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Robert M. Califf, M.D., MACC
Commissioner, U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: FDA Regulatory Oversight of Laboratory Developed Tests -- Medical Devices; Laboratory Developed Tests (Docket No. FDA–2023–N–2177)

Dear Commissioner Califf:

The American Society of Human Genetics (ASHG), founded in 1948, is the world's largest professional society dedicated to advancing genetics and genomics research, supporting a community of 8,000 members representing all areas of research and application in human genetics. A large proportion of ASHG's members work in academic settings and the community also welcomes and integrates public and private sector research professionals. ASHG's community is a driving force in creating and applying new knowledge and technology for the field, including laboratory-developed tests (LDTs). Over the last decade, as emerging genetic knowledge has moved rapidly and consistently into clinical use, ASHG's community has also led the way in adapting testing to integrate a consistent stream of new genetic knowledge in ways that directly benefit patients and advance science.

As ASHG articulated in comments to the FDA in 2015, we support FDA's efforts to address the very real regulatory issues in genomic research, but the task calls for measured efforts. Responsible human geneticists agree that due oversight of clinical tools and technologies is important, as new knowledge informs ways to improve the health of the American people. And as leaders in academic medicine and research organizations with a deep commitment to quality care, we decry the idea that unscrupulous or fly-by-night companies would provide poorly predictive laboratory tests that could leave patients inaccurately diagnosed or under informed. At the same time, we express deep concern about harms to the nation's biomedical research agenda of an overly broad, unnecessary, and unwieldy regulatory framework that the FDA has proposed. In our view, it risks slowing and preventing benefits to patients and research participants, stifling scientific advancement, and harming the academic medicine training infrastructure. We share the views of our primary clinical society peer, the American College of Medical Genetics and Genomics (ACMG), that regulation should focus on modernizing standards and requirements found in Clinical Laboratory Improvement Amendments (CLIA) oversight, which is nimbler and more efficient in enabling rapid, constructive review, oversight and enhancement of laboratory testing and the larger laboratory environment. Moreover, there should be focus on educating the consumer on the differences between screening and diagnostic tests and impact of individual risk that is informed by the impact of disease prevalence on the sensitivity and specificity of specific tests.

While we and other ASHG members and leaders often work across biomedical research, academic medicine, and clinical care, we focus our comments here on the negative impact of FDA regulation for genetics and genomics research and academic research training. We also strongly encourage the FDA to hear from and integrate the feedback of the clinical testing community, including ACMG and the Association for Molecular Pathology (AMP).

Implications for Research & Academic Training:

1. **Return of Research Results:** We reaffirm the primary concern ASHG articulated in 2015, which we consider unresolved: Although the draft guidance is directed mainly at LDTs used in clinical care, harms remain to the research endeavor and there would be considerable negative consequences for the return of clinically actionable results generated through a research study. Indeed, LDT regulations would apply "if test results are returned to patients without confirmation by a medically accepted diagnostic product or procedure." We continue to express grave concern that this requirement would functionally end 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. In the intervening eight years since ASHG's last comments, this issue has only become more acute: as human genetics research is ever more clinically actionable, the translation of basic knowledge into clinical research has increased substantially. Researchers face an even more acute need and obligation to return potentially actionable information to patients. Indeed, recognizing this need, ASHG issued field guidance on the matter in 2020, which can be found here: https://www.ashg.org/publications-news/press-releases/201904-recontact/. Increasingly, the return of actionable results in genomics research is advancing as an ethical goal.

   We continue to believe there are meaningful ethical and legal distinctions that exist among: (a) data sharing, (b) return of results in research settings, and (c) clinical care. 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.

2. **Slowed Discovery, Increased Cost:** In the clinical *research* environment, proposed regulatory requirements would harm the steady and transformative advancement of genomic knowledge into eventual, evidence-based care regimens that we have seen over the last decade. This would be due to dramatically slowed studies and much higher costs to navigate the FDA regulatory processes. This outcome is inevitable as we believe that FDA could not possibly establish clinical validity for most DNA variants in a timely manner, causing deep research protocol delays and untold regulatory and administrative burden and legal costs. The Association for Molecular Pathology estimated recently a 5,000% increase in FDA workload based on 144 currently *authorized* clinical genetic tests versus nearly 75,000 currently *offered* tests and suggested that an anticipated 40,000 existing LDTs would need immediate review. Moreover, as indicated in 2015, the FDA should recognize 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 the FDA must acknowledge the value of such data accumulation, via post-market data collection.

3. **The Impact on U.S. Global Competitiveness:** We also reiterate ASHG's 2015 concern that FDA could be over-construing its narrowly circumscribed legal authority to regulate research—a move that potentially threatens our nation's leadership in genetic and genomic discovery. Genomics is a multinational, information-based enterprise that could easily shift offshore if FDA's policies render the US-based research venue unduly

cumbersome for investigators and human subjects of genomic research. If a regulatory structure is not carefully constructed and efficiently and effectively implemented, the FDA would jeopardize U.S. clinical research leadership for a field that is growing in both clinical and economic importance. For example, an ASHG report issued in 2020 found that in 2019 alone, the economic and functional impact of human genetics and genomics research directly generated more than $100 billion and the total economic impact exceeded $265 billion. That impact is only going to increase as genomic medicine and other promising applications mature in coming years. See report here: https://www.ashg.org/advocacy/the-economic-impact/.

4. **FDA Authority: Genomic Interpretation as a Process, not a Product:** As articulated in 2015, 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." We are concerned that the meaning of "clinical use" and the process for assessing "intent" are unclear when applied to genomics. 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. Moreover, 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.

5. **Possible training and workforce impact:** Much, if not all, of the clinical training of the clinical genomic medicine workforce in the U.S. occurs under the aegis of the American College of Graduate Medical Education (ACGME) approved programs at U.S. medical schools. A critical component of the training of physicians and laboratory directors in the performance and interpretation of genomic information generated by LDTs that are often performed within the academic setting. In addition, a very significant component of human genetics and genomics biomedical research training at the Ph.D. graduate and postgraduate levels depend on federally funded programs that support and leverage data generated from LDTs. The proposed regulatory framework may directly impact clinical and research training by hindering access to LDT generated data and information. This will ultimately impact the health of the U.S. population and the competitiveness of the U.S. research enterprise.

Sincerely,

Brendan Lee, M.D., Ph.D.
President
American Society of Human Genetics