

Public Comments
FDA's Draft Guidance:
Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)

The American Society of Human Genetics
Submitted 2 February 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5600 Fishers Lane, rm. 1061
Rockville, MD 20852
<http://www.regulations.gov>

Document Citation: 79 FR 59776

Agency/Docket Number: FDA-2011-D-0360

Topic area: clinical validity/intended use

The American Society of Human Genetics (ASHG), founded in 1948, is the world's largest genetics professional society, with some 8,000 members representing all areas of research and application in human genetics. Most of ASHG's members work in academic settings. They create new knowledge and technology in the field, including laboratory-developed tests (LDTs), and are instrumental in their use and evaluation. We appreciate the opportunity to share our thoughts with you about the proposed regulatory oversight of LDTs.

Our comments derive in general from the recognition that FDA is still actively evaluating the nature of genetic and genomic tests and the regulatory issues they present. We therefore question whether the scheme for regulation that FDA has proposed is premature insofar as it affects genomic testing. Specific examples illustrating our concerns follow.

1. FDA defines a "*laboratory developed test (LDT)* as an in vitro diagnostic device (IVD) that is intended for clinical use and designed, manufactured and used within a single laboratory" (p. 5). We are concerned that the meaning of "clinical use" and the process for assessing "intent" are unclear when applied to genomics. This lack of clarity raises subsidiary concerns about FDA's view of genomics and its assumptions in proposing to regulate genomics as a medical product (see 2, below). Sometimes genomics involves products that are suitable for FDA regulation, but other times it involves the practice of medicine or forms of research and scientific speech that likely lie outside FDA's regulatory authority and whose regulation would raise serious constitutional problems, e.g., federalism and First-Amendment concerns. The prospective regulation of genomics as a medical product also raises a large set of ancillary legal issues—such as potentially subjecting genomics to the states' strict product liability tort regimes – that have implications the draft guidance has not adequately explored.

Recommendation: define "clinical use" more precisely

2. Interpretation of clinical significance of variants is a process. We do not view interpretation as a product, but as the provision of informational services. As a service, interpretation of clinical significance of gene sequencing does not fall under the regulatory purview of FDA.

Recommendation: Gene-sequencing products—such as analyzers and reagents—are devices, and it is appropriate for FDA to ensure their analytical validity in detecting the genetic variants that a patient possesses. Deciphering the clinical significance of the detected variants, however, is in the nature of an informational service/professional service and is not suitable for FDA regulation.

3. The draft guidance is directed mainly at LDTs used in clinical care. We appreciate the agency’s effort on pages 36-37 to clarify impacts on research, but appropriate policy on genomic research requires a more nuanced and deliberate analysis than is possible as an afterthought to FDA’s general LDT guidance. Application of this draft guidance to genomic research risks serious unintended consequences. An example is on page 37, where the draft states that FDA’s Investigational Device Exemption regulations apply “if test results are returned to patients without confirmation by a medically accepted diagnostic product or procedure.” This stricture holds the prospect of ending the bioethically important process of return of results in the research setting, where confirmatory products and procedures may not exist for most variants. Moreover, confirmation is generally done only for positive results—those where a change in sequence is detected—yet the absence of a change also is important information that research participants may desire. Research subjects have ethical and privacy rights—including legally enforceable rights under the HIPAA Privacy Rule^{1,2}—to request information that research testing has revealed about them. Empirical data indicate that people’s willingness to contribute biospecimens and to volunteer for genetic research depends on whether they will receive return of results.^{3,4} Policies that block the return of results could in a very real way impede the genomic research enterprise.

We believe the statement on p. 37 is overbroad and needs nuance. It disregards meaningful ethical and legal distinctions that exist among: (a) data sharing, (b) return of results in research settings, and (c) clinical care.^{5,6,7} Not every communication of research data to tested individuals amounts to a “clinical use” that triggers FDA regulation of the test as an *in vitro* diagnostic product, nor does simple communication constitute a “significant risk” activity that triggers FDA’s IDE requirements. Indeed, the return of results is a *risk-reducing* activity insofar as it alerts participants to incidental research findings that, while unconfirmed, may suggest a need for further evaluation by their own physicians. It is ironic but

¹ 45 C.F.R. § 164.524.

² Evans BJ, Dorschner MO, Burke W, Jarvik GP. Regulatory Changes Raise Troubling Questions for Genomic Testing. *Genet Med* 16(November 2014):799-803.

³ Parker LS. Returning Individual Research Results: What Role Should People’s Preferences Play? *Minnesota J Law Sci & Tech* 13(Spring 2012):449-484.

⁴ Terry SF. The Tension Between Policy and Practice in Returning Research Results and Incidental Findings in Genomic Biobank Research. *Minnesota J Law Sci & Tech* 13(Spring 2012):691-736.

⁵ Lunshof JE, Church GW, Prainsack B. Raw Personal Data: Providing Access. *Science* 24(January 2014):373-74.

⁶ Evans BJ. Minimizing Liability Risks Under the ACMG Recommendations for Reporting Incidental Findings in Clinical Exome and Genome Sequencing. *Genet Med* 15(June 2013): 915- 920.

⁷ Burke WM, Evans BJ, Jarvik GP. Return of Results: Ethical and Legal Distinctions Between Research and Clinical Care. *Am J Med Genet* 166C(2014): 105-111.

true that an unnuanced application of FDA's IDE requirements in the research setting has the potential to violate the rights of research subjects and place them at heightened risk.

Of deeper concern is that the statement on page 37 signals that FDA may be overconstruing its narrowly circumscribed legal authority to regulate research involving IVD tests—a move that potentially threatens our nation's leadership in genetic and genomic discovery. Genomics is a multinational, information-based enterprise that can – at the click of a mouse – shift offshore if FDA's policies render the US-based research venue unduly cumbersome for investigators and human subjects of genomic research. We support FDA's efforts to address the very real regulatory issues in genomic research—but the task calls for cautious efforts.

Recommendation: ASHG urges FDA to sever issues related to research uses of genomic testing for separate and more focused consideration. FDA's recent notice of the public workshop entitled "Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests" 75 Fed. Reg. 72, 092 (Dec. 29, 2014) extends the ongoing and important dialogue about special challenges in regulating genetic and genomic testing. It may make sense to address the issues surrounding research genomic tests in that context, rather than as a subtext of the general-purpose LDT draft guidance. This approach is especially germane insofar as many research-based genomic tests incorporate components from multiple commercial suppliers and laboratories and do not appear to fall within the agency's definition of "laboratory developed test" on page 5 of the draft guidance.

4. We believe that FDA is overly optimistic in its assumption that it can establish clinical validity for most DNA variants in a timely manner on the basis of peer-reviewed literature (p. 13). In the foreseeable future, there simply will not be a substantive literature that explains the function or clinical significance for most genetic variants. The FDA should recognize, however, that the determination of clinical validity for a genetic test accrues over time. That is, as tests are deployed and applied, data accumulate that inform the future value and validity of additional DNA variants. This once again reflects the importance of clearly distinguishing the definition of "clinical use." Genetic testing is an area where FDA must acknowledge the value of such data accumulation, via post-market data collection.

Recommendation: support post-market data collection and analysis to help establish clinical validity of genetic tests.

Joseph D. McInerney
Executive Vice President
On behalf of the American Society of Human Genetics