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Written Public Testimony of
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Introductory remarks

My name is Sharon Terry, I am the mother of two children with a genetic disease, pseudoxanthoma elasticum (PXE). If it takes its course, they will loose their vision at about age 40. They both already experience moderate to severe wrinkling of the skin, another manifestation of the disease. I was catapulted into the world of genetics and biomedical research when they were diagnosed 15 years ago. I now run not only a genetic disease foundation for PXE, but also Genetic Alliance. Relevant to this testimony, I also serve on the Health and Human Services Office of the National Coordinator's Standards Committee for Health Information Technology.

Genetic Alliance is the world's leading nonprofit advocacy organization committed to transforming health through genetics. We bring together diverse stakeholders to create novel partnerships in advocacy; we integrate individual, family, and community perspectives to improve health systems; we revolutionize access to information to enable translation of research into services and individualized decision-making. Genetic Alliance's network includes more than 10,000 organizations, including disease-specific advocacy organizations as well as universities, private companies, government agencies, and public policy organizations. The network is a dynamic and growing open space for shared resources, creative tools, and innovative programs. Over the past 24 years, Genetic Alliance has been the voice of advocacy in health and genetics.

Advocacy in the 21st century, however, requires new definitions and new focus. We dissolve boundaries to foster dialogue that includes the perspectives of all stakeholders: from industry professionals, researchers, healthcare providers, and public policy leaders to individuals, families, and communities. In a rapidly changing world, Genetic Alliance understands that nothing short of the transformation will suffice to transform health.

My world revolves around the hundreds of millions of men, women and children in the US and throughout the world that wait, and sometimes die, for tests and therapies. It is my passion to accelerate translation of the phenomenal explosion of information surging through the biomedical research pipeline today. I grow more certain each day that the outcomes we seek, better health for all, are dependent on a solid foundation. That foundation is standards that allow high quality diagnostics and therapeutic development.

I have witnessed enormous waste and disparities in test and drug development. I will give some examples and recommendations that illustrate the enormous payoff we would have as a nation with increased participation of NIST in the biomedical enterprise.

The National Institute of Standards and Technology is the premier standards agency in the world. The success of the biomedical research enterprise, and America as a leader in innovation depends on NIST providing standards upon which to build personalized medicine.

At this time, each provider of biomedical tests and therapies is creating their own system, leading to widespread inconsistencies between these practices. American's believe that they are receiving healthcare that is high quality, accurate, valid, useful and consistent. They do not realize that a PSA test from one lab, cannot be compared to another lab. They have no idea that the 4 million newborns who received screening at birth this year, are subjected to different screening cutoffs in each of the 51 programs in the states and territories. Most measurements are relative, internal to one lab, or one state, or one company. Every manufacturer applies relevant measurement technology with their own standard references and controls, for example in housekeeping genes and general control reagents. The Food and Drug Administration, as a regulatory agency, is challenged with ascertaining the accuracy and precision of these technologies based on the manufacturers supply control and references. Ultimately they must trust the manufactures' standards.

These technologies, in genetics, genomics, laboratory science and imaging, are migrating into clouds of care. At this point, the iterative cycle is over because a static product is being introduced into healthcare. We absolutely need new standards. They can be called clinical standards, but this should be a regulatable gray clinical standard in which all technology is measured if it's going to be used to treat patients. NIST needs to take a leadership role in creating the standards necessary to integrate new technologies into medicine.

Metrology can be considered less than exciting science, because it is thankless and invisible in the medical system. The valiant work of NISTs scientists produce incredible standards of temporal and spatial value with little recognition.

I have witnessed public health laboratories and companies develop precise measurements, and have them eschewed by their peers. However, the community won't use them because they are not independently judged or assessed, and because they would create the opportunity for comparisons that might be good for public health, but are generally not welcome by industry or laboratories. The community will use the least expensive alternative. If NIST standards, underpinned FDA requirements, the industry would be incentivized to improve life science measurement. Then companies and academic labs would not be differentiating themselves against the least expensive alternative. They'd be differentiating themselves against a performance standard, which is a completely different exercise.

The highest standard for laboratory performance is Clinical Laboratory Improvement Amendment (CLIA). CLIA is structured in such a way that it avoids standards because it doesn't have them to use. Labs just need internal standards for the laboratory, the machines, the operators, and the protocol. At the present time, every single standard for every single test is unique to the test provider. This has created an untenable morass. The 2700 genetic tests currently listed in GeneTests (http://www.ncbi.nlm.nih.gov/sites/GeneTests/?db=GeneTests) are actually somewhere in the hundred thousands tests because of the variability across the labs performing these tests in the US and beyond.

Current, future and nascent areas of biomedicine that could be best served by NIST if it expands its involvement in performing measurement science to develop measurements, reference materials, reference standards, standard processes, and validation procedures in the biomedical area.

In the future, schizophrenia, rheumatoid arthritis, asthma, attention deficit disorder, autism and other spectrum disorders may be treatable if there were control standards to measure various attributes of phenotype. At present, these all rely on subjective patient reporting.

Linearity studies can be conducted that show standards are accepted and work well for the technologies. This is the challenge for substrate microarrays for DNA measurement. There is a need an artificial control, a ladder control. It would create a benchmark for accuracy in measurement that would bring biomedical research and technologies a level of evidence it sorely needs to move to personalized medicine.

In all cases, handling, storage, preparation all have influence on the accuracy of a laboratory measurement. It is difficult to control for all these variables in a measurement science. NIST at times appears paralyzed because of the large number of variables, wondering where to start, and seeming to be overwhelmed. If the biomedical universe is too big for one to tackle everything, then NIST should begin by producing methods standards.

We need measurement standards of controls for pseudoxanthoma elasticum (PXE). The gene, ABCC6 has a 99% homology fossil gene that can produce erroneous test results for patients. In addition, at least 17 other genes that have similar profiles and there are no controls. How many of these scenarios exist in the humane genome? Many, perhaps, but the genome is a fixed repository. It's a recipe and a cookbook for biological processes that has 23,000 functioning genes and probably 100,000 alternate transcripts that could be mapped today and easily catalogued. These could have standards created for them. NIST could collaborate in a much more effective way with the FDA in the submissions they receive and integrate standards more frequently into the regulatory regime. Certainly at first we would be demanding more of a perfection standard from new technologies than what was cleared in the predicate standard, but one hopes science improves medicine. A good point for the intervention of high standards can be the point where something migrates into a regulatory schema for clinical use.

Genetic Alliance submitted a citizen's petition for the creation of a genetic subspecialty under the Clinical Laboratory Improvement Act (CLIA). CLIA's response indicated that there were few standards for the 2700 hundred tests that are being offered to patients. They indicated that they would be able to create a specialty when there were standards. This was in 2002, and there has been no progress since.

Assisting NIST in ascertaining current and future metrology needs for the biomedical community:

- **Advisory board of industry experts**

I believe advisory boards can be very effective, provided they are given authority to make recommendations and the leadership of the agency is receptive. I am serving at this time on the

HIT Standards Advisory committee and am impressed with the level of commitment of the members from industry and academia alike. We feel urgency and we feel like we are having an impact. A body with these attributes would be very good for NIST.

- **University center for biomedical research**

The creation of multiple standards in many disciplines may be too broad a waterfront for NIST to tackle alone. A granting mechanism would be very effective. For example, academic groups could reply to RFPs that asks for referencing control standard for the biology of the highest priority cancers for NIH, including the encyclopedic genome of these cancers; for standards for all of the conditions in the current recommended panels for newborn screening, and/or the 2700 or so Mendelian disorders. Another RFP could ask for standards that would allow comparison of the fidelity of one machine to the next for mutation detection.

Other recommendations for implementing these elements (advisory board, university center and/or user facility) or others?

It may be beneficial to set up a laboratory network dedicated in part to standards. The Collaboration Education and Test Translation program of the Office of Rare Disease Research at the National Institutes of Health has such a network associated with it. Laboratories share reference standards and controls for rare diseases. These could be codified in a standards based system at NIST. The model of this network might be deployed to other problems.

Concluding remarks:

NIST must take a leadership role in creating the standards necessary to integrate new technologies into medicine. These technologies, in genetics, genomics, laboratory science and imaging, are migrating into health care, sometimes to point-of-care. It is critical that patients know that these healthcare services are based on the certitude that only standards can bring.

With Congress's increased support, NIST should:

1. Create a life sciences infrastructure, catalog, and distribution system for reference materials and standards for quality assurance for <u>all</u> clinical diagnostic tests
2. Integrate measurement standards and technologies into the FDA regulatory regime
3. Partner with the National Institutes of Health on resolving the measurement challenges at the intersection of patient care
4. Conduct a comprehensive analysis of the life sciences to determine the highest needs for measurement science

In this age of emerging personalized medicine, delivered through new technologies to patients today, we cannot wait any longer, having far outstripped the standards available to biomedical enterprises. Leading Genetic Alliance, and feeling the urgency of the hundreds of millions of people who need answers today, I know we need excellent leadership in an exceptional age. Let us take this charge seriously. Every one of us has a role to play, and NIST is poised to do great things. Thank you for the opportunity to contribute to the important work of this committee.