation of the continuously evolving nature of genetic linkage analysis.8,9 But safety concerns with LDTs remain, and there is need for further oversight of NGS LDTs in particular.

This note recommends that in the place of the FDA draft guidance, the American College of Medical Genetics and Genomics (ACMG) should design standards for the specificity of NGS technologies and clinical validity of LDT genetic tests. The ACMG has more specialized expertise and is better suited than FDA to work with the evolving nature of genetic testing and better able to evolve its evaluations without the inflexible requirements in the draft guidance. In contrast, FDA lacks the structure or capability to evaluate changing variant significance. The ACMG should also steer away from inflexible disclosure requirements that would harm the economic and operational environment for progressing NGS technologies.

LEGAL AUTHORITY OVER LDTs

Before 2012, it was understood that the CMS would evaluate the clinical validity of LDTs.10 As stated by the Clinical Laboratory Improvement Amendments (CLIA), CMS is charged with ‘maintain[ing] a quality assurance and quality-control program adequate and appropriate for the validity and reliability of the laboratory examinations

3 Peter Lurie, FDA Voice—Why FDA Should Oversee Laboratory Developed Tests (2015) http://blogs.fda.gov/fdavoice/index.php/2015/11/why-fda-should-oversee-laboratory-developed-tests/ (accessed Oct. 17, 2016).
4 Stephan C. Schuster, Next-Generation Sequencing Transforms Today’s Biology, 200 Nature 16 (2007), http://www.nature.com/nmeth/journal/v5/n1/full/nmeth1156.html.
5 Use of Standards in FDA Regulatory Oversight of Next-Generation Sequencing (NGS)-Based In Vitro Diagnostics (IVDs) Used for Diagnosing Germline Diseases—Draft Guidance for Stakeholders and Food and Drug Administration Staff, 81 Fed. Reg. 131, 44,614 (Jul. 8, 2016), http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM509838.pdf.
6 Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next-Generation Sequencing (NGS)-Based In Vitro Diagnostics—Draft Guidance for Stakeholders and Food and Drug Administration Staff, 81 Fed. Reg. 131, 44,611 (Jul. 8, 2016), http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm509837.pdf.
7 Turna Ray, GenomeWeb–FDA Holding Off on Finalizing Regulatory Guidance for Lab-Developed Tests, https://www.genomeweb.com/molecular-diagnostics/fda-holding-finalizing-regulatory-guidance-lab-developed-tests (accessed Nov. 30, 2016).
8 FDA, supra note 5, at 2, 21, 25.
9 FDA, supra note 6, at 2, 4.
10 Jones, supra note 2.
and to meet requirements relating to the proper collection, transportation, and storage of specimens and reporting of results— in essence, CMS evaluates LDTs and provides standards for their performance. Under the law, CMS thus has jurisdiction over tests designed for the ‘purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings’. 

However, in the years since Congress passed CLIA, the scope and capability of LDTs have increased far beyond anything envisioned by the drafters. This applies to both genetic tests and non-genetic tests (eg, pertussis diagnosis, molecular biomarkers), but the rapid advances and growth of the genetic industry pose special challenges. In 2005, 454 Life Sciences, Illumina, and other companies revolutionized the industry in marketing NGS technologies that allowed sequencing of large amounts of DNA (and other genomic material) simultaneously. NGS includes testing for germline traits (inherited phenotypes that may be linked to disease, traits, or pharmaceutical response) and somatic mutations (mutations that happen in vivo—largely, the variants in tumors that cause cancer). NGS does in days or weeks what would have required years of work and millions of dollars at the time of CLIA. These developments have sparked concerns about the current regulatory regime, which only lightly regulates advanced genetic tests that provide substantial medical information.

As FDA officials have pointed out, the agency does have legal justification for regulating LDTs. FDA has the right and the obligation to regulate if LDTs no longer ‘(A) employ methodologies that are so simple and accurate as to render the likelihood of erroneous results by the user negligible’, or [are at a level that] ‘(B) the Secretary has determined to pose no unreasonable risk of harm to the patient if performed incorrectly (harm or risk based evaluation)’, as added to CLIA in the Food and Drug Modernization Act of 1997. As an example, FDA challenged genetic testing company 23andMe’s direct-to-consumer (DTC) LDT in November 2013 on the grounds of potential patient harm, arguing that there was enough potential psychological and medical harm from an inaccurate result to justify FDA oversight of 23andMe’s test. Following FDA’s warning letter, 23andMe was required to validate all genetic variants linked to an increase in medical risk, providing its analysis of each genetic marker for FDA confirmation before it was allowed to resume delivering data. CLIA thus authorizes FDA to

11 42 U.S.C. § 236a (1988).
12 Id.
13 US Food and Drug Administration, The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies, http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf (accessed Oct. 5, 2016).
14 Schuster, supra note 4, at 16.
15 Elaine R. Mardis, Next-Generation Sequencing Platforms, 6 ANN. REV. ANAL. CHEM. 287, 302 (2013), http://www.annualreviews.org/doi/full/10.1146/annurev-anchem-062012-092628
16 Lurie, supra note 3.
17 42 U.S.C. § 236a.
18 US Food and Drug Administration, Warning Letter Re: Personal Genome Service, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm376296.htm, Oct. 22, 2013, (accessed Oct. 25, 2016).
19 Andrew Pollack, 23andMe Will Resume Giving Users Health Data, NEW YORK TIMES, Oct. 21, 2015, at B3, http://www.nytimes.com/2015/10/21/business/23andme-will-resume-giving-users-health-data.html?_r=0 (accessed Dec. 7, 2016).
act in cases where it finds a significant level of harm in CLIA-controlled tests or devices, potentially demanding premarket evaluation and approval of LDTs prior to sale.\textsuperscript{20}

**PROBLEMS WITH CURRENT OVERSIGHT**

The question now is whether the particular type of regulation that FDA has decided to apply makes sense. On the substantive merits, FDA has been concerned over alleged abuses of the system under CMS. Two Government Accountability Office (GAO) reports illuminated issues that plagued genetic LDTs.\textsuperscript{21} Personalized DTC genetic testing companies misled their customers about the utility of the testing, advertised unproven pharmacogenomic medications, and even told one customer that she could send in her fiancé’s genetic material without his knowledge or consent, as a ‘surprise’.\textsuperscript{22} The current oversight regime has allowed companies great freedom to promote and sell ‘medical tests’ — telling consumers, for instance, that they had a genetic mutation that dramatically increases their risk of ovarian cancer or Alzheimer’s Disease.\textsuperscript{23} The 2010 report stated that one of GAO’s biggest issues with the test providers was that ‘donors often received risk predictions that varied across the four companies, indicating that identical DNA samples lead contradictory results’.\textsuperscript{24} Of course, while conflicting results may be the result of testing or precision error, they may also be legitimately varying interpretations of the data. The weights assigned to different genetic variants in causing disease are variable, and influenced by expert opinion.\textsuperscript{25} Moreover, even when such factors as varied penetrance (the proportion of people with the disease-causing mutation who exhibit symptoms of the disease), age-of-onset, and inheritability are consistent across evidence, it is not necessarily incorrect to give different causal weights to different variants based on the strength of the evidence collected.\textsuperscript{26} However, GAO and FDA have seen this inconsistency as a problem for genetic LDTs.

LDTs, which are designed, manufactured, and analysed in a single laboratory, are not subject to the same high standard of clinical validity as tests done in multiple laboratories, or ones outside of the company that sells the product. Instead, LDT providers are merely required to comply with good lab practices: basic standards of cleanliness, qualifications of lab technicians, accuracy, and precision of tests.\textsuperscript{27} CLIA does not include guidelines for whether LDTs correctly describe the impact of genetic variants, or rates of false positives that are acceptable. These issues—marketing claims, conflicting

\textsuperscript{20} FDA, \textit{supra} note 5, at 3.

\textsuperscript{21} Direct-to-Consumer Genetic Tests: Misleading Test Results Are Further Complicated by Deceptive Marketing and Other Questionable Practices: Testimony Before the Subcomm. on Oversight and Investigations, Comm. on Energy and Commerce, House of Representatives, (2010) (statement of Gregory Kurtz, Managing Director, Forensic Audits and Special Investigations, GAO), \url{http://www.gao.gov/assets/130/125079.pdf}.

\textsuperscript{22} \textit{Id}.

\textsuperscript{23} FDA, \textit{supra} note 13, at 6.

\textsuperscript{24} GAO, \textit{supra} note 21, at ii.

\textsuperscript{25} Editorial, \textit{Improving Databases for Human Variation}, 13 \textit{Nat. Meth.} 2, 103 (2016).

\textsuperscript{26} ‘Clinical laboratory geneticists are encouraged to document in the patient’s record the rationale for the use of a particular procedure or test, whether or not it is in conformity with these Standards and Guidelines’. Sue Richards et al., \textit{Standards and Guidelines for the Interpretation of Sequence Variants: A Joint Consensus Recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology}, 17 \textit{Genet. Med.}, 5, 405–423 (2015).

\textsuperscript{27} Centers of Medicare and Medicaid Services, \textit{Clinical Laboratory Improvement Amendments (CLIA)}, \url{https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=/clia/}, (accessed Oct. 26, 2016).
results, and unknown validity—help justify heightened regulatory intervention beyond CLIA’s requirements.

It is a harder question whether LDTs pose a risk of harm. In issuing its draft guidance, FDA made a de facto finding of risk or harm in LDTs. The agency has also curated examples of improper marketing and result disclosure in the field to support this assertion. However, the finding is subject to debate. Various articles and studies have concluded that FDA and regulatory agencies are overestimating the harm done by consumer genetics. For example, the psychological effect of increased medical risk seems to have minimal impact unless the gene is nearly certain to cause a serious disease (and even then, evidence for psychosocial impact for mutations like Huntington’s and BRCA1/2 is mixed), and it is even rarer for individuals to make significant medical or lifestyle changes on the basis of the information, making the risk to the individual in the case of a false positive or negative often negligible. Regardless of the ultimate conclusion, the FDA’s proposal implicitly suggests that the current approach to LDTs is giving rise to potentially serious harm.

INTELLECTUAL PROPERTY IMPLICATIONS OF FDA’S DISCLOSURE REQUIREMENTS

Subjecting LDTs to FDA regulation would have significant implications for the intellectual property claims and economic incentives of companies doing research in the sector. The FDA draft guidance on databases requires that ‘[a]t the time of recognition [of the significance of a specific variant by the FDA], the database administrator should make this information publicly available and accessible’. At the moment, the ‘database’ applies to publically available databases, not private companies. But FDA is clear in its intentions: the draft guidance is meant to ‘encourage the deposition of variant information in such databases [and] reduce regulatory burden on test developers’—to incentivize NGS LDT companies to submit proprietary variant information to and to use public databases. This move would increase transparency in genetic data in allowing all companies and individuals to see the information behind variant classification. But disclosure would have economic implications as well.

Population genetic databases (sometimes called ‘biobanks’) are valuable commodities. For example, Genome Wide Association Studies (GWAS) take genetic, personal, and medical information about participants and look for genetic variants that occur

28 Lurie, supra note 3.
29 FDA, supra note 13.
30 Robert C Green & Nita Faranhany, The FDA is Overcautious on Consumer Genomics, 505 Nature 286–287 (2014), http://www.nature.com/news/regulation-the-fda-is-overcautious-on-consumer-genomics-1.14527.
31 Corin Egglestone, Anne Morris & Ann O’Brien. Effect of Direct-to-Consumer Genetic Tests on Health Behaviour and Anxiety: A Survey of Consumers and Potential Consumers, 22.5 J. GENET. COUNSEL. 565–575 (2013), http://link.springer.com/article/10.1007/s10897-013-9582-6.
32 Cinnamon S. Bloss et al. Impact of Direct-To-Consumer Genomic Testing at Long Term Follow-up, 50 J. MED. GENET. 393–400, 393. https://www.ncbi.nlm.nih.gov/pubmed/23559530?dopt=Abstract.
33 S Crozier, N Robertson & M Dale. The Psychological Impact of Predictive Genetic Testing for Huntington’s Disease: A Systematic Review of the Literature, 24 J. GENET. COUNSEL. 29–39 (2015), http://link.springer.com/article/10.1007/s10897-014-9755-y.
34 Ray, supra note 7.
35 FDA, supra note 6, at 10.
36 FDA, supra note 6, at 2.
more frequently in individuals with a given trait than in the general population, to see if these traits have genetic linkages. A larger population makes it easier to detect genetic variants that have associations with disease. In general, increases in sample size lead to greater predictive power in GWAS.\textsuperscript{37} While formal legal protections for intellectual property generally do not apply to these databases, they are often kept confidential, and other institutions frequently pay to access anonymized genetic information.\textsuperscript{38} These NGS LDTs both create, and rely upon, biobanks, which is why FDA released the draft guidelines for NGS LDTs and genetic variant databases together.\textsuperscript{39}

While assembling large databases is time consuming and expensive, having large numbers of genotypes and genomes lets genetic testing companies offer more definitive insights into genetic information.\textsuperscript{40} A larger sample size thus provides benefits to consumers: more confidence in medical testing results, a wider variety of variants associated with a given disease, greater accuracy in ancestry determinations, etc. Besides this competitive advantage, proprietary biobanks can also lead to partnerships with pharmaceutical or treatment companies worth hundreds of millions of dollars.\textsuperscript{41} One prominent example is breast cancer and the research connected with BRCA variants. Myriad Genetics, which held a patent on testing for BRCA1/2 until 2012, has a massive advantage in the world of BRCA research and treatment due to its extensive library of genetic variants linked with BRCA.\textsuperscript{42} One drug trial showing that a test designed with Myriad’s proprietary data was not necessary to determine the efficacy of a given pharmaceutical treatment sent the company’s stock down dramatically.\textsuperscript{43} Many companies’ business models rely upon these databases.\textsuperscript{44} By pushing for public analysis of genetic variants, FDA would lessen investment incentives and could cause companies to absorb the expense of gathering all this information.

**ISSUES REGARDING THE STANDARD OF PROOF**

Requiring databases to publicly disclose research conclusions could lead to more accurate variant determination across tests, but it would not answer the question of conflicting results between variant classifications or databases. It is unclear how to set a uniform

\textsuperscript{37} Yik Y. Teo, *Common Statistical Issues in Genome-wide Association Studies: A Review on Power, Data Quality Control, Genotype Calling and Population Structure*, 19 Curr. Opin. Lipidol. 133, 133–143 (2008).

\textsuperscript{38} Saminda Pathmasiri et al., *Intellectual Property Rights in Publicly Funded Biobanks: Much Ado About Nothing?*, 29 Nat. Biotechnol. 319 (2011), http://www.nature.com/nbt/journal/v29/n4/full/nbt.1834.html.

\textsuperscript{39} FDA, *supra* notes 5, at 2 and 6, at 2.

\textsuperscript{40} Donna A. Messner, *Informed Choice in Direct-to-consumer Genetic Testing for Alzheimer and Other Diseases: Lessons from Two Cases*, 30 New Genet. Soc. 59, 59–72 (2011).

\textsuperscript{41} It has traditionally been a challenge to objectively evaluate the value of these genetic databases, and the utility they provide to their providers, but the NIH is currently attempting to gather data for policy purposes: see ‘As Research Budgets Contract, NIH Seeks Metrics to Assess the Value of Biomedical Data Repositories’ by Uduak Grace Thomas in GenomeWeb.

\textsuperscript{42} Turna Ray, *GenomeWeb—Genomic Variant Data Sharing Gains Support; Collaboration Seen as Key to Interpretation Challenge*, https://www.genomeweb.com/informatics/genomic-variant-data-sharing-gains-support-collaboration-seen-key-interpretation (accessed Oct. 10, 2016).

\textsuperscript{43} *GenomeWeb—Myriad Genomics’ Stock Drops After Study Shows Niraparib May Not Need CDx*, https://www.genomeweb.com/cancer/myriad-genomics-stock-drops-after-study-shows-niraparib-may-not-need-cdx (accessed Oct. 13, 2016).

\textsuperscript{44} John M. Conley, Robert Cook-Deegan & Gabriel Lázaro-Muñoz, *Myriad After Myriad: The Proprietary Data Dilemma*, 15 N. C. J. Law Technol. 597–637 (2014), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4275833/.
standard for these evolving conclusions. Participants at a recent FDA forum regarding the draft guidances noted that there was ‘little consensus within the life sciences community’ around issues such as labeling variants as ‘pathogenic’ versus ‘likely pathogenic’ and how to best classify variants.45 Although FDA claims that the guidelines in the draft guidance for evaluating genetic variant databases are similar to the ones already used in the scientific community, regulation would effectively codify the standards for a given database and accompanying research conclusions. By rejecting databases with insufficient evidence, regulation could stifle smaller research groups and effectively undercut the private genetic research of large companies and institutions. Organizations that are slowly gathering individual sequences might not be able to prove their accuracy under FDA’s standard of proof, reducing incentives to gather more sequences and provide valuable research, instead of using the evidence of other databases.

Conclusions in genetics are complicated. Complex diseases, comprised of interactions between multiple genetic variants and environmental risk factors, generate conflicting research on a given variant’s penetrance and pathogenicity. As Heidi Rehm, co-chair of the National Institute of Health-funded Clinical Genome Resource (ClinGen) has said, ‘there is no true truth for most variants. Most interpretations are expert opinions based on an evaluation of evidence’.46 Our knowledge and understanding of this type of inheritance changes daily: as new information comes in from expanding population databases, we gather more evidence regarding a given disease and how variants can cause or prevent that disease. FDA oversight could require companies to continuously submit updates on the interactions of countless genes and how they contribute to disease and risk, rather than allowing researchers and databases to make gradually evolving evaluations based on nuanced expertise. It would additionally be difficult to remove this requirement from the draft guidances: FDA would not be able to assert regulatory authority over LDTs while refraining from regulating from what it and GAO claim to be one of the most pressing problems in the industry: contradictory evaluation of the meaning of a given variant.47

Requiring proof for each individual trait or medical risk would also require a great deal of time and effort for regulatory agencies. FDA’s system of premarket approval and device classification is not prepared to deal with the continuous evaluation and evolution of variant meanings, weights, and penetrance inherent to genetic LDTs.48 It would mean a near-constant re-evaluation and submission process, for tests that can examine more than 40,000 genes and regulatory areas and their significance to the human body.49 It is unclear how often companies and databases will have to submit these updates, or what degree of change (eg shifting from a 0.001 per cent risk to a 0.002 per cent risk for a single gene variant) would require resubmission of a test. The draft guidances

45 Turna Ray, GenomeWeb–FDA Engages Lab, Dx Players by Proposing NGS Regulatory Standards Come From Community, https://www.genomeweb.com/molecular-diagnostics/fda-engages-lab-dx-players-proposing-ngs-regulatory-standards-come-community (accessed Oct. 10, 2016).
46 Editorial, supra note 25, at 103.
47 Lurie, supra note 3.
48 Kyle M. Fargen et al., The FDA Approval Process for Medical Devices: An Inherently Flawed System or A Valuable Pathway For Innovation?, 5 J. NEUROINT. SURG. 269 (2013).
49 Veritas Genetics, My Genome, https://www.veritasgenetics.com/mygenome (accessed Dec. 4, 2016).
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offer a preview:

‘Include a procedure to account for updates to internal and external databases and their potential impact on the clinical interpretation of variants’

‘...Publicly accessible genetic variant databases could voluntarily apply to FDA for recognition, and how FDA would review such applications and periodically reevaluate recognized databases’

But external and internal databases are constantly changing. It may not be feasible to require companies to document every update, especially in large databases that constantly receive submissions of variants and genetic data and often release updates to existing variants. FDA has no precedent for classifying something as ‘likely pathogenic’—a common term in the genetic community where there is less-than-definitive evidence that a variant causes disease. Would companies therefore be banned from sharing information about strong but not absolute genetic linkages? Additionally, ‘voluntary’ application, as set out by the draft guidance for validity of public genetic variant databases, is likely not voluntary in effect. Databases not submitted for FDA approval would be functionally unusable for institutions and companies that want their LDTs to be exempt from FDA premarket review (a much cheaper and easier process for market access). An organization would thus be at a disadvantage in the market if they did not use one of the approved databases and research sets.

Finally, there are additional issues relating to clinical practice that no FDA draft guidance will be able to determine. For example, what disease-causing genetic variants should be disclosed in different types of tests (e.g., carrier screening for reproductive purposes or newborn screening)? It may be appropriate to permit parents to test their infants for serious and well-established early-onset diseases, while prohibiting them from testing for diseases in their infants with complex inheritance patterns until the children are old enough to make decisions for themselves. Guidelines issued by medical associations currently outline what is appropriate to disclose to different groups of patients. Which variants have clinical utility (usefulness in treating or preventing disease) varies by setting and judgement, and what is disclosed in a given situation is, again, a matter of ethical evaluation and expert opinion. This is an issue beyond the scope of FDA regulation. Federal regulation will not be able to deal with important issues regarding

50 FDA, supra note 5, at 25.
51 FDA, supra note 6, at 4.
52 One example is ExAC, a publically available whole genome and exome database. Monkol Lek et al., Analysis of Protein-coding Genetic Variation in 60,706 Humans, 536 Nature 285 (2016), http://www.nature.com/nature/journal/v536/n7616/full/nature19057.html
53 According to the guidance, test reports must include: ‘The relationship between reported variants and the clinical presentation of the patient’ and ‘a prominently placed list of pathogenic or actionable variants on the first page of a test report. If variants of unknown significance will be reported, clearly separate these from pathogenic or actionable variants in the test report, and include a statement that their clinical relevance is not known’. FDA, supra note 5, at 24.
54 FDA, supra note 6, at 4.
55 FDA, supra note 6, at 8.
56 Ray, supra note 44.
57 Genetic Alliance UK, How Can I Access Preimplantation Genetic Diagnosis?, http://www.geneticlealliance.org.uk/information/services-and-testing/how-can-i-access-preimplantation-genetic-diagnosis/, (accessed Dec. 1, 2016).
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The role for industry standards

To summarize, FDA regulation of NGS embodied in LDTs is problematic for a number of reasons: (1) evidence of significant harm from LDTs—a legal prerequisite for FDA regulation because of CLIA’s clear assignment of LDT oversight to CMS—is ambiguous at best; (2) FDA’s overbroad disclosure requirements could undercut economic incentives, slowing new population-intensive research into genetic correlations; (3) The federal regulatory process is inherently slow moving in a rapidly evolving industry; (4) there is often no clear scientific consensus to embody in a regulation; and (5) no FDA regulation will be able to address important issues in NGS LDTs.

A better answer would be a more flexible set of guidelines, designed by the ACMG. Given the limited evidence of harm, and the fast-moving nature of the research, it seems appropriate for now to encourage industry-wide self-regulation: quality guidelines that determine whether the scientific bases of trait reports are sufficiently robust for the results to be delivered to consumers or medical professionals. These standards should be determined by the scientific community as recommendations, rather than mandates, for LDT companies. ACMG is in an excellent position to organize and administer these standards. It has expertise and experience in determining professional standards around NGS. It is able to update its recommendations based on medical developments and community input, without waiting for bureaucratic or congressional approval. And by advocating for standards of practice, ACMG would not need to require sweeping disclosure of research results, reducing incentives for the next generation of researchers.

CMS could play a complementary role in this process. Despite being specifically named as the regulatory authority with jurisdiction over LDTs, CMS has traditionally shied away from being the arbiter of genetic test approval. It has have stated that it does not have the capability to evaluate clinical validity of LDTs, given the wide range of LDT production and use. But CMS does continue to provide CLIA certification, which includes critical testing analysis. It may be that CMS, given sufficient financial support, could take on some of the responsibilities of evaluating NGS LDTs. CMS is well suited to evaluate basic accuracy and precision, as described in FDA’s draft guidance: ‘define and document a minimum set of metrics (eg accuracy) that should be evaluated for an adequately analytically validated test’ (emphasis theirs). CMS could evaluate the laboratories, aligning with the work its inspectors are already doing for CLIA oversight. This would be a departure from the FDA draft guidance, because it would not evaluate the variants’ link to disease, but rather the sensitivity and specificity of the test.

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58 Heidi L. Rehm et al., ACMG Clinical Laboratory Standards for Next-generation Sequencing, 15 GEN. IN MED. 733 (2013).
59 Jamie K. Wolszon & Jeffrey N. Gibbs, FDA—Law Blog—FDA Plans to Issue Final LDT Framework in 2016; Subcommittee Members, CMS and FDA Officials Critique Proposed Legislative Approach that Would Give CMS LDT Premarket Review Authority, 2015, http://www.fdalawblog.net/fda-law-blog-hyman-phelps/2015/12/fda-plans-to-issue-final-ldt-framework-in-2016-subcommittee-members-cms-and-fda-officials-critique-p.html (accessed Oct. 10, 2016).
60 FDA, supra note 5, at 8.
61 Amy S. Gargis et al. Assuring the Quality of Next-generation Sequencing in Clinical Laboratory Practice, 30 NAT. BIOTECH. 11, 1033–1036 (2012).
namely, confirming that the test is not providing false positives or negatives regarding basic data to prevent incorrect results.

Additionally, moving toward an industry standard for genetic variant databases would help with conflicting results, reducing the need to publicize genetic data or proprietary conclusions. ACMG has created guidelines for tests for Huntington’s disease and inherited colorectal cancer, and has provided standards for evaluation of NGS technologies.\(^{62}\) Expanding these guidelines, creating a general standard of proof for variant significance and pathogenicity, would be a natural next step. Allowing ACMG to determine these scientific standards and validity would protect companies’ biobank investments and offer a degree of consistency amongst genetic LDTs (indicating factors such as population sizes and penetrance rates that would signify clinically significant variants) without requiring public disclosure or removing the flexibility of expert evaluation. Much as ClinVar’s website contains star ratings to indicate the scientific basis on which each trait is proven (fewer stars indicating a weaker link, conflicting reports, or traits still under research consideration), a ‘four-star’ rating under ACMG guidelines could indicate that given current knowledge, the validity of a given trait is firm.\(^ {63}\) While this could also occur under FDA guidance, it would require frequent submissions and reevaluation with new evidence or variant reclassification to be used in NGS LDTs.

With complex diseases, or diseases where having the mutation does not necessarily mean the disease will occur, there must be discretion among experts, especially as research progresses at a rapid rate. Although the draft guidance states ‘standards for use of evidence appear to parallel the types of evidence appropriate to support an FDA premarket submission’, continued research on and evaluation of genetic variants make changes to NGS LDTs very different from a one-time premarket submission.\(^ {64}\) Additionally, decisions to report in LDTs remain variable. Given that variants thought to be harmful for years are now being found to be non-pathogenic, and that is appropriate for institutions to choose databases with conflicting variant interpretations, the knowledge base at this point is not exacting or beyond debate.\(^ {65}\) Given our knowledge of variant significance evolution, these databases cannot be held up as thresholds, or seen as firm proof of linkages.\(^ {66}\) ACMG guidelines and continued recommendations would offer a flexibility and opportunity for continued evaluation that the FDA draft guidelines could not. With less stringent recommendations from ACMG, there would be evolving standards without premarket submission and continued evaluation, and, as previously mentioned, these guidelines can differentiate between the appropriateness of disclosure for different groups. Additionally, it is not prepared for the system of premarket evaluation and continued submission it proposes.

\(^{62}\) Rehm, supra note 58.

\(^{63}\) ‘ClinGen helped implement a ranking system to denote the quality associated with each submission to ClinVar. For a single submitter to obtain a one-star entry, variants need to be classified into at least three clinical-significance tiers, and the methods used for the assignment and supporting evidence must be provided... Two-star entries describe variants from multiple submitters with no conflicting interpretation, and three- and four-star submissions come from expert panels and large consortia with ClinGen-approved methods for variant interpretation’. Editorial, supra note 25.

\(^{64}\) FDA, supra note 6, at 3.

\(^{65}\) FDA, supra note 6, at 3.

\(^{66}\) Ray, supra note 44.
FDA has stated that it wants its guidances, and its evaluation of clinical validity, to be based on the scientific literature regarding NGS LDTs. But the scientific literature is both evolving and conflicting, and FDA has no track record of being able to effectively and continuously evaluate tests of this nature. The right initial step to oversight would be to rely on the experts in industry and to call on the CMS to provide basic test evaluation. As scientific consensus grows, and FDA has the ability to prepare for continued evaluation and oversight of NGS devices, it may be appropriate to shift regulatory oversight to FDA. But at this juncture, a premature wholesale shift to a regulatory model and entity best suited to make static black-and-white decisions would risk undercutting the tremendous progress being made in the field.

67 FDA, supra note 5, at 5.