

## Participating in Next Generation Sequencing

Sharon F. Terry

ON FEBRUARY 20, 2015, as part of the Precision Medicine Initiative, announced by President Obama, the Food and Drug Administration (FDA) held a meeting at the National Institutes of Health (NIH) all day. The meeting was titled “Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic Tests” (Food and Drug Administration, 2015). The meeting convened thought leaders in laboratory science and clinicians in industry, academia, and advocacy. The President earmarked \$10 million in his fiscal year 2016 budget for the FDA to acquire additional tools and expertise to help generate knowledge about which genetic changes are important to patient care and foster innovation in genetic sequencing technology, while ensuring that the tests are accurate and reliable.

Next generation sequencing (NGS) can be used for many things, and that makes it difficult to regulate under the existing framework. If used in a clinical context, NGS might be considered an *in vitro* diagnostic test. The FDA would typically regulate those tests (although this regulation is also very controversial [Pathak and Terry, 2014]). However, NGS identifies more than one or two specific biological markers and may find much variation in one test application. Because some of these, perhaps the majority in the coming years, will be of unknown significance, clinicians and patients may not know what to do with the information.

With the goal of appropriate oversight of NGS, the FDA posed several questions to five panels throughout the workshop. These included the topics of analytical and clinical performance. Many of the analytical questions were focused on the better use of standards and on a standard-based approach to regulating whole exome and genome sequencing. The clinical performance discussion ranged from what to communicate to whom and when, to the sharing of data in large databases, such as ClinGen. There appeared to be a great deal of consensus that sharing variants should be the norm. In addition, most clinicians and laboratorians clearly do not want the FDA to regulate the practice of medicine.

I spoke at this meeting from the point of view of a patient/participant in genomic medicine. I do have some “science cred”: I am the curator of the part of the Leiden Open Variation Database at the National Center for Biotechnology Information for *ABCC6*; this gene causes the condition that affects my children, pseudoxanthoma elasticum. Most of my comments arose from Genetic Alliance’s work with all of the stakeholders of NGS. In recent years, we have conducted both focus groups and structured interviews with individuals who have conducted NGS.

My personal perspective is that we don’t really base much of medicine on strict evidence—it’s a combination of art and science, and its actual implementation varies widely because of the choices individuals make in response to recommendations and prescriptions. It seems to me that we are attempting to apply more rigid standards to an NGS just because it is digital and we think we can measure it better

than other kinds of testing. The solution to understanding what all of these data mean, and doing it sooner than later, is to deliver results to people. With it, we must convert patients to participants, a place many people want to go anyway. Data sharing with phenotypic information is going to be critical to get us to where we understand the results of NGS. Transformation of the oversight system is required. The President is asking for this.

There is no one-size-fits-all answer for what NGS results should be returned. It seems we wish there were a simple answer to the question “What should we be giving back to people, back to patients?” In most areas of our lives, we have some ability to articulate our preferences for knowing or not knowing something. We need to apply this to NGS, and we have the technologies to do it. There is a robust science around uncertainty and risk in other disciplines from which we can borrow, including studies on what it means to return results to individuals, even when those results might indicate risk for high morbidity (Chung *et al.*, 2009).

The FDA is conducting some innovative work in patient preference: the patient-focused drug development work from the Center for Drug Evaluation and Research and some of the patient preference work with algorithms on obesity by the Center for Devices and Radiological Health. The same patient/participant preference work should be considered in the oversight of NGS. The preferences of participants are critical in a learning healthcare system.

### References

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Address correspondence to:

Sharon F. Terry, MA

President & CEO

Genetic Alliance

4301 Connecticut Avenue, NW

Suite 404

Washington, DC 20008

E-mail: [sterry@geneticalliance.org](mailto:sterry@geneticalliance.org)