4301 Connecticut Avenue, NW
Suite 404
Washington, DC 20008
202.966.5557
info@geneticalliance.org
http://www.geneticalliance.org

January 5, 2015

VIA email to: cures@mail.house.gov

Honorable Fred Upton, Chairman
Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515

RE: 21st Century Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

Dear Chairman Upton:

On behalf of Genetic Alliance, I respond to your request for responses to the questions you posed to stakeholders regarding the regulation of innovative diagnostic tests.

Genetic Alliance is a network of patient organizations and other health organizations that work toward individuals, families and communities transforming health. We create products and processes to enable action and advocacy. Examples of our work include: Genetic Alliance was the lead organization in the passage of the Genetic Information Nondiscrimination Act in 2008, and Genetic Alliance has a leadership role in the Patient Centered Outcomes Research Network (PCORnet) Patient Powered Research Network (PPRN).

I am just a mom, a mom of two kids who have a genetic condition - pseudoxanthoma elasticum (PXE). In 2000, as a lay person (I have a master's degree in theology) with my husband (who was a construction engineer having only attended high school), we discovered the gene associated with PXE. We then attempted, with the help of a diagnostic company (Transgenomic), to create a FDA cleared diagnostic test – we always take the high road. That process took three years, and cost Transgenomic enormous amounts of money. In the end, we did not have a cleared test, despite having data on hundreds of individuals. This is because FDA did not have a way to oversee this development, the goal posts kept moving, and in the end it was clear that the test belonged in a service environment. Having patented the gene to be good stewards of it, we licensed the test to a lab, GeneDx, for $1. We learned a great deal in the process. What I comment here is hard earned knowledge from an experience few people or companies have had.

Our responses follow the Committee's language in bold.

1. **Multiple stakeholders have expressed the urgent need to have clear and logical lines separating the practice of medicine, the actual conduct of a diagnostic test and the development and manufacturing of diagnostic tests. How should these lines be defined and what are the key criteria separating each of these activities?**

We agree there should be clear lines separating the development and manufacturing of a diagnostic test, the actual conduct of a diagnostic test, and the practice of medicine. A test is developed by laboratory and is then 'manufactured' in the sense of having the various physical materials assembled. A test is then 'conducted'; steps like baking a cake by following a recipe are taken. Then the practice of medicine occurs – the test is interpreted by a licensed healthcare practitioner. At this point the test might be used to guide treatment, or make a diagnosis.

2. **In FDA's draft regulatory framework, the agency describes the extent to which it proposes to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FFDCA). It is relatively clear with respect to distributed test kits what constitutes a "device", but less clear when considering a test developed and performed in a laboratory. What should comprise the "device" subject to regulation by the FDA?**

The 'device' is the collection of physical materials required to run the test (e.g., reagents, supplies, equipment) together with the directions for use. The 'development' and 'manufacturing' of these materials may be appropriate for regulation by the FDA.

Conducting the test and interpreting it is subject to regulation under CLIA, state laboratory licensure, and practice of medicine laws and should not fall under regulation by the FDA.

3. **FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?**

Risk should be assessed in a number of ways. Families risk a great deal every day in their management of disease. That baseline and the standard for caring for that disease must be taken into account. The use of the test is critical in assessing risk. But the development and manufacture of the test is not where the risk lies except for the rather cut and dry assessment of analytic and clinical validity. Much of the 'risk' in the use of the test is a result of the interpretation that is conducted in the practice of medicine. This is not like a therapeutic in which the actual administration of the therapy can pose a risk. The 'administration' of the test is relatively benign. The healthcare professional's actions pose a greater 'risk' and are covered by healing arts laws.

It is hard to see how tests can be regulated as 'devices' since they are not an intervention and are not inserted into the body as such. A test is an activity used to make a decision. The FDA is relying on antiquated categories when it attempts to make a test a devise.

4. **The current pre-market review standards that apply to *in vitro* diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?**

The concepts of "safety" and "effectiveness" are not relevant to the critical elements of diagnostic test performance. As above, analytical validity (i.e., accurate, reliable, and reproducible) and clinical validity (i.e., that the result reported by the test accurately diagnoses diseases, determines prognosis, or predicts clinical outcomes) are key.

5. **Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?**

In all cases, our healthcare system should be learning. Learning requires post market data capture and analysis. This is done far to little in the administration of medicine in general. Precision medicine inherently means that every person has the potential to be different from the next person. Therefore, it would be very productive to emphasize post market processes to improve patient access.

However, our current healthcare structure is not configured to make this easy or inexpensive. Laboratories are often outside the loop of outcomes and only provide a service. This is an area that calls for a large (majority of the nation) national cohort, ready and willing to participate in an end-to-end learning system. Every day that we wait, we lose data that is critical to our health and our loved ones.

6. **A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?**

The beauty of laboratory medicine is that it does learn in its contained in vitro system. Thus tests should be regularly improved. No extra burden should be put on test developers unless the change in a test actually has a clinically meaningful impact on test performance. One WANTS a gene panel to add a new relevant gene, or test for more mutations, as the lab's body of knowledge grows and the overarching feedback loop into the test development creates a more precise test. A good example of this is the BRCA1/2 tests. A lab should certainly report on variants in a gene that were previously classified as 'variants of uncertain significance' and are now known to be benign or pathogenic without requiring submission of a supplemental clearance or approval.

7. **We have heard a lot of about the practice of medicine and its relationship with medical product "labeling". What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?**

The 'labeling' for a diagnostic test may include the packaging and any other written, printed, or graphic material that is included with the packaging for or that otherwise accompanies the physical materials that are used in performing the diagnostic test. However, standards for dissemination of scientific information regarding diagnostic tests should differ from the standards applicable to 'traditional' medical devices.

A laboratory test is a clinical service. CLIA regulations require a number of elements for that service: clinical consultation to clients, assist clients in ensuring that appropriate tests are ordered, ensure that test result reports include patient information so that patient's can interpret the result, and ensure that consultation is available and communicated to patients on matters related to the quality of the test results reported and their interpretation concerning specific patient conditions. Labeling requirements for diagnostic tests should not stand in the way of fulfilling these requirements. This disseminated information should be truthful.

8. **The Section 1143 guidance documents raise important questions about the relationship between the FFDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?**

There is duplication between the requirements outlined in the draft LDT guidance documents and those assessed under CLIA. A careful description of these should be made and duplication removed. The overall system suffers from a lack of resources and any extra expense that doesn't add value should be avoided. Further, clarity through a single set of requirements would great benefit the testing industry and the patients they serve.

9. **How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g., rare cancers or blood disorders, Ebola)?**

Rare diseases, neglected diseases and public health threats through infectious diseases suffer an enormous burden. They are rarely interesting to developers, and certainly are not of much interest to the investment community because the return on investment is

limited. These tests deserve an expedited regulatory pathway, and manufacturers and laboratories that develop diagnostic tests used for rare diseases and unmet medical needs should be incentivized, not penalized.

'Rare disease' is defined in the Orphan Drug Act as a disease or condition affects fewer than 200,000 people in the United States. The FDA also has a device-specific exemption for rare conditions (the humanitarian device exemption (HDE)), and this exemption is available only for devices intended to treat or diagnose a disease that affects fewer than 4,000 people in the United States per year. Because *in vitro* diagnostics are often used for purposes of treatment selection – i.e., to identify a subset of patients with a condition in whom a treatment may be appropriate – it would be appropriate to make "rare" status consistent with those used to designate orphan drugs, not devices under HDE. The same consideration should be given to neglected diseases.

10. **Any new regulatory system will create transition challenges. How should existing products be handled? Should all current diagnostic tests be "grandfathered" into the marketplace? What transition process should be used for new product introductions?**

Here, Genetic Alliance supports the recommendations of the Coalition for 21st Century Medicine:

- Existing distributed test kits – i.e., tests that are currently regulated as medical devices by the FDA – should be allowed, for a period of time after the implementation of the new framework, to comply with the requirements for medical devices under the FFDCA or the requirements of a new diagnostics-specific framework. After a period of time, a previous approval or clearance under the FFDCA should be deemed an approval under the new framework, and distributed test kits should be required to comply with the regulatory requirements established under the new scheme.
- Existing LDTs should continue to be under enforcement discretion for a period of time after the implementation of the new framework. Eventually, however, an LDT should be required to obtain an approval from the FDA to the extent such approval is required under the new framework. In deciding which LDTs should be subject to the regulatory scheme first, the FDA should prioritize the LDTs that pose the greatest risk to patient health based on a risk scheme that has been proposed, vetted by the public, and adopted through regulation prior to implementation so that providers have sufficient notice and time to adapt to the new regulatory process.
- New distributed test kits should, for a period of time after the implementation of the new framework, be permitted to submit a marketing application as either a medical device under FFDCA or under the new framework applicable to diagnostics. Insofar as a new distributed kit is approved or cleared under the FFDCA, such approval or clearance should be deemed an approval under the new framework at the same time such deeming occurs for existing distributed tests.

- New LDTs should be required to comply with the new regulatory framework from the date of implementation of the statute. This may involve notification and adverse event reporting when requirements for such notification and adverse event reporting under the new framework are implemented. With respect to pre-market submission, this should follow the same prioritization as for existing LDTs, above, considering which LDTs pose the greatest risk to patient health.

11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?

I co-chair the Institute of Medicine's Roundtable on Translating Genomic-based Research for Health. This is a subject we have debated over the seven years the Roundtable has been deliberating. I think we understand that a solid and predictable regulatory system is critical. Test developers must not face high burdens for evidence that exceed the practical value of the tests. The overall system must 'learn' – without a learning healthcare system, more accurate and efficient tests will continue to elude the healthcare system. Finally, partnerships between advocacy organizations, clinicians and test developers must be formed in order to take advantage of continual system improvement.

Sincerely,

Sharon F. Terry

President & CEO