Perspective

A Measure of Truth in Genetic Testing

Kristi D. Zonno, Patrick F. Terry, and Sharon F. Terry

THE POWERFUL INFORMATION available through genetic testing is a product that involves multiple collaborations and stakeholders. As genetic testing has evolved from karyotyping to complex tests such as multivariate index assays, several issues, barriers, and gaps in the system have been identified and articulated by a broad range of stakeholders. Evolution of the field has produced important tools to change the practice of medicine and transform the health-care system. With so much promise, it is unfortunate that the potential of this field is inhibited by a framework that has not grown, expanded, or effectively adapted itself in the face of new technology and innovation.

We are likely all too familiar with several interconnected issues that are discussed everywhere from Capitol Hill and federal advisory committees to laboratories, clinics, and even to the homes of individuals and families for which we intend to provide access to new tests and treatments as they become available. These issues include informational transparency, oversight, regulation, quality, coverage and reimbursement, among others. We have become experts at identifying issues and sometimes proposing solutions, but collectively we have not effected the necessary systems change to benefit all stakeholders, most importantly the end users seeking high quality information and confidence as an output of the system.

Individuals, families, health-care providers, and perhaps even entire disease communities seek understanding through genetic testing. In the clinical arena, testing may answer questions such as: What is the diagnosis? What is the risk of developing a condition? What is the risk of having a child with a specific condition? What is the optimal treatment? What is the predicted benefit of a specific intervention? The heart of this process involves seeking the truth, a truth that can change a life, improve the quality of life, or may have the power to save a life, whether through providing information, confirming a diagnosis, or determining treatment options. Seeking truth through genetic testing and using that information to make informed decisions with confidence assumes that one can trust a system that strives to serve patients and families in the best possible manner while maximizing benefits and minimizing harm.

The truth revealed by genetic testing is fundamentally dependent upon analytic validity of a test. Analytic validity has been defined by the Clinical Laboratory Standards Institute (CLSI, formerly National Committee on Clinical Laboratory

Standards) and international organizations such as Organisation for Economic Co-operation and Development (OECD). These definitions have been adapted by groups within the genetics community to make this concept clearly applicable to genetic tests. The ACCE Evaluation Project for Genetic Tests within the Office of Public Health Genomics at the Centers for Disease Control and Prevention describes analytic validity as follows:

The analytic validity of a genetic test defines its ability to accurately and reliably measure the genotype of interest. This aspect of evaluation focuses on the laboratory component. The four specific elements of analytic validity include analytic sensitivity (or the analytic detection rate), analytic specificity, laboratory quality control, and assay robustness.

- * Analytic sensitivity defines how effectively the test identifies specific mutations that are present in a sample.
- * Analytic specificity defines how effectively the test correctly classifies samples that do not have specific mutations (although the term “mutation” is used here, the terms “polymorphism” or “variant” may be more appropriate for certain situations).
- * Quality control assesses the procedures for ensuring that results fall within specified limits.
- * Robustness measures how resistant the assay is to changes in pre-analytic and analytic variables.

Genetic Alliance convened a small group of experts in the field to discuss analytic validity from federal, academic, industry, and consumer perspectives. Consensus emerged on the strong need for a measure of truth in genetic testing, as currently there is no coordinated system of oversight to ensure important characteristics of tests, such as analytic validity, are defined before a test is available to consumers. Stakeholders do not coordinate their efforts in this arena, and there are insufficient incentives for metrology and comparative reference standards. Opportunities for regulatory and nonregulatory solutions exist to ensure analytic validity, and groups within the system must work together to craft a system for genetic testing that involves coordination of involved agencies and representation of all stakeholders. This is crucial, as even the federal agencies involved in genetic testing are not coordinated in their efforts.

In crafting this system, one critical basic element is the establishment of infrastructure that enables and ensures accurate and reliable testing. Some of the key considerations for this infrastructure include availability and application of

required reference materials, software integrity, and performance standards. Tensions arise when complex testing is built on the basis of simplified minimalistic standards. Identifying and defining different types of standards to integrate into the test development process and post-development quality assurance systems will contribute greatly to ensuring analytic validity across testing complexity. We collectively need to determine what type of standards should apply to what type of genetic tests and develop documentary, evidentiary, methods, and physical standards as needed. Success and challenges related to development of existing products can be mined for lessons learned to apply going forward and to inform development of responsive standards for emerging genetic testing technologies. Furthermore, tests must be established on reliable reference materials and quality control methods in a manner that allows and supports expanding the set of necessary standards material currently available. A final key consideration for infrastructure is to ensure that, like materials, the software used in the testing process has high integrity, which includes internal and external quality control assurances as well.

Without cooperation among stakeholders in crafting a system to ensure analytic validity in genetic testing, and an overall genetic testing evaluation system that balances needs to benefit all stakeholders, we are at risk for bad, overly burdensome regulation that would stifle innovation and opportunities for timely improvement of health outcomes. As new technology and new approaches to prevention, diagnosis, and treatment arise, there must be an accessible, clearly defined path forward for product development and delivery. While analytic validity is the foundation of truth in genetic testing, it alone does not ensure quality tests and other key components, including demonstrated evidence for clinical validity and clinical utility. Addressing the ethical, legal, and social implications of a given test must also receive equal attention in crafting a system. In the first instance, ensuring that analytic validity is based on standards would certainly be a great step forward.

Perhaps it would help if we compare genetic testing to a fine wine. It would, at the very least, be more interesting! A wine is the product of excellent ingredients combined in a robust process to ensure quality and high value. Investing in

the vineyard, the soil, the root stock, and hydration is money well spent, and is the basis for one wine being superior to another. Adherence to and maintenance of high standards of the soil, root, and hydration would increase the quality and availability of wine. This upstream approach is far more effective than a downstream regulatory approach that would allow for many varieties of bad wine to be available. Focusing on simple steps early in the process can ensure the availability of good wine, which would in turn drive innovation and inspire competition and novel collaborations while ensuring quality and sustainability of a growth industry.

The measure of truth for genetic testing in this age of genomic and personalized medicine has never been in higher demand. We all must commit to move forward on advancing the caliber of that truth.

Address reprint requests to:

Kristi Zonno, M.S., C.G.C.

Director of Genetics and Health Policy

Genetic Alliance

4301 Connecticut Avenue, NW

Suite 404

Washington, DC 20008

E-mail: kzonno@geneticalliance.org

Patrick F. Terry, CEO

Technic Solutions, LLC

2700 Abilene Dr.

Chevy Chase, MD 20815

E-mail: patrickfterry@gmail.com

Sharon F. Terry, M.A.

President and CEO

Genetic Alliance

4301 Connecticut Avenue, NW

Suite 404

Washington, DC 20008

E-mail: sterry@geneticalliance.org