INVITAE

United States House of Representatives
Committee on Energy and Commerce, Subcommittee on Health

Hearing on

"21st Century Cures: Examining the Regulation of Laboratory Developed Tests"

Written testimony submitted by
Invitae Corporation

September 9, 2014

Chairman Pitts and Ranking Member Pallone,

Thank you for the opportunity to submit written testimony for the hearing titled, "21st Century Cures: Examining the Regulation of Laboratory Developed Tests." Founded in 2012, Invitae is a genetic information company whose mission is to bring comprehensive genetic information into routine medical practice to improve the quality of healthcare for billions of people. Specializing in genetic diagnostics for hereditary disorders, Invitae is aggregating the world's genetic tests into a single service with better quality, faster turnaround time, and a lower price than most single-gene diagnostic tests today.

Invitae currently operates a CLIA-certified laboratory in San Francisco, California, from which we offer tests for over 200 hereditary conditions using a single assay for a price of $1500, regardless of the test ordered. As required by CLIA, all of our testing services are physician-mediated; only licensed medical professionals can order tests from Invitae. Since the launch of our service in late 2013, we have seen rapid growth in testing volume, which indicates to us that there is an unmet need for high quality, low cost genetic testing services with enhanced customer service.

As you undoubtedly know, policy discussions on whether or not to modify the United States Food and Drug Administration's (FDA) position of enforcement discretion for laboratory developed tests (LDTs) have been occurring for more than a decade now. Invitae is generally supportive of a regulatory approach that provides medical professionals and their patients with confidence in the quality of the testing services they receive, without unduly interfering with rapid progress in a dynamic area of the health care system that has the promise of delivering better care to patients while reducing overall healthcare costs.

Since the FDA's announcement of its intention to publish guidance documents establishing a framework to regulate LDTs in 2010, stakeholders from numerous perspectives including patients, providers, clinical laboratories, and diagnostic companies have called for clarity in the review requirements and regulatory pathways that may be applied to some categories of LDTs. Given the significance of the change in regulatory policy detailed in the Notification to Congress, Invitae plans to submit comments during the public comment period and at the anticipated public meeting. In the interim, we greatly appreciate the Committee focusing its attention on this very

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important issue and we hope our comments help inform your discussion as you consider FDA regulation of LDTs and policy opportunities to advance the Path to 21st Century Cures initiative.

In several respects the FDA's draft guidance takes into account industry feedback from prior discussions. While the FDA believed the framework described in its Notification to Congress and the soon to be published draft guidance documents would indeed provide clarity, in fact it raises many questions and poses some risks that could have a profound impact on Invitae's ability to improve its tests so that patients have access to the highest quality and most up to date testing services. For that reason, as the Committee continues its work on the Path to 21st Century Cures initiative and explore the complicated issue of regulation of LDTs, we encourage you to consider the following areas that require additional clarification.

Clarifying the definition of a LDT:

The definition of LDT included in the FDA's notification to Congress remains unclear. Several ambiguities could create particular problems for Invitae and other labs providing tests for hereditary conditions.

For example, the draft guidance seems to imply that a testing service is not an LDT if the provider operates more than one facility from which it delivers the test. It is unclear how such a service would be regulated as soon as the operator opens a second laboratory. Given the early demand that Invitae has seen for its testing services, we certainly anticipate the need for a second lab in the not-too-distant future. We currently have a mirror CLIA-certified lab in Santiago, Chile, which we expect will address some of the international demand for our services. It would certainly be unfortunate if FDA regulation limited Invitae's ability to deliver tests to US patients, with the result that patients in foreign countries would have greater access to new tests than those in the United States.

As this is a central component underlying the regulatory framework, FDA needs to provide further explanation as to what tests the agency considers to be LDTs that would be subject to the proposed regulatory framework.

Documenting clinical validity:

Clinical laboratories utilize a variety of data, tools, and resources to develop and validate their tests. While the ideal trial design for drug approvals is randomized controlled trials, for the majority of diagnostics, this is unnecessary due to the availability of information already in existence. According to the National Institutes of Health (NIH) Genetics Home Reference, clinical validity refers to how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease. The Human Genome Project, subsequent research publications, NIH biomarker databases, and more have provided an abundance of peer reviewed literature, coalesced information, and other resources to establish the clinical validity of genetic variants.

The Notification to Congress does state that the FDA expects that for many LDTs, clinical validity has already been established in the literature. However, it does not provide clear guidance that a review of retrospective data in lieu of a randomized controlled trial is sufficient and an acceptable manner to evaluate clinical validity in moderate risk LDTs. In the case of hereditary

conditions, there is a great deal of literature documenting the role of particular genes, and the impact of genetic variations in those genes, on particular diseases. At the same time, novel variants in those genes are identified all the time. At Invitae, the determination that a novel variant is likely pathological, likely benign, or has unknown significance, involves the judgment and analysis of highly trained genetic experts.

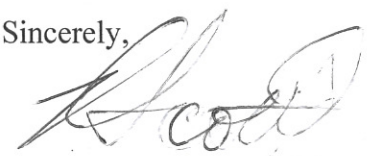
A participant in the Free the Data initiative, Invitae shares anonymized versions of these conclusions, along with their bases, with publicly-available databases such as ClinVar, operated by the NIH, so that clinicians and researchers can provide peer review and benefit from Invitae's experience. If the proposed FDA regulations limited Invitae's services not only to genes whose relations to hereditary diseases have been validated, but also to specific variants, this medical progress would be significantly impeded, as would the comprehensiveness of the results provided to individual patients.

Maintaining the ability to modify and improve LDTs already cleared or approved:

The scientific understanding of genomics is continuously growing and as such, molecular diagnostics are often updated to improve the test's sensitivity or to reduce costs and expense to the healthcare system. Often times, a LDT will be modified for use in a different sample type such as blood or saliva. However, these changes do not affect the tests' clinical validity and their relevance to clinical decision making. If a modification is made to an already FDA cleared or approved LDT, the draft guidance says that these modified tests must be subject to a subsequent premarket review. This would be a very burdensome process to complete each and every time a modification to a LDT is warranted and in the end, would only delay innovation, eliminate any motivation to continuously update and improve a test, and ultimately create barriers to patients' access to the latest advances in molecular diagnostics. The current CLIA standards, if appropriately enforced, should provide adequate assurance as to the validity and reproducibility of tests incorporating these modifications without requiring pre-market approval every time a laboratory implements a process improvement. Some of the hallmarks of laboratory medicine are its ability to be nimble, quickly develop tests for emerging diseases, and bring the latest technology to the clinic. The FDA should promote policy that supports the laboratory's ability to be nimble and modify tests as needed.

Thank you again for the opportunity to submit this written testimony for your hearing on the regulation of LDTs. Please do not hesitate to contact me by phone (650-823-3949) or by email (randy.scott@invitae.com), if we may be of assistance in the future or if you have any questions about our testimony.

Sincerely,



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