HOW CAN NIST BETTER SERVE THE NEEDS OF THE BIOMEDICAL RESEARCH COMMUNITY IN THE 21ST CENTURY?

HEARING

BEFORE THE

SUBCOMMITTEE ON TECHNOLOGY AND INNOVATION

COMMITTEE ON SCIENCE AND TECHNOLOGY

HOUSE OF REPRESENTATIVES

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February 24, 2010

HOW CAN NIST BETTER SERVE THE NEEDS OF THE BIOMEDICAL RESEARCH COMMUNITY IN THE 21ST CENTURY?

WEDNESDAY, FEBRUARY 24, 2010

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON TECHNOLOGY AND INNOVATION
COMMITTEE ON SCIENCE AND TECHNOLOGY
Washington, DC.

The Subcommittee met, pursuant to call, at 2:10 p.m., in Room 2318 of the Rayburn House Office Building, Hon. David Wu [Chairman of the Subcommittee] presiding.

HEARING CHARTER

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE AND TECHNOLOGY
SUBCOMMITTEE ON TECHNOLOGY AND INNOVATION

How Can NIST Better Serve the Needs of the Biomedical Research Community in the 21st Century?

WEDNESDAY, FEBRUARY 24, 2010
2:00–4:00 P.M.
2318 RAYBURN HOUSE OFFICE BUILDING

1. Purpose

On February 24, 2010, the Subcommittee on Technology and Innovation will hold a hearing to examine ways in which NIST could better serve the needs of the biomedical community. This hearing is a follow-up hearing to the hearing held on September 24, 2009, entitled: *The Need for Measurement Standards To Facilitate Research and Development of Biologic Drugs*.

2. Witnesses

Dr. Thomas M. Baer is the Executive Director of Stanford Photonics Research Center at Ginzton Lab.

Sharon F. Terry, MA is the President and CEO of Genetic Alliance.

Dr. Daniel Sullivan is a Professor and Vice Chair for Research in Radiology at Duke University Medical Center and Science Advisor to the Radiologic Society of North America.

3. Background

On September 24, 2009, the Science and Technology Committee for the House of Representatives, Subcommittee on Technology and Innovation, held a hearing to examine the need to develop measurements, reference materials, reference standards, standard processes, and validation procedures to improve the research, development and regulatory approval of biologics.[1] In the September 24th hearing, industry and the FDA expressed that there is a need for NIST to perform basic measurement science research to support the growth of the biologics industry.

Additional initiatives in the biomedical field have been proposed by NIST, including performing metrology research to support better diagnostic testing and the development of personalized medicine. Developing reference standards and materials in each of these areas could potentially lead to a substantial savings in the cost of healthcare, supporting innovation in the biomedical field, leading to job creation. For example, in the area of personalized medicine, the development of basic measurement science, particularly in the area of proteomics and biomarker discovery, could enable small biotech companies to utilize their more limited resources to develop therapies targeted to specific populations of patients. This, in turn, could lead to the growth of the biotech industry which has traditionally fostered innovation through small and start-up biotechnology companies.

As another example, interpreting the results of diagnostic tests can be inconsistent and inaccurate, leading to the need for multiple testing of the same patient and/or the use of less effective treatment options. In the area of imaging tools, such as x-rays, magnetic resonance imaging (MRI) and positron emission tomography (PET), interpretation of the results is a subjective task; however the treatment of disease is an increasingly objective process given the multiple options available to patients. In addition, medical imaging devices vary from hospital to hospital, thus increasing the likelihood that results obtained from different machines using dif-

[1] Hearing available at: *http://science.house.gov/publications/hearings_markups_details.aspx?News1D=2597.*

ferent standards and methods will not be comparable. Hence, better reference standards are needed to assist doctors in interpreting diagnostic medical imaging results objectively and consistently to improve patient treatment options.

In a third example, as recently as 1980, the measurement uncertainty for cholesterol tests was more than 10 percent. This wide margin of uncertainty meant that large numbers of people were misdiagnosed as needing treatment when they did not, or not needing treatment when they did. After an investigation by the Subcommittee, NIST, in collaboration with the Centers for Disease Control and Prevention, developed a Standard Reference Material, which reduced the uncertainty level of these tests to 5 percent saving millions of dollars per year in unneeded treatment costs and improving the quality of health care for patients.[2]

All of the initiatives proposed by NIST in the biomedical field will require a substantial investment of resources and funding. As suggested in the September 24th hearing, in addition to providing increased funding to NIST for these programs, structural and managerial improvements would also be desirable to help NIST accomplish its goals in the biomedical area.[3] The National Research Council, while approving of the efforts of NIST in the biomedical area, has indicated that improvements may also be made to NIST, and particularly to the Chemical Science and Technology Laboratory (CSTL), in order to maximize the impact of these efforts on the advancement of biomedical science.[4]

The Subcommittee will examine ways in which the NIST Director could improve biomedical research at NIST to accurately and effectively reflect the needs of the biomedical community. In particular, biomedical research at NIST should be structured to achieve the following: (1) increase NIST's technical expertise through collaborations with academic institutions, private industry and nonprofits; (2) increase and improve NIST's outreach efforts to industry, academia and nonprofits; and (3) develop mechanisms that allow for NIST to obtain effective and targeted input and feedback from industry, academia and nonprofits.

As examples, the Subcommittee, with input and comments from experts in the biomedical field, will examine whether the following proposals may improve the ability of NIST to serve the needs of the biomedical community:

1. Development of an advisory board or panel of experts, largely from industry, in the biomedical field to provide guidance on focal areas and to discuss CSTL's official activities.
2. Proving for the establishment of joint NIST university centers for biomedical research at universities with strong reputations for their biotechnology programs.
3. The establishment of a user facility at NIST that could be used by industry and academia, similar to the NIST Center for Neutron Research.

Further, the Subcommittee has asked witnesses to provide comments on any additional changes that the NIST Director may implement that would improve NIST's ability to achieve the goal of providing the most effective service to the biomedical community, patients and doctors.

4. Witness Questions

The following questions were asked of each witness:

- If NIST expands its involvement in performing measurement science to develop measurements, reference materials, reference standards, standard proc-

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[2] *See http://www.nist.gov/public_affairs/techbeat/tb9709.htm.*

[3] *The Potential Need for Measurement Standards to Facilitate the Research and Development of Biologic Drugs*, Hearing before the Subcommittee on Technology and Innovation, Committee on Science and Technology, House of Representatives, 111th Congress, 1st Session (September 24, 2009), Ser. No. 111–53 at p. 86.

[4] The National Research Council, for example, suggested that:

> The Biochemical Science Division should identify what it considers to be success in the context of NIST. There may be too many small efforts to make a major impact. An overarching strategy should be articulated and priorities set, based on identifying what kinds of activities can best be done in the NIST environment. Many of the groups have done this, but a top-down alignment of research with the division mission is missing. Once this is achieved, the management team will have less difficulty in sifting through the projects to determine which are the most important to pursue going forward.

An Assessment of the National Institute of Standards and Technology Chemical Science and Technology Laboratory, Fiscal Year 2009, Panel on Chemical Science and Technology Laboratory Assessments Board, Division on Engineering and Physical Sciences, National Research Council of the National Academies (p. 17).

esses, and validation procedures in the biomedical area, what future and nascent areas of biomedicine will be most affected and how?

- Would the following elements assist NIST in ascertaining current and future metrology needs for the biomedical community? If so, how?
  - an advisory board for CSTL.
  - a NIST university center for biomedical research.
  - a user facility at NIST that could be used by industry and academia.
- What other recommendations would you make regarding the implementation of these or other elements?

Chairman WU. This hearing will come to order. Good afternoon. I would like to welcome everyone to today's hearing on improving the biomedical program at NIST [National Institute of Standards and Technology].

This is the second hearing of this Subcommittee to examine how NIST can better serve the needs of the biomedical community. Our first hearing focused on what NIST could do to meet the metrology needs of the biologics industry.

Today, the Subcommittee will hear testimony on how NIST can better respond to the metrology needs of the broader biomedical community, including performing research support, not just biologic drug development, but also personalized medicine and diagnostic testing.

We all know that people across the country have recently been engaged in an ongoing debate over healthcare reform. We will not be debating that issue today, but that debate has focused, in part, on who should bear the costs for providing healthcare. This Subcommittee will take the discussion further and examine how we can use science to potentially reduce our healthcare costs, while improving care for patients.

The growth of the biomedical sciences is essential to providing better care for patients, and better treatment options for doctors. Earlier, more accurate diagnoses of chronic diseases, such as heart disease and cancer, would save billions of dollars each year in medical costs. Moreover, better diagnostic tools, and the use of personalized medicine can lead to more effective treatments that are tailored to a patient's needs.

In short, advancing the biomedical sciences promotes patient health and will lead to job creation in biotechnology and healthcare industries. We have heard from the biomedical community that metrology research is necessary to take biomedical science to the next level, and that NIST needs to be more connected to industry and academia to innovatively respond to the demands of this rapidly changing industry.

That is the focus of today's hearing: innovation. Today, we will hear about new, innovative biomedical treatments, and how NIST may develop new, innovative processes to better provide service and support to this growing industry.

I want to thank our witnesses for being here, for making a long trip on the part of many, and we plan to act on their guidance in the process of reauthorizing the America COMPETES legislation.

And now, I would like to recognize the ranking member, Mr. Smith, for his opening statement.

[The prepared statement of Chairman Wu follows:]

PREPARED STATEMENT OF CHAIRMAN DAVID WU

Good afternoon. I'd like to welcome everyone to today's hearing on improving the biomedical program at NIST.

This is the second hearing the Subcommittee has held to examine how NIST can better serve the needs of the biomedical community. Our first hearing focused on what NIST could do to meet the metrology—or measurement—needs of the biologics drug industry. Today the Subcommittee will hear testimony on how NIST can better respond to the metrology needs of the broader biomedical community, including performing research to support not just biologic drug development, but also personalized medicine and diagnostic testing.

We all know that people across the country have recently been engaged in an ongoing debate over health care reform. That debate has focused in part on *who* should bear the costs for providing health care. This Subcommittee will take the discussion further and examine how we can use science to *reduce* our health care costs while improving care for patients.

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In short, advancing the biomedical sciences promotes patient health, saves medical costs, and will lead to job creation in the biotechnology and health care industries.

We have heard from the biomedical community that metrology research is necessary to take biomedical science to the next level and that NIST needs to be more connected to industry and academia to innovatively respond to the demands of this rapidly changing industry.

That is the focus of today's hearing—innovation. Today we will hear about new, innovative biomedical treatments and how NIST may develop new, innovative processes to provide better service and support to this burgeoning industry.

I want to thank our witnesses for being here. We plan to act on their guidance in the process of reauthorizing the *America COMPETES Act*.

Mr. SMITH. Thank you, Mr. Chairman, Chairman Wu, for calling today's hearing to examine ways in which the National Institutes of Standards and Technology can better serve the needs of biomedical researchers.

At our first hearing on this topic last September, we had the opportunity to hear from NIST and the Food and Drug Administration [FDA] regarding what they believe to be their appropriate roles in supporting biomedical research, and about new initiatives NIST would like to implement to support this rapidly advancing field of research.

It is clear from past experience there is a constructive role for NIST to play as a standard-setting body in biomedical research. Past advances by NIST have improved the accuracy and comparability of medical research and testing in numerous fields, and as diagnoses and treatments become more and more individualized, the need for such criteria will certainly only increase.

As we work to ensure NIST's authorization meets the evolving needs of the biomedical research community, we must also remain mindful of our responsibility to ensure NIST's standardization efforts enhance and ease ongoing research, but actually do not replace it. Although this has not often been an issue, we would be remiss to not continue monitoring this concern.

We must also address how expanded activities at NIST will be funded. One idea discussed at our last hearing was whether benefiting agencies such as FDA and NIH [National Institutes of Health] should fund NIST's work in these areas from their budgets. Although shifting funding from these agencies to NIST may appear less than ideal, if NIST's work catalyzes these agencies' efforts, it may be an option worthy of pursuit, as such arrangements are not without precedent.

Thank you again, Mr. Chairman. I am looking forward to a constructive session with today's witnesses, and I yield back the balance of my time.

[The prepared statement of Mr. Smith follows:]

PREPARED STATEMENT OF REPRESENTATIVE ADRIAN SMITH

Thank you, Chairman Wu, for calling today's hearing to examine ways in which the National Institute of Standards and Technology can better serve the needs of biomedical researchers.

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Thank you again, Mr. Chairman. I am looking forward to a constructive session with today's witnesses and I yield back the balance of my time.

Chairman WU. Thank you very much, Mr. Smith. Other Members who wish to submit additional opening statements, your statements will be added to the record at this point.

Now, it is my pleasure to introduce our witnesses. First, Dr. Thomas Baer is the Executive Director of the Stanford Photonics Research Center at the Ginzton Lab, and is a consulting professor in the Applied Physics Department at Stanford University.

Now, I would like to recognize the gentlelady from Illinois, Ms. Biggert, to introduce our next witness.

Ms. BIGGERT. Thank you, Mr. Chairman, and I am honored to introduce Sharon Terry, who is the President and CEO of the Genetic Alliance, a network that is transforming health by promoting an environment of openness, centered on the health of individuals, families, and communities.

I have had the opportunity to work with her for quite a few years, on what we consider as a very important bill. It is called GINA, that is the *Genetic Information Nondiscrimination Act*, which passed two years, and I think the regs have just come out. But it was something that Louise Slaughter of New York and Ted Kennedy and Olympia Snowe and I worked on, and it took over ten years. And it passed out of the House with about 420 to 2 votes. You wonder why it took that long, but there was a lot of work that it went into it, and it really is going, I think, to change healthcare, and I am very proud of that.

And Sharon put it all together, with her enthusiasm, and her way of bringing together advocates and, diverse advocates, and get them all to work together.

I welcome her here.

Chairman WU. Thank you very much, Ms. Biggert.

And our final witness is Dr. Daniel Sullivan, who is Professor and Vice Chair for Research in Radiology at Duke University Med-

ical Center, and Science Advisor to the Radiological Society of North America [RSNA].

You will each have five minutes for your spoken testimony. Your written testimony will be included in the record in its entirety, and when you complete your testimony, we will begin with questions, and each Member of the panel will have five minutes to question the panel.

Dr. Baer, please proceed.

STATEMENT OF DR. THOMAS M. BAER, EXECUTIVE DIRECTOR, STANFORD PHOTONICS RESEARCH CENTER, GINZTON LAB

Dr. BAER. Thank you, Chairman Wu. And I would like to thank you and the rest of the Committee for the opportunity to testify about how NIST can better serve the needs of the biomedical research community in the 21st Century.

I am a physicist, but I have worked in the biomedical area, primarily in the private sector, for the last twenty years, developed instrumentation and technology for HIV and AIDS diagnosis, as well as bone marrow transplant quality control, and breast cancer diagnostics, and know very well the importance of accurate measurement for precise diagnosis.

I also have a background with NIST. I served for six years on the NRC [National Research Council] panel for both the Physics Lab and Chemistry Science and Technology Lab, as well as served for the last four years on the Visiting Committee for Advanced Technology [VCAT], and chaired the Biosciences Healthcare Subcommittee as a part of my VCAT responsibilities.

Today, I will be presenting my personal perspective, and not speaking for the VCAT Committee, but of course, my opinion has been shaped by many discussions with my colleagues on the VCAT Committee, and they share many of the opinions that I will be presenting today.

My long history with NIST has instilled in me a great respect for what NIST can accomplish when it focuses its effort to support U.S. industry through world-leading measurement research and standards development.

I am very pleased to be here with my colleagues, Sharon Terry and Dan Sullivan. Sharon is going to present, very eloquently, a patient point of view, and Dan, a clinical point of view. And I thought I would take my time to present my perspective on the industry, the biomedical and bioscience industry, and the exciting potential that new technology offers there.

We are here today because of a technological revolution that has occurred over the past several decades. In general, new products bring benefit to society through creating new industries, and these new products are based on innovative engineering. And engineering usually has its foundation in the quantitative sciences, which have traditionally been mathematics, physics, and chemistry.

However, over the last 30 years, there has been tremendous progress in the life sciences, and it has entered into this regime of quantitation. Through remarkable advances in technology, which allow very precise measurements of DNA, RNA, and proteins. Many of these advances were developed here in the United States, based on research funded by the U.S. Government, the polymerase

chain reaction, DNA microarrays, four color sequencing, all evolved here in the United States.

There are many industries that depend on this industry, besides the healthcare industry, and they are listed here, but the healthcare industry, which we are focusing on today is a $2.5 trillion industry. It represents 20 percent of the U.S. gross domestic product, and it employs ten million people. And it is truly an enormous industry here in the United States.

It is a rapidly growing industry. It is not only big, it is one of the fastest growing. It is one of the largest areas of investment in Silicon Valley for venture capital. Dozens of companies are formed each year, creating thousands of new jobs.

The goal of these companies, and of this industry, is to improve the quality of healthcare and save lives. It is to reduce the cost of healthcare, to create new jobs, and to keep the U.S. biomedical healthcare industry competitive worldwide.

As an example of the types of advances that have occurred, here is one illustration. In 1975, if you used a sequencing instrument back then, you could generate about a nucleotide sequence of about 2,000 base-pairs. And if you printed out this data, it would take up one half a page in a book. To sequence the human genome using a single instrument from that technology would have taken 4,000 years. In 1990, when lasers were introduced as a part of the instrumentation in capillary electrophoresis, you could generate data on 100,000 base-pairs per day, and to sequence the human genome would have taken about 80 years. To print out all this data would have taken a chapter in a book. Today, a single instrument can generate two billion base-pairs of data in a single day, and that data would fill ten encyclopedia's worth, to print out all of that data.

Chairman WU. Dr. Baer.

Dr. BAER. Yes.

Chairman WU. Let me interrupt you just for a second. Your slide says, it takes—it would take one day to sequence a single human genome.

Dr. BAER. Yes.

Chairman WU. You mean, like, the entire genome of a human being?

Dr. BAER. Yes. A single human genome has three billion base-pairs in it, and one of these instruments now—one of the state of the art instruments—can do that process in a single day.

Chairman WU. You have to understand that, given that I am a child of the mid to late '70s doing biochemistry, I was in a basement lab at Stanford, at Stanford Medical School. This is just jaw-dropping. Sorry to interrupt.

Dr. BAER. Not a problem. And to put it in perspective, some of the testimony from Sharon Terry, her accomplishment, searching for the PXE [pseudoxanthoma elasticum] gene, would be like looking for one misspelling in a word within that ten encyclopedias. It is a phenomenal accomplishment that she and her husband worked on. Yes. So, this example is one of the challenges facing medical science today, what to do with this enormous amount of data.

As another example, the type of data that is generated by a high resolution CT [CAT/computer tomography] scan that Dr. Sullivan

will be talking about, that CT scan generates a comparable amount of data, about two billion data points.

So, the role of NIST is to make sure that this data is high quality, to be able to develop the technology and software to extract from this data the critical elements that can be used in diagnosing diseases.

Currently, NIST is primarily organized by discipline. It has a number of very high quality laboratories, primarily focused around the traditional areas of mathematics, physics, and chemistry. It does not have a life science laboratory focused on the biomedical and healthcare industry, or the technology that has evolved over the last several decades. And I think, it is clear to us that NIST needs to expand its efforts in the biomedical area, and to do so effectively, and optimize its interface to the biomedical industry. It may be necessary for NIST to consider forming a separate operating unit and laboratory in the bioscience and healthcare area.

Let me close my remarks by commenting on the strong leadership provided by the current director of NIST, Dr. Patrick Gallagher. Dr. Gallagher indicated at the last VCAT meeting that we had in February that he is working with the NIST lab directors and senior managers to develop a new NIST structure that will improve NIST's ability to address the pressing needs of U.S. industry and fellow government agencies.

NIST can best be organized to service its many diverse stakeholders, I believe, and capitalize on this great opportunity to reorganize and expand NIST resources, by potentially introducing a new biomedical and healthcare laboratory. I look forward to working with Dr. Gallagher to bring about these types of changes.

Thank you very much, Mr. Chairman.

[The prepared statement of Dr. Baer follows:]

PREPARED STATEMENT OF THOMAS M. BAER

Chairman Wu, Congresswoman Edwards and Biggert, and Committee Members:

Thank you for this opportunity to testify before the Technology and Innovation subcommittee on *How NIST Can Better Serve the Needs of the Biomedical Research Community in the 21st Century*.

My name is Tom Baer, and I am the Executive Director of the Stanford Photonics Research Center and a Consulting Professor in the Applied Physics Department at Stanford University. Although my early training and scientific research was in Physics, I have spent most of my career working in the fields of biotechnology and biomedicine, primarily in the private sector. I have been a research scientist, founder, CEO, and senior manager in several biomedical companies in Silicon Valley and have developed technology used in the diagnosis of AIDS, quality control of bone marrow transplants, and the molecular analysis and diagnosis of breast and lung cancer.

I have a long association with NIST, having worked with several directors and lab managers, serving six years in the 1990s on the NRC review panels for both the Physics and Chemical Science and Technology Laboratories. I have also served for the past four years on the Visiting Committee for Advanced Technology (VCAT). I want to clearly state that in my testimony today I am presenting my own perspective on the topics being discussed, and I am not speaking on behalf of the VCAT committee. However, my perspective has been influenced by many in-depth discussions held with my colleagues on the VCAT, and we share similar views on many of these issues.

My long association with NIST has instilled in me a deep respect for this government agency, its personnel, and its unique mission. NIST's world class measurement science and standards development activities can form an important framework for innovation, enhancing competitiveness of US industry, and supporting job

creation. This is particular true in the area we are discussing today of bioscience and healthcare.

As one of the largest sectors of our economy, estimated at $2.5 trillion, healthcare makes up 20% of the total US gross domestic product and employs approximately ten million Americans. These workers provide services essential to our quality of life in this dynamic, rapidly growing sector. In spite of the recession, US venture capital firms clearly foresee tremendous growth potential in biomedicine and biotechnology. Venture capital firms in Silicon Valley continue to fund life science startups, creating dozens of companies each year, employing thousands of workers. Startup companies translating scientific advances into important, new therapeutic and diagnostic medical procedures have been one of the largest areas of venture capital investment in Silicon Valley for the last ten years. This area is clearly one of the most important, dynamic sectors of our economy, and one in which NIST can and must play a vital role.

What is causing this tremendous growth? Technology innovation and new product engineering historically have been based on a foundation provided by the quantitative sciences: physics, chemistry and mathematics, strong areas of focus at NIST. However over the past 30 years tremendous advances in instrumentation and new technologies have stimulated extraordinary progress in the life sciences. Innovative instrumentation has opened up unprecedented capabilities for precise measurement of biological macromolecules such as DNA and proteins. Thirty years ago, using an instrument of that era, it would have taken several thousand years to sequence a human genome. The newest generation of high throughput gene sequencing instruments can sequence a human genome in less than one day. Similarly, 3 decades ago measuring the expression level of a single gene in a tumor would have taken several days or weeks in a biomedical research lab. Today we can measure the expression levels of thousands of genes simultaneously in under an hour. These measurements provide the possibility for more precise classification of cancer tumors and much more effective methods for quickly and effectively choosing optimal drug therapy. These advances make possible *personalized medicine* where custom therapies are developed and prescribed based on a patient's individual genetic makeup. Medicine is being transformed by these developments, moving from a primarily observational science to a truly quantitative discipline, hopefully soon to fully join the ranks of physics, chemistry and mathematics.

This progress presents tremendous potential for lowering medical costs by reducing the number of tests necessary to diagnose disease and by helping physicians choose the best therapies and thus helping patients avoid unnecessary medical procedures. However, capitalizing on these therapeutic and diagnostic opportunities presented by recent advances in biotechnology requires the development of standardized procedures, new reference materials, instrument calibration protocols, and a much better understanding of the science underlying these new technologies, areas where NIST can make critical contributions.

Despite the introduction of many new, effective diagnostic tests numerous challenges remain: the lack of standards, cross platform inconsistencies, and lab-to-lab variability are significant barriers to optimizing their impact. Two examples of current problems are illustrated by tests performed millions of times each year in the US: measuring levels of prostate specific antigen (PSA) to diagnose prostate cancer and thyroid stimulating hormone (TSH) essential to diagnose and treat thyroid disease. Results of PSA or TSH tests cannot be reliably compared if they are performed at different diagnostic laboratories using different measurement methods. A recent laboratory report had the following warning in a footnote "PSA values from different methods cannot be used interchangeably." Patients are warned to be careful about interpreting TSH laboratory results if they have moved to a new location or change laboratories. This lack of reproducibility in test results confuses patients, causes much concern in medical practitioners, makes appropriate therapeutic intervention much more difficult, and often increases medical costs by creating a demand for multiple, repeated testing. NIST, specializing as it does in measurement science and standards development, could help to vastly improve test consistent and accuracy, substantially reducing medical costs.

Translating the tremendous advances in quantitative biology instrumentation into effective diagnostic tests will require developing standard reference materials, reproducible consensus protocols, and understanding the basic measurement science underlying these new quantitative biomedical instruments. Much of this work has yet to be done and lack of this standards framework is impeding the translation of these new technologies into medical practice, affecting the lives of many critically ill US citizens who could benefit from accelerated introduction of these breakthrough technologies. NIST can play a pivotal role in accelerating deployment of these remarkable new instruments and procedures. Other government agencies, such as the FDA

and NIH focus, on different aspects of health care, regulatory affairs and disease research respectively. Both of these agencies have strongly encouraged greater involvement by NIST in supporting the health care industry by developing standards and by expanding its ongoing research efforts bioscience and healthcare.

As part of my VCAT responsibilities I chaired the Subcommittee on Bioscience and Healthcare. This Subcommittee included fellow VCAT members Lou Ann Heimbrook and James Serum, two highly experienced senior executives from the pharmaceutical and biotechnology industries. We have been working with several of the laboratory directors at NIST to help guide formation of a strategic plan to address the wide ranging needs of the Biomedical Health Care industry and research communities, as well as coordinate this program with the ongoing efforts at NIST to develop electronic medical records standards. I have found working with NIST senior management to formulate a roadmap for NIST in biomedical and healthcare to be a challenging but rewarding task, and it is still a work in process. NIST does not have a completely conceptualized and articulated a vision for how to best serve US industry needs in this area. I do feel strongly, however, that NIST management recognizes that there is an urgent need to complete this process and that there is a very exciting, critical role for NIST to play in the rapidly expanding arenas of healthcare and bioscience. One of the results of this planning was a conference designed to initiate a dialogue between NIST and stakeholders in the Biomedical Industry. The proceedings of this conference have been published in a document summarizing the opinions of the participants.

NIST is at present organized by discipline with very strong laboratories in the traditional quantitative sciences. The Physics, Chemical Science and Technology, and Information Technology laboratories provide essential support to many US industries. Unfortunately NIST does not have a laboratory devoted specifically to supporting the biomedical and healthcare industry. In my opinion, NIST currently needs to add more staff familiar with the challenges facing the pharmaceutical, diagnostic and medical device industries. NIST also needs additional resources for expanding its facilities and acquiring the equipment to develop the research programs necessary to meet the needs of these industries. Currently there are several excellent groups within NIST making very important contributions, focused on research impacting significant, specific biomedical problems. However, the VCAT has commented in past annual reports that these groups are often isolated from one another in different NIST laboratories, their efforts are not well coordinated, and they often lack sufficient resources to optimize their impact. I believe that to be truly effective NIST needs to be provided with additional resources to expand efforts in this area and establish an operating unit or laboratory specifically focused on servicing the needs of the US Biomedical/Healthcare industry.

For over a century NIST has played a very important role in many areas of quantitative science and technology providing standards and world-leading measurement science for precise reproducible measurement of many physical constants, chemical analytes, and important information on material properties. The standards and technologies developed by NIST have led to many very important and diverse advances such as GPS navigation, microelectronics and software standards, and critical standards for building materials which are integral parts of US fire codes. It is thus very appropriate for NIST to develop the expertise and facilities to play a comparable pivotal role in the 21st century in this new era of quantitative biomedicine.

Let me close my remarks by commenting on the strong leadership provided by the current director of NIST, Dr. Patrick Gallagher. Dr. Gallagher indicated at the last VCAT meeting in February, 2010 that he is working with NIST lab directories and senior managers to develop a new NIST structure that will improve NIST's ability to address the pressing needs of US industry and fellow government agencies. He is formulating a significant, exciting new vision for how NIST can best be organized to service its many, diverse stake holders. I believe that this is a great opportunity to reorganize and expand the NIST resources supporting the US biomedical and healthcare industry, and I look forward to working with him to bring about these changes.

In my testimony, Mr. Chairman, you asked me to address several specific questions:

If NIST expands its involvement in performing measurement science to develop measurements, reference materials, reference standards, standard processes, and validation procedures in the biomedical area, what are the current, future and nascent areas of biomedicine that could be best served by NIST and how?

The areas where I see NIST providing the greatest service are:

1. Diagnostic medicine
   - In particular developing standards, consistent protocols, and advancing measurement science in applying quantitative molecular analysis technology to diagnostic tests
   - Supporting the application of the newest generation of quantitative imaging instruments (CT, MRI, ultrasound)
2. Working with the drug development industry to accelerate the drug development process
   - Improving our understanding of the technology needed to perform the measurements necessary to provide accurate assessment of the safety and efficacy of new drugs.
3. Working with universities and private industry to development methods for new classes of therapy enabled by advances in stem cell science. With applications, in diseases such as diabetes and organ replacement
4. Providing a sound basis for measurement science in the area of neuroscience and neuromedicine. With applications in Parkinson's disease and Alzheimer's disease.

Would the following elements assist NIST in ascertaining current and future metrology needs for the biomedical community? If so, how?

- **An advisory board made up of industry experts.**

I recommend that NIST develop several advisory boards comprised of experts from the private sector and other government agencies representing different sectors of the biomedical industry. For example, separate panels could be formed with experts from molecular diagnostics, imaging diagnostics, drug development, medical devices and biomedical materials. These advisory panels should meet regularly with NIST personnel working in these areas to help identify the critical problems that need to be addressed and to establish the most effective strategic and tactical focus for biomedical programs at NIST.

- **A university center for biomedical research**

University collaborations and joint institutes have played an important and very successful role in other NIST programs, and I believe this approach would work extremely well in the biomedical healthcare area. Specifically a university center focused on research into the fundamental measurement science underlying biomedical instrumentation and a joint institute studying the measurement science challenges inherent in the measurement of complex biological systems.

- **A user facility that could be used by industry and academia**

A separate operating unit or laboratory would provide a critical central focus for research at NIST in biomedicine. Such a facility could support visiting scientists from industry to provide input to NIST research activities, as well as physical location for NIST researchers, postdocs, and graduate students to associate with multidisciplinary teams working in similar or related biomedical areas.

BIOGRAPHY FOR THOMAS M. BAER

Thomas Baer is the executive director of the Stanford Photonics Research Center. He has been active in many scientific areas employing optics: atomic and molecular spectroscopy, optical metrology, ultrafast lasers, pulse compression, solid-state lasers, laser scanning fluorometry of blood cells, laser capture microdissection of biopsy samples and microgenomics. He has worked in industry and academia, and has participated in a number of successful collaborations with academic and government research groups, resulting in numerous commercial products that incorporate lasers and optics.

Tom graduated with a BA in physics from Lawrence University and received his PhD in 1979 from the University of Chicago, where he studied atomic physics with Isaac Abella and Ugo Fano. After that, he worked with John Hall at JILA on high resolution spectroscopy and co-invented new techniques for frequency stabilizing lasers.

In 1981, he joined Spectra-Physics (SP), where he held positions as vice president of research and Spectra-Physics Fellow. His research there focused on ultra-fast lasers, pulse compression, diodepumped solid-state lasers and non-linear optics. His group developed and patented the first commercial optical pulse compressor, high power, fiber-coupled diode-pumped solid-state lasers, and mode-locked Ti-Sapphire lasers. His commercial products received several industry awards for design innovation.

After leaving SP, he joined Biometric Imaging (BMI) and changed his research focus to biophotonics. At BMI, he led an interdisciplinary group that developed the scanning laser instruments used in diagnostic tests for bone marrow transplant therapy and immune system monitoring in AIDS patients.

Following his departure from BMI, Tom founded Arcturus Bioscience and served as CEO and chairman until 2005. Arcturus Bioscience pioneered the area of microgenomics—the precise molecular analysis of microscopic tissue samples. Arcturus technology is widely used in life science research laboratories and in molecular diagnostic tests for cancer. He left the company in 2005 and joined Stanford University, where he is the executive director of the Stanford Photonics Research Center and a member of the Applied Physics department. Tom has co-authored scientific publications in the fields of atomic physics, quantum electronics, laser applications and biotechnology.

He is an inventor on over 60 US patents and a co-author on many scientific papers. He was named Entrepreneur of the Year for emerging companies in Silicon Valley in 2000 by the Silicon Valley Business Journal. He is an alumnus of Harvard Business School, and has received the Distinguished Alumni Award from Lawrence University. Tom also serves on visiting committees and advisory groups with NIST, NIH and the Physical Sciences Division of the University of Chicago. He is a Fellow of The Optical Society and the American Association for the Advancement of Science. He served as President of the Optical Society of America in 2009 and is currently serving as Past President.

Chairman WU. Thank you very much. Thank you very much, Dr. Baer.

I think that many of us are very excited about Dr. Gallagher's installation at NIST, and look forward to a long and stable administration there.

And thank you very much for this perspective on the progress of gene sequencing. I don't know if I am more gratified about the progress made, or more concerned about how long it has been since I was a college student.

Ms. Terry, please proceed.

STATEMENT OF MS. SHARON F. TERRY, MA, PRESIDENT AND CEO, GENETIC ALLIANCE

Ms. TERRY. Thanks very much, Chairman Wu, and thank you very much, Congresswoman Biggert, for your introduction. Congresswoman Edwards, and to the Committee.

Today, you are hearing from accomplished researchers and leaders in the fields of their study, from Stanford and Duke. These individuals are scientists, entrepreneurs, biotechnology innovators, and certainly great leaders.

I come here primarily as a mom. I am here today to address the critical link between my experience as a mother, striving for treatments for my kids and millions of others, and the question before this Committee, how could NIST be more effective in influencing innovation in the life sciences?

I begin with a plain statement about NIST and its activities. It can appear to be boring, non-interesting, and terribly esoteric. NIST suffers from being hidden, embedded in the foundational infrastructure of the scientific and early commercial enterprise of innovation, as well as having the thankless task of creating measurement standards for a whole array of scientific disciplines. However, it is precisely because of these elements that this Committee needs to champion a more active role for NIST in the life sciences.

Some have quite convincingly argued that the next century of scientific and technological innovations will be the most profound in the life sciences. NIST is critical to a robust medical, biomedical

enterprise, and must contribute high quality materials, methods, and expertise for the field to advance on a platform of certainty and high quality measurements.

My two children were diagnosed with a genetic disease, pseudoxanthoma elasticum, 15 years ago. As a result, I chose to leave my career as a college chaplain, and become involved with the life sciences and biotechnology in search for a solution for their disease. I started a foundation called PXE International, organized patient populations around the world, created a bio-bank, isolated the disease gene, developed a commercial diagnostic, created animal models, and have supported clinical interventions for adults living with the disease.

We still do not have a treatment intervention for my children or any of the individuals with this disease, and we are still hard at work. This is typical of most diseases. We have been stymied by a number of measurement and experimental roadblocks in advancing clear understanding of the disease, and the function of the altered protein that causes pseudoxanthoma elasticum. We have run smack into the wall of both scientific and technological limitations.

My foundation's research work has been written about in prestigious journals as a model of innovation, and an example of the power of patient-driven translational research. Some have said our work will change the field. But I am telling you that we are limping toward the finish line of our objective, because of the current limitations in measurement science. This science has real world impact on patients, families, and communities.

At this time, each provider of biomedical tests and therapies is creating their own system, leading to widespread inconsistencies between these practices. Americans believe they are receiving healthcare that is high quality, accurate, valid, and consistent. They do not realize that a PSA [prostate-specific antigen] test from one lab cannot be compared to another lab. They have no idea that the four million newborns who are screened every year are subjected to different screening cutoffs in every state program, for the somewhere between 29 to 54 tests. The states count the number of screens they conduct differently from one another, because there are no standards. The 2,700 genetic tests that are now protected by GINA, thanks to Congresswoman Biggert and others, listed in gene tests, are purported to be actually hundreds of thousands of tests, because of the variability across labs performing these tests. No one knows how many tests there are, and there are only standards for 35 of the analytes used in all these tests.

Every technology manufacturer applies relevant measurement technology with their own standard references and controls. For example, housekeeping genes and control agents. The FDA, as a regulatory agency, is challenged with ascertaining the accuracy and precision of these technologies based on the manufacturer-supplied standards. Ultimately, they must trust the manufacturers.

Just this morning, I was at NIH, where Secretary Sebelius announced a collaboration between NIH and FDA, and Drs. Collins and Hamburg announced that they will be doing regulatory science and the study of that science. Very seriously, there is not any way they can do it without the standards that NIST needs to produce, and a collaboration in that regard is necessary.

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 healthcare, sometimes to the 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' increased support, I believe NIST should create a life sciences infrastructure catalog and distribution system for reference materials and standards for quality assurance for all clinical diagnostic tests, integrate measurement standards and technologies into the FDA regulatory regime, partner with the National Institutes of Health on resolving the measurement challenges at the intersection of patient care, and 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 your Committee.

[The prepared statement of Ms. Terry follows:]

PREPARED STATEMENT OF SHARON F. TERRY

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 manufacturers' 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 meas-

urement 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 *all* 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.

BIOGRAPHY FOR SHARON F. TERRY

Sharon F. Terry is President and CEO of the Genetic Alliance, a network transforming health by promoting an environment of openness centered on the health of individuals, families and communities. She is the founding Executive Director of PXE International, a research advocacy organization for the genetic condition pseudoxanthoma elasticum (PXE). Following the diagnosis of their two children with pseudoxanthoma elasticum (PXE) in 1994, Sharon, a former college chaplain, and her husband, Patrick, founded and built a dynamic organization that enables ethical research and policies and provides support and information to members and the public.

She is at the forefront of consumer participation in genetics research, services and policy and serves as a member of many of the major governmental advisory committees on medical research, including the HIT Standards Committee for the Office of the National Coordinator for Health Information Technology, liaison to the Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children and the National Advisory Council for Human Genome Research, NHGRI, NIH. She serves on the boards of GRAND Therapeutics Foundation, the Center for Information & Study on Clinical Research Participation, The Biotechnology Institute, National Coalition of Health Professional Education in Genetics, and the Coalition for 21st Century Medicine. She is on the steering committees of Genetic Association Information Network of NHGRI, the CETT program, the EGAPP Stakeholders Group, and the editorial boards of *Genetic Testing and Biomarkers*, and *Biopreservation and Biobanking*, and the Google Health and Rosalind Franklin Society Advisory Boards. She is the chair of the Coalition for Genetic Fairness that was instrumental in the passage of the Genetic Information Nondiscrimination Act. She is a member of the IOM Roundtable on Translating Genomic-Based Research for Health. In 2005, she received an honorary doctorate from Iona College for her work in community engagement and haplotype mapping; in 2007 received the first Patient Service Award from the UNC Institute for Pharmacogenomics and Individualized Therapy; and in 2009 received the Research!America Distinguished Organization Advocacy Award. She has recently been named an Ashoka Fellow.

Ms. Terry is a co-founder of the Genetic Alliance Biobank. It is a centralized biological and data [consent/clinical/environmental] repository catalyzing translational genomic research on rare genetic diseases. The BioBank works in partnership with academic and industrial collaborators to develop novel diagnostics and therapeutics to better understand and treat these diseases. Along with the other co-inventors of the gene associated with PXE (ABCC6), she holds the patent for the invention. She co-directs a 33-lab research consortium and manages 52 offices worldwide for PXE International.

Terry is committed to bringing together diverse stakeholders that create novel partnerships in advocacy; integrating individual, family, and community perspectives to improve health systems; and revolutionizing access to information to enable translation of research into services and individualized decision making. She lives with her husband Patrick and their two children in Maryland.

Chairman WU. Thank you very much, Ms. Terry. Thank you for your work as an advocate. I think that many children would benefit from your work.

Your testimony has already opened eyes on this panel, in that I don't think any of the Members knew that no two PSA tests are comparable. That is really quite stunning.

Dr. Sullivan, please proceed.

STATEMENT OF DR. DANIEL SULLIVAN, PROFESSOR AND VICE CHAIR, RESEARCH IN RADIOLOGY, DUKE UNIVERSITY MEDICAL CENTER AND SCIENCE ADVISOR, RADIOLOGIC SOCIETY OF NORTH AMERICA

Dr. SULLIVAN. Thank you, Chairman Wu and Members of the Committee. Thank you for this opportunity to offer brief testimony on how NIST could help better serve the needs of the biomedical research community in the 21st century.

It is increasingly clear that the value of medical scans would be significantly greater if we could extract more objective, quantitative information from scans, rather than relying on radiologists' subjective, qualitative interpretations.

This is an important priority for the RSNA, and we have several related activities, including the Quantitative Imaging Biomarkers Alliance, which brings together representatives from the medical scanner manufacturers, the pharmaceutical industry, and academicians, to work with manufacturers, to have them engineer medical scanners to be accurate measuring devices and not simply imaging devices. And also, the Imaging Biomarkers Roundtable, which facilitates communication among many organizations.

In my brief testimony today, I would like to show you three examples of common diseases, using three different scanning methods, to illustrate why standards for extracting quantitative information are critically needed. First, the CT scan of a patient with chronic obstructive pulmonary disease, or emphysema. All digital images are made up of numbers. Here are some of the numbers behind the pixels in this scan. These numbers carry tissue information, but to be useful in medical care, these numbers have to be standardized, so that we know, for example, what tissue quality each number signifies on a given scanner, and what it means when that number changes. Right now, such standardization does not exist.

For example, here, the red areas are areas of destroyed lung tissue, identified by a computer analyzing these numbers. A percentage number is what the treating physicians want to know, so that they could determine from future scans whether the patient is responding to therapy or not. If the patient is not improving, or getting worse, physicians have other treatment options they could use.

However, right now, we radiologists cannot provide this kind of objective information about the actual percentage of lung destroyed, or other measurements, because the numbers are not standardized.

The second example is cancer. These are PET [positron emission tomography] scans of a patient with lymphoma. PET scans show a radioactively tagged glucose that is being used in the body. In these scans, yellow is the highest level of glucose uptake. Because tumor cells are growing so rapidly, they take up much more glucose than normal cells, and the yellow areas represent tumor. If this glucose activity decreases after a couple of weeks of therapy, as shown here, it is a good sign the therapy is working. Oncologists need to know this early, because if the therapy is not working for a particular patient, there are usually alternatives that can be given.

However, there are insufficient standards for PET scanners to ensure that you would get the same number for the amount of glucose measured in a tumor on one scanner as on another scanner, or even on the same scanner after an interval of a few weeks.

My third example is Alzheimer's disease. We desperately need objective measures to determine whether lapses of memory are due to the ordinary stresses of everyday life or early dementia. Without objective markers for diagnosis, or to determine whether the disease is responding to new drugs or not, it will be impossible to develop effective therapies.

One objective measure that could be used is the volume of the hippocampus on MRI [Magnetic Resonance Imaging] scans, as shown here. However, subtle volume differences in this small brain structure cannot be discerned by radiologists subjectively reading MRI scans. The scans have to be done on scanners that are calibrated with appropriate reference objects so that computer algorithms would calculate the same accurate and reproducible hippocampal volume no matter which scanner was used.

These are just a few examples where clinicians clearly need more objective diagnostic tests. NIST can be a critical participant to help manufacturers meet this need. We need NIST to develop reference materials, standards, and validation procedures in the biomedical imaging area, especially for CT, PET, MRI, and medical optical imaging.

To determine the metrology needs for the biomedical imaging community, NIST should appoint an advisory board made up of both industry experts and representatives of the imaging device users, such as patient advocates and professionals.

Prior collaborations between scientists at NIST and university centers have been very productive. Such collaborations should be fostered by establishing one or more NIST academic centers for biomedical research. The private sector will continue to be a source of innovative reference objects, algorithms, and other devices for quantitative imaging. A NIST managed user facility that could be used by industry and academic developers to test their devices under standardized, controlled conditions would be an important asset.

Finally, and very importantly, there is a critical need for a neutral broker, trusted by the public, to develop an accreditation and performance levels program, with associated policies and procedures. NIST is ideally suited to perform this role.

Thank you again, Mr. Chairman and Members of the Committee, and I appreciate this opportunity to express the imaging community's view on this important topic.

[The prepared statement of Dr. Sullivan follows:]

PREPARED STATEMENT OF DANIEL SULLIVAN

Chairman Wu and Members of the Subcommittee—Thank you for this opportunity to offer brief testimony on *How NIST Can Better Serve the Needs of the Biomedical Research Community in the 21st Century*.

I am Daniel Sullivan, Professor and Vice Chair for Research in Radiology at Duke University Medical Center, and Science Advisor to the Radiological Society of North America (RSNA). RSNA is an international organization with more than 40,000 members (*http://www.rsna.org/*). Its mission is to improve patient care through education and research. RSNA hosts one of the world's largest annual medical meetings, publishes two highly respected peer-reviewed journals, offers opportunities to

earn CME, and provides research and education grants to young investigators. It is not a lobbying organization and has no government relations office or staff. My area of expertise is in diagnostic radiology and my remarks will therefore focus on that topic.

Statement of the Problem:

The quality and cost of health care are major issues facing all Americans. In the past decade, discoveries about the basic biology of disease and technological advances in computers, imaging devices and laboratory methods have made it possible to imagine treatment plans that are individualized and optimized for each patient's unique pattern of disease. The term "Personalized Medicine" is used frequently these days. Of course, physicians have always, probably from the time of Hippocrates, tried to personalize their approach to treating patients based on the information available. What's different now is that we can get basic molecular information from each patient about the genetic and biochemical basis of their disease. Using each patient's unique biochemical signature of disease to individualize treatment is what the modern use of the term "personalized medicine" refers to.

However, there are some major roadblocks on the path toward that vision. One is that diagnostic medical tests suffer from a lack of standards—in far too many cases we do not know whether test results are either accurate or comparable over space and time. Even though approximately 70 percent of health care decisions are based upon results from a test performed in a clinical laboratory, standards exist for only about 10 percent of the 700 most commonly ordered clinical tests. In the area of medical imaging, where it is estimated that U.S. healthcare consumers spent a combined $50 billion on medical imaging tests (MRI, CT scans, etc.) in 2008, the software and standards needed to enable physicians to extract and compare relevant data and to make definite determinations as to whether or not a tumor actually shrank or grew do not exist. These measurements and standards shortcomings result in repeat testing, misdiagnosis, and ineffective treatment decisions—all of which contribute to a second major roadblock on the path toward personalized healthcare, the dramatic rise in health care spending. These dramatic cost increases are being driven by multiple inefficiencies throughout the health care system. One area in which significant improvements could be made, which would both decrease costs of and improve the overall quality of healthcare, is in developing and implementing better validated standards for laboratory medicine and medical imaging. Although modern clinical imaging methods are widely used, it is increasingly clear that the value of clinical imaging would be significantly enhanced if we moved toward extracting more objective, quantitative information from scans rather than relying on radiologists' variable, subjective, qualitative interpretations, which is the norm now. My comments today are focused on the need to develop measurements and standards infrastructure for medical imaging.

Background Activities:

In addition to its high standing in the professional communities, RSNA enjoys a reputation as trusted, neutral party for industry. My role with the RSNA is to develop and coordinate programs to move radiology from subjective interpretations to objective, quantitative interpretations (i.e., "imaging biomarkers"). In November 2006 the RSNA convened a group of stakeholders to advise the organization on what role it could most constructively play with regard to imaging biomarkers. The RSNA subsequently launched, and continues to sponsor, multiple initiatives to promote the quantitative, objective extraction of information from clinical images, focusing on imaging in clinical trials as an appropriate approach to establishing the necessary groundwork to support the use of imaging as biomarker.

Among our various activities I would like to highlight just two: the Quantitative Imaging Biomarkers Alliance (QIBA) explicitly brings together representatives from the medical device imaging companies, representatives from the pharmaceutical industry and academicians to improve the accuracy and reproducibility of numbers extracted from medical scans (*http://www.rsna.org/Research/giba_intro.cfm*). Current scanners can be thought of as elaborate cameras, designed to produce exquisite pictures. They are not engineered to make precise measurements. A "sound bite" version of QIBA's mission is to encourage the vendors to produce ***measuring devices*** rather than just ***imaging devices***.

The second activity to mention today is the Imaging Biomarkers Roundtable, which brings together representatives from any and all organizations with an interest in or activities related to improving quantitative imaging biomarkers (*http://www.rsna.org/Research/roundtable.cfm*). These activities were in fact started by a joint meeting including various government agencies, with a particularly important

workshop in 2005 hosted by the NIST. Although I am not speaking on behalf of all these organizations today, my remarks are informed by the opinions of a diverse array of stakeholders. The Imaging Biomarker Roundtable and the technical committees formed under QIBA together comprise a collaborative enterprise addressing the need for quantitative imaging methods. Over the last two years, it has convened regular working groups for specific actions needed for specific imaging biomarkers, and proposed an organizational context that has potential to be self-sustaining to move the industry forward.

Clinical Examples:

In my brief time for testimony today I would like to show you three examples of common diseases, using 3 different scanning methods, where standards for extracting quantitative information are critically needed. NIST's participation in this endeavor is essential.

First, some technical background. All digital images, whether on your digital cameras, your computer screens, or a medical scanner, are made up of numbers. Every pixel or voxel has a number associated with it. Figure 1 shows a chest CT scan with some of the underlying numbers superimposed on the scan. Those numbers carry information, but to be useful in medical care those numbers have to be standardized so that we know, for example, what tissue quality each number signifies, and what it means when that number changes over time. Right now, such standardization does not exist.

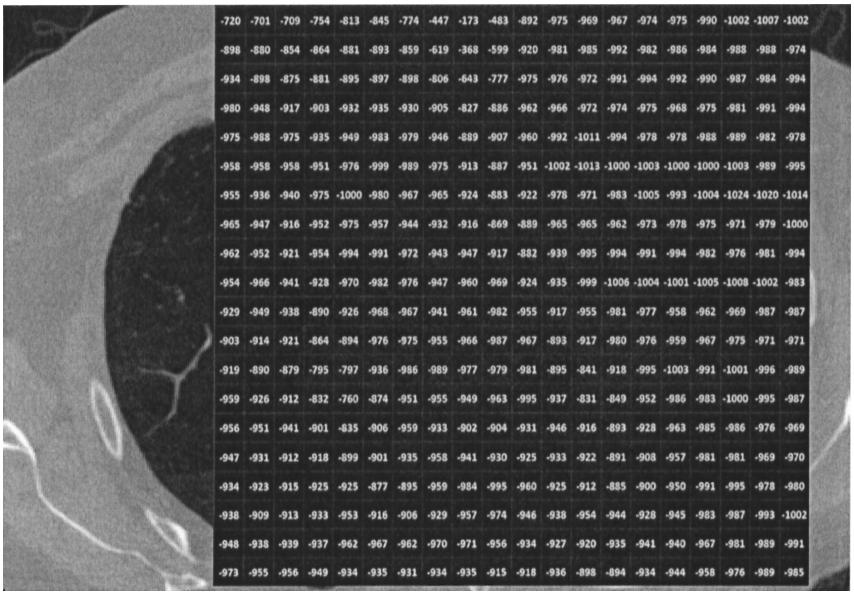

Figure 1. Pixel numbers superimposed on a chest CT scan.

The first clinical example is chronic obstructive pulmonary disease, COPD, often called emphysema. Figure 2 shows a patient who has COPD, and all the black areas are areas of destroyed lung tissue. The radiologist's interpretation would include a general statement about the degree of COPD present, but no objective information about, for example, the actual percentage of lung destroyed, or the thickness of the walls of the airways. Those objective measures are what the treating physician wants to know, so that he or she can determine on the next scan whether the patient is responding to therapy or not. If the patient is not improving or getting worse, the physician has other treatment options that he or she could use. The treating physician needs to have such objective measures of response prior to the time that the anatomic changes are so obvious that a radiologist can see it on the film. Right now we radiologists cannot provide that information because the numbers are not standardized.

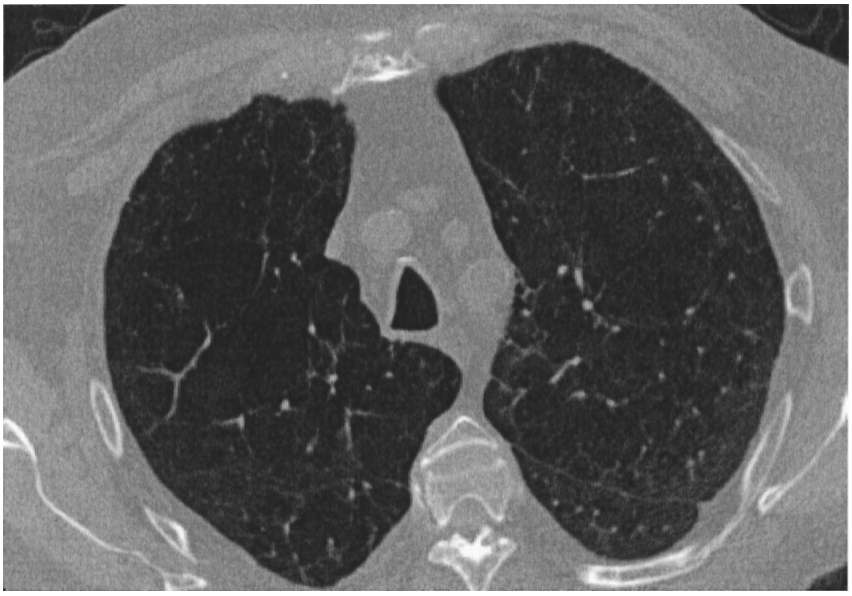

Figure 2. Chest CT scan of a patient with COPD.

The second clinical example is cancer. PET scans, or positron emission tomography scans, are now widely available at hospitals in the US and reimbursed by third-party payers for cancer. These scans show where glucose is being used in the body. Tumor cells take up much more glucose than normal cells because they are so rapidly growing. For PET scanning, patients receive an intravenous dose of glucose that has a radioactive label. The amount of radioactivity is very small, but the amount of uptake activity in the tumor tells us how actively the tumor is growing. If this activity has decreased after therapy has been given for a couple of weeks, it is a very good sign that the therapy is working. Oncologists need to know this with accuracy because, if the therapy is not working for a particular patient, there are often alternatives that can be given. However there are insufficient standards for PET scanners to ensure that you would get the same number for the amount of glucose measured in a tumor on one scanner as on another scanner, or even on the same scanner after an interval of a few weeks or more. NIST has already been extremely helpful in this area by developing a reference object with a source of germanium-68 radioactivity that is traceable back to a source at NIST. This paves the way for groups such as QIBA to promulgate recommendations for calibrating scanners that will improve the comparability of measurements from one scanner to another. However, there is much that remains to be done, and continued participation by NIST experts is essential. Figure 3 is a combined PET/CT scan of a patient with lymphoma, showing a decrease in glucose uptake (yellow) after therapy has been given.

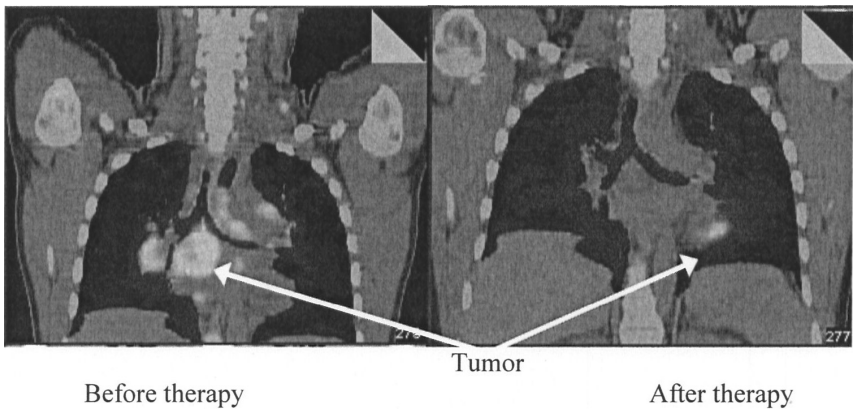

Figure 3. Combined PET/CT scans of lymphoma before and after therapy.

The third clinical example is Alzheimer's disease. Many of us experience lapses of memory such as forgetting where we left our keys or what we came into the kitchen for, and sorting out whether such symptoms are due to early dementia or simply the stress of everyday life is extraordinary difficult. We desperately need objective measures for Alzheimer's and other dementias. This is true not only for routine clinical diagnosis in individual patients but also for drug trials to develop therapies for Alzheimer's. Without objective markers of whether the disease is responding to a drug or not, it will be impossible to develop effective therapies. A reliable diagnosis of Alzheimer's will probably require a combination of objective tests, as is increasingly true for many diseases, and there are several imaging candidates for such a multi-factorial approach for Alzheimer's disease. One such imaging test, for which there is considerable supporting evidence, is the volume of the hippocampus on MRI scans (Figure 4). However, the subtle volume differences between normal and abnormal in this small brain structure, or small changes over the course of several months, cannot be discerned by radiologists subjectively reading MRI scans. The scans need to be done on scanners that are calibrated with appropriate reference objects, and the images need to be acquired with standardized image acquisition methods, so that computer algorithms would calculate the same accurate and reproducible hippocampal volume no matter which scanner was used.

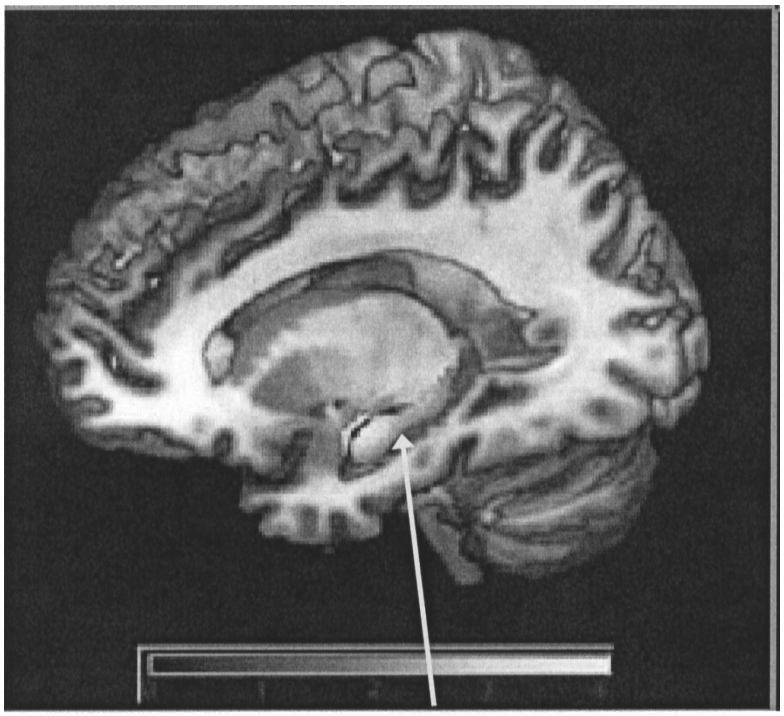

Figure 4. MRI scan of Alzheimer's Disease.

Discussion:

It has been well-established in many industries and in scientific research that reference standards play a critical role for all stakeholders. Reference standards provide a transparent and widely available toolkit that enables regulators, manufacturers, researchers, and others to know whether a product is what it purports to be. Comparable processes do not exist today for many biomedical products and activities. NIST could apply its in-house expertise to enhance existing and develop new analytical tools for the biomedical sector, characterizing relevant reference standards and providing a repository for such reference standard materials. These improvements are necessary not only to improve routine clinical care, but also to reduce the size and time of clinical trials. The "statistical noise" due to the current variability in diagnostic methods forces investigators to accrue large numbers of subjects to clinical trials to achieve statistical validity. In addition, the adoption of standardized analytical methods and consistent reference standards would greatly enhance the interactions of companies with the FDA. Such improvements would establish a consistent approach to comparability assessments and create a level playing field for all companies.

NIST has the potential to develop the measurement tools to support improved accuracy and reproducibility of current clinical diagnostics, enable quantitative and comparable medical imaging on current and future imaging platforms, and develop the methods necessary to enable and validate the next generation of medical measurement tools. Improvements to the accuracy and precision of clinical and diagnostic measurements will have significant short- and long-term economic impacts in the areas of drug/therapeutic development, and most importantly, the quality of patient care.

It is clear that the development of standard methods, validation procedures, and reference materials for a variety of imaging methods will be of direct benefit to patients as well as to the biotechnology industry. If researchers working in Federal agencies such as NIST, government regulators, industry and academic scientists work together in this effort, it is much more likely that the outcomes will be suc-

cessful—for government, for industry, and ultimately for the benefit of patients. NIST has begun to work with industry, academia, and other government agencies to identify the measurement tools and standards required to improve the quality of current biomedical measurements. NIST has made notable contributions already in the area of reference standards for x-ray, CT, PET and MRI (*http://www.nist.gov/public_affairs/releases/mri.html)* (*http://collaborate.nist.gov/twiki-div818/bin/view/Div818/BioMagneticImaging*). A list of representative publications is included in the Appendix to this written testimony. This preliminary work has set the stage (and raised community expectations) to establish a coordinated program aimed at providing national standards for all the major imaging diagnostic methods being used clinically, and supporting industrial and medical researchers in developing new and better medical imaging instruments and methods.

An expanded NIST program in quantitative medical imaging should be focused on:

- Developing quality assurance processes for CT, PET, MRI, and Medical Optical clinical imaging.
- Identifying, evaluating, and minimizing or eliminating sources of variability and error in imaging modalities.
- Developing well-characterized phantoms (reference objects) to reliably and accurately calibrate a variety of instruments and systems.
- Developing measurement methods traceable to NIST-maintained standards.
- Developing standardized image databases for comparing internal dose models for radiation-based imaging modalities, and also for evaluating image processing algorithms.
- Conducting and evaluating round-robin inter-comparisons of devices and software.
- Working with industry and agencies to optimize image processing and reconstruction software, and to develop automated (or semi-automated) image analysis.
- Implementing a proficiency testing process to ensure the inter-comparability of imaging data across different clinical sites and across different modalities.
- Developing standards and methods for inter-comparability of clinical imaging data to support improved analysis of change to determine drug efficacy.

This work will improve healthcare quality and lower costs through:
Improved reliability of medical imaging, resulting in:

- Increased accuracy of medical imaging
- Greater comparability over time and space
- Fewer misdiagnoses and unnecessary repeated tests.
- More accurate monitoring of disease progression and therapeutic response
- Earlier detection of disease facilitating more effective treatment decisions
- Improved reliability and accuracy of clinical trial data.

Increased quality of the information that goes into electronic health records, resulting in:

- Fewer medical errors
- Increased efficiency in healthcare delivery to mobile patients
- Greater confidence for patients and healthcare providers in the information used to make medical decisions.

NIST scientists have had productive interactions with academic scientists in the imaging community, and the expanded program described above would be enhanced by NIST–Academic Centers of Excellence for Biomedical Research. Industry could contribute to NIST–academic centers in terms of problem specification.

Another important collaborator would be the American Association of Physicists in Medicine (AAPM). Currently, the AAPM produces many detailed scientific, educational and practical reports for technology and procedures in medical imaging and radiation therapy. These reports include specific processes for radiation dose measurement and calibration, quality assurance and peer review. These are presented in educational forums at national and regional meetings and are also publicly available. AAPM has recently called attention to the need for a technology assessment institute to provide industry with independent pre-market or post-market evaluations. AAPM could provide key complementary expertise to the scientists at NIST. For example, when well-defined physical or engineering differences exist between products, unrelated to different anatomic or physiological phenomenon, comparative effectiveness can be determined by assessing technology using quantitative metrics.

This would be particularly useful and cost-effective in situations where simple modifications of an existing medical technology are introduced or a new technology is available that is changing rapidly in its potential for proving efficacy. An example includes the optimization of radiation dose in CT. Image quality can be assessed quantitatively on different CT scanners at the same radiation dose levels, providing an objective measure of comparative effectiveness that may not require a clinical trial. These comparisons could also include the analysis of safety mechanisms to avoid accidental over doses as well as a review of quality control procedures. Another example is the comparative evaluation of mammography, breast CT, and breast tomosynthesis in detecting and assessing the extent of breast cancer using various metrics of physical and psychophysical image quality (e.g., spatial resolution, noise, or conspicuity) and balancing the results in terms of cost and radiation dose level. In those cases and at those times, relatively inexpensive physical measurements or observer-based diagnostic accuracy studies may be very appropriate. A biomedical research group or institute focusing on the science behind those topics would be valuable.

In addition to scientists at NIST and at academic centers, the private sector will continue to develop reference objects, software and other products that can contribute to the goal of more accurate and reproducible quantitative measurements in imaging. A valuable activity for NIST would be to create a user facility where industry and academic scientists can test, demonstrate and calibrate their products for optimal use in this arena. For example, different imaging modalities currently have either none or too many phantoms that are not standardized, evaluated etc. There are many proprietary solutions that are difficult to compare and to integrate. The imaging industry would benefit from a standard for equipment development and sales. The pharmaceutical industry needs it for clinical testing and having a comparable quality information source (comparable to clinical lab data with its existing quality standards).

Very importantly, there is a critical need for a neutral broker, trusted by the public, to develop an Accreditation of Performance Level program, with accompanying policies and procedures. NIST is ideally suited to perform this role. An example of one function of such an accreditation program would be for NIST to be the secure holder of image databases. For the independent test of a new algorithm, NIST could have the system run on randomly selected scans from its database based on the type of population requested. NIST would give the sensitivity and specificity of the system, without informing the company about the specific cases. For each testing event a different distribution of cases would be selected for the examination. This would preserve the integrity of the testing cases and also allow testing across applicable populations.

Conclusion:

Clinicians clearly need more objective diagnostic tests, and the imaging device manufacturers want to provide their customers with such tools. NIST can be a critical participant in this endeavor because of its Mission, because of its experience in working with industry on metrology issues, and because of its expert staff. Though it is possible for the private sector to pursue many of these ideas without NIST help, it is easy to believe that they would be strengthened were NIST to be involved on one or more of these ways. Since the foundational meeting in 2005, we have made great progress in the private sector and continue to do so. Now is a very auspicious time to loop back and again consider the most appropriate role that NIST can play in what is arguably an inevitable development in the radiology community for the public good.

- Speaking on behalf of the imaging community in general, we need NIST to expand its involvement in performing measurement science to *develop reference materials, reference standards, standard processes, and validation procedures in the biomedical imaging area*, especially for CT, PET, MRI, and medical optical clinical imaging.
- To determine current and future metrology needs for the biomedical imaging community, NIST would be well served by an *advisory board made up of both industry experts and representatives of imaging device users* (patient advocates and professionals).
- There is precedent for excellent progress being made from collaborations between scientists at NIST and university centers. Such collaborations would be enhanced in the future by establishing *one or more NIST–Academic Centers for Biomedical Research*. An example of such a Center would be one to determine the sources of variability in numbers derived from CT, MRI, PET and optical scanners, and developing mitigation strategies for the sources of vari-

ance. This is an activity that no single manufacturer can do alone, and is an activity that academic physicists or engineers are not funded to do.

- The private sector will continue to be a source of innovative reference objects, algorithms, and other devices to improve accuracy and reproducibility of imaging devices. A NIST-managed *user facility that could be used by industry and academic developers* to test their devices under standardized, controlled conditions would be an important asset for this work.
- Finally and very importantly, there is a critical need for a neutral broker, trusted by the public, to develop an *Accreditation of Performance Level program*, with accompanying policies and procedures. NIST is ideally suited to perform this role.

Thank you again Mr. Chairman and Members of the Committee. I appreciate this opportunity to express the imaging community's views on this important legislation. I welcome your questions.

Appendix

Representative Medical Imaging Publications from NIST:

1. Coletti JG, Pearson DW, DeWerd LA, **O'Brien CM**, **Lamperti PJ**. Comparison of exposure standards in the mammography x-ray region. Med Phys 1997;**24**:1263–7.
2. DeWerd LA, Micka JA, Laird RW, Pearson DW, **O'Brien M**, **Lamperti P**. The effect of spectra on calibration and measurement with mammographic ionization chambers. Med Phys 2002;**29**:2649–54.
3. Clarke LP, **Sriram RD**, **Schilling LB**. Imaging as a Biomarker: Standards for Change Measurements in Therapy Workshop Summary (2006). Acad Radiol 2008;**15**:501–30
4. Baer TM, **Clark CW**, **Karam L**. "Programs Supporting Quantitative Imaging in Biomedicine at the National Institute of Standards and Technology," In: Mulshine JL, Baer TM, editors. Quantitative Imaging Tools for Lung Cancer Drug Assessment. New York: Wiley; 2008. p. 111–22.
5. **Zimmerman BE**, **Cessna JT**, **Fitzgerald R**. Standardization of ^{68}Ge/^{68}Ga Using Three Liquid Scintillation Counting Based Methods. J Res Natl Inst Stand Technol 2008;**113**:265–80.
6. **Levine ZH**, Grantham S, Sawyer DS IV, Reeves AP, Yankelevitz DF. A Low-Cost Fiducial Reference Phantom for Computed Tomography. J Res Natl Inst Stand Technol 2008;**113**:335–40.
7. **Karam LR**, Radiation-based quantitative bioimaging at the National Institute of Standards and Technology. J Med Phys 2009;**34**(3):117–21.
8. **Zimmerman B**, Kinahan P, Galbraith W, Allberg K, Mawlawi O. Multicenter comparison of dose calibrator accuracy for PET imaging using a standardized source. J Nucl Med. 2009;**50**:123.
9. **Levine ZH**, Li M, Reeves AP, Yankelevitz DF, Chen JJ, Siegel EL, Peskin A, and Zeiger DN. A Low-Cost Density Reference Phantom for Computed Tomography. Med. Phys. 36:286:288 (2009)

BIOGRAPHY FOR DANIEL SULLIVAN

Daniel C. Sullivan, M.D. is Professor and Vice Chair for Research, Department of Radiology at Duke University Medical Center, coordinator of imaging activities for the Duke Comprehensive Cancer Center (DCCC), and Director of the Imaging Core of the Duke CTSA program. He is also Science Adviser to the Radiological Society of North America (RSNA). He completed radiology residency and nuclear medicine fellowship in 1977 at Yale-New Haven Hospital, and was in academic radiology for 20 years before joining the National Cancer Institute at NIH in 1997. From 1977 to 1997 Dr. Sullivan held faculty appointments at Yale University Medical Center, Duke University Medical Center, and University of Pennsylvania Medical Center. His areas of clinical and research expertise are in nuclear medicine and oncologic imaging. From 1997 to 2007 Dr. Sullivan was Associate Director in the Division of Cancer Treatment and Diagnosis of the National Cancer Institute (NCI), and Head of the Cancer Imaging Program (CIP) at NCI. Dr. Sullivan's current responsibilities at Duke include heading the Imaging Core of Duke's CTSA program, and the Imaging Program in Development for the Duke Comprehensive Cancer Center. These activities focus on improving the use of imaging as a biomarker in clinical trials and facilitating translational research involving new and established imaging methods.

In his role with the RSNA Dr. Sullivan coordinates integration of a wide range of national and international activities related to quantitiative imaging, including the evaluation and validation of imaging methods as biomarkers in clinical research.

Chairman WU. Thank you very much, Dr. Sullivan.

At this point, it is appropriate to open for questions. I want to let everyone know that votes will be called fairly soon on the floor.

Mr. Smith has informed me that he has some scheduling challenges in coming back after the votes, as do I, and unless Members object, I will do my level best to get through a first round of questions for all Members. And I want to thank the witnesses for making the trip here, but we will also get you questions in writing through the staff, and look forward to your responses to all.

So, my five minutes. Dr. Baer, you referred to this, and I would be interested in hearing from the entire panel about this. NIST has had some role in biologics, and yet, it has not played a significant role in standards-setting for the healthcare industry as a whole.

What do you see as impediments, what has prevented the healthcare industry from using NIST more broadly, and what do you think NIST can contribute to some of the current challenges. I know that much of the testimony went to that, but I would like to give you all another pass at this, because I think it is such an important topic.

Dr. Baer, would you like to go first?

Dr. BAER. That would be fine, Chairman Wu.

I think NIST has tremendous capacity to supply the perspective on standards development and building consensus within the biomedical, bioscience research area. So, there is no lack of will or perspective.

I think that at NIST, they do lack some of the expertise and personnel in the drug development area, and they also lack the appropriate interfaces to the pharmaceutical and drug development industry.

And I think establishing those interfaces through an advisory panel, as has been suggested, is an excellent first step. And then, I think we have to do a very serious gap analysis, in terms of the personnel and expertise at NIST, to see do they have the appropriate personnel there to address this rapidly changing industry within the biomedical and healthcare sector.

Ms. TERRY. I certainly would agree with that, and I think the industry, while not eager for standards in some ways, is very eager in other ways. And so, I think in the development of diagnostics, of imaging, they are looking for ways to make these measures.

And what I have seen at NIST, also, in my work with them, but largely on genetic testing, is excellent individuals who really want to do the best job, but don't seem to have the overall structural or architectural support they need there, and so——

Chairman WU. You mean in the organization?

Ms. TERRY. In the organization, and so a division or a program of biological or biomedical metrology would seem to make the greatest sense to me.

Dr. SULLIVAN. I would just add I think it is an organizational matter of creating a formal program there, because biology is quite complex. Every patient is unique. It isn't quite the same as developing other types of devices in industry, and I think some of the

staff there would benefit from an ongoing interaction with what the real clinical problems are, and how it relates to the measures.

Chairman WU. OK, then let me follow that up, and just go right down to how do you see the organizational structure at NIST best centered on, say, a joint university/NIST research center, biomedical research center, or, and something that includes industry, also? Let us just go across the row again.

Dr. BAER. Well, I think NIST has shown, in many occasions, the benefits of working closely with academia, and I think joint institutes, joint research centers, have proven to be one of the best ways for NIST to advance measurement science.

So, I think that is an excellent approach. However, I do feel that NIST needs at its Gaithersburg or Boulder facility, a center of expertise, as Dr. Sullivan was saying, where they can guide these interactions, and they also need to have that center properly interfaced to industry.

Chairman WU. Are they short on personnel, or do they have the people, but just not properly organized?

Dr. BAER. I think there are some distinct gaps. I feel that they definitely lack sufficient experts in the drug development industry and knowledge of the drug development industry in other areas of bioimaging and molecular analysis. So, there is definitely a lack of personnel.

I also think that there is a need for a centralized organization. Many of these individuals are located in different laboratories. And the VCAT has commented, in several reports, that though they do expert work on their own, they are not coherent. They are not organized efficiently, because they are separated across different locations and different facilities.

So it is both a lack of personnel and a lack of real central focus.

Chairman WU. Thank you, Dr. Baer. My time is expiring, but I want to give Ms. Terry and Dr. Sullivan a cut at this question.

Ms. TERRY. So, I will be quick.

So, I completely agree with that, and in addition, Chairman Wu, to your question, I would say that the novel partnership between academia, industry, and government, done well, is the right thing here. Each of them have very different things to bring to the equation, and they really could make the right package for biomedical sciences.

Chairman WU. Thank you very much. Dr. Sullivan.

Dr. SULLIVAN. And I would just add, I think there are two separate things here. One is the partnerships, the collaborations, that can take place anywhere, sort of virtually. Second, I think there does need to be a physical user facility, Boulder might be a place, or Gaithersburg, where there can be the machines to document compliance with profiles and standards.

Chairman WU. Would the Neutron Facility be one of the important physical assets?

Dr. SULLIVAN. Could be. Could be part of that. Yes.

Chairman WU. OK. Thank you. Mr. Smith's five minutes.

Mr. SMITH. Thank you, Mr. Chairman, and I will try to be quick.

Dr. Baer, you mentioned in your testimony interaction with NIST on development electronic medical standards. Where are we in the process?

Dr. BAER. Well, I think NIST has been tasked to be a key player in this whole effort, and the Information Technology Lab, under the direction of Cita Furlani, is being very effective in leading the discussion of these standards.

I think this is an enormous challenge, and requires the coordination of both the private sector and the government sector to accomplish the task. I think they are making great progress, and I think it is one of their, if not their highest priority, it is one of the major priorities in the ITL [Information Technology Laboratory] Lab, and I greatly admire the efforts that Cita and her staff have put into this.

I think they are making tremendous progress.

Mr. SMITH. So, how far off would you say?

Dr. BAER. I think that is best to ask Cita Furlani. What I will tell you is it is an enormous challenge, and they have been making good progress. I think that Cita is the best person to ask that—answer that question.

Mr. SMITH. OK. All right. Thank you.

And Dr. Sullivan, in the medical imaging field, what percentage of clinics and other organizations use the suggestions or standards set out by the Radiological Society of North America, RSNA, and what interaction does RSNA have with NIST in standards development?

Dr. SULLIVAN. The programs that I described on the slide are relatively new, only about a year and a half old, and we do have representatives from NIST involved in our technical committees—been very effective working with the physicists who are at academic sites.

So, the guidelines, we call them profiles from that program, because we don't want to call them standards or recommendations, but they are relatively immature at this point, so we are not yet in a compliance phase, but we do need a compliance phase, and that is where NIST could be the key player.

Another organization, the American College of Radiology, that I did not mention, which is a large organization, does have what is called appropriateness guidelines for clinical practice, and virtually all radiologists in all medical centers follow those. But they don't get to the kinds of standards we are talking about in the scanners.

Mr. SMITH. OK. Anyone else wishing to comment on either of those questions? If not, that is fine, but I just——

Dr. SULLIVAN. I just want to add, back to your question about the electronic health record. I think there are two major impediments to that, which are not technical. The technology to do this exists, but the impediments—one is a unique patient identifier across all of the institutions in the United States, and second, is the incentives for the organizations and medical centers to do that, from a business/cultural/social perspective.

Mr. SMITH. So, when you say unique patient identifier, would you elaborate?

Dr. SULLIVAN. When patients go to different medical centers there, because we don't use Social Security numbers anymore for privacy reasons, they get some kind of a new number, their name maybe is spelled differently at different places, include the middle initial or not, and so, identifying records from one place that

matches up with the same patient in another place is a huge problem. We don't have a standard way to do that across the United States.

Mr. SMITH. And what are your recommendations in addressing that?

Dr. SULLIVAN. I think we need to look at something like the bio-identifiers, face recognition, iris scans, something like that. OK.

Mr. SMITH. Thank you very much. I yield back.

Chairman WU. Thank you very much, Mr. Smith.

And now, I recognize the gentlelady from Maryland, Ms. Edwards. Five minutes.

Ms. EDWARDS. Thank you, Mr. Chairman. And thank you to the witnesses. I am in the Fourth Congressional District in Maryland. It is home to the NIST Gaithersburg facility. I have had a chance to visit there, and I think that the folks at NIST actually would agree with some of your comments today about the need for capacity in some of these areas, and some of the organizational challenges that they face, so thanks for pointing those out.

My question actually has to do with this idea of establishing an advisory board to address the needs of the biomedical community. Because I want to talk for a minute about firewalls, and I think we have had other examples, and we don't have to name agencies, where we have had these kind of advisory boards where you incorporate the private sector, academia, government, and you have to deal with issues around conflicts of interest, around sort of how you are perceived, whether it is perceived or real, in the public, to make sure that there is real accountability and transparency in process.

And so, I wonder if you could give us some suggestions or recommendations about how to avoid some of the mistakes that we have seen in similarly situated advisory boards, and how that could operate differently in the context of the work at NIST.

Ms. TERRY. So, I would like to take a stab at that, Congresswoman Edwards.

So, I think there is the saying that without a conflict, there is no interest, and I usually begin things that I speak about saying I have the greatest conflict, because I have the greatest interest, and children with a disease certainly make one, sometimes, crazy.

I think the way that we avoid this, and in fact, the health information standards committee that I am sitting on right now is a mixture of the industry, the vendors, the universities, and the people who need this information for the electronic health record, is by mixing those people together, and by having strong leadership for the committee.

And in many cases, a kind of chairpersonship by industry and government, or industry and the nonprofit world, seems to be able to balance interests, and also, to lay down the right rules. And again, I will use this committee as an example. It has been remarkable to see the hard work that everyone is doing, the turf battles that happen in public instead of in private, and in the resolutions that seem to be able to take into consideration those conflicts, because they are named.

So, I think as long as they are transparent, obvious, available to everyone, sunshine on the data, I have seen real wonderful advances in groups like these.

Dr. BAER. I would agree completely with Sharon's comment, and stress the importance of having patient advocacy groups, which can be somewhat more neutral brokers and watchdogs. I think that transparency is the issue, and her statement without conflict, there is no interest is absolutely right on.

The other comment I would make is NIST is used to acting like a neutral broker in many, many areas of the industry within the United States. So this is not a unique problem, and I think NIST has established a tradition of being able to function very adequately in this role as a neutral broker.

Dr. SULLIVAN. I don't have anything to add. I agree.

Ms. EDWARDS. Thank you. Thank you, Mr. Chairman.

Chairman WU. Thank you very much, and now, the gentlelady from Illinois, Ms. Biggert, five minutes.

Ms. BIGGERT. Thank you, Chairman.

One of the first years that I was here, we had the report on the Human Genome Project, which Dr. Francis Collins, of course, worked on, so and now, he has moved to chair NIH, which I think is fabulous, because he worked so much with us, and did so much, obviously, on that project.

But what is the current interaction between NIH and NIST to assist in demand for stricter medical standards? Dr. Sullivan?

Dr. SULLIVAN. In the imaging area, I know there have been connections between, particularly, the National Cancer Institute [NCI] and NIST, going back over about a decade. There was a major workshop in 2006, organized by NIST, with cooperation from NCI and FDA kind of laying out a path forward for some of these issues related to medical scanners.

And there have been some continued interactions. I mentioned that some of the folks involved in that workshop are now in the committees we are working with the QIBA [Quantitative Imaging Biomarker Alliance] activity, the NCI people as well.

So there some precedent for those kind of interactions. I think they could be strengthened by making this more a priority from the management perspective within NIST.

Ms. BIGGERT. OK, then. And looking at all of your backgrounds, and you have all done so much and so many different things, but when I look at Sharon Terry, and how she got into this because of a family situation, and yet, she has got a patent on this genetic disease, finding the gene diagnostic and then, the research and having a patent for the invention associated with the gene, how do you all get together and work on this?

It seems like you have got the framework with NIST, and you have got your offering, but how do you get to this way where you are talking about standards, and how the whole group comes together?

Ms. TERRY. So, I will take a crack at that.

I think that is an excellent question, because I think what happens is, as I said, you know, in our case, we are sort of slammed up against walls. So, essentially, what we do is we consult with people like Dr. Sullivan or Dr. Baer and say, "we can't find a way

to measure this or measure that, how do we make a"—for example, for all of us, a clinical trial is important. So, I have colleagues who are trying to do trials where imaging is going to be the biomarker, the end mark, endpoint, and they can't do the right trial, because they can't measure what they need.

And so, our collaborations, I think, are as good as they can be without the standards, but with the standards, I think it would be much clearer what is my job, what is their jobs, and how we can work with one another toward real endpoints in clinical medicine that will produce drugs and therapies and treatments that we need.

Ms. BIGGERT. Go ahead.

Dr. BAER. Just to build on Sharon's comment, you know, there is a natural tendency within all of these communities to want standards. Again, this is not regulation. This is consensus building standards, and in the discussions we have had at all levels, with NIH, the FDA, and the CDC [Centers for Disease Control], they really want NIST's efforts in this area, because they do not focus on building these consensus standards. It is not their role.

The same thing is true in the private sector and academic research. These standards just accelerate progress, so there is a natural tendency for people to want this to happen, and the resources provided by the U.S. Government are absolutely critical to support these efforts.

Ms. BIGGERT. But with the medical costs rising, obviously, this is something that we are facing, in the country, and what is going on as far as healthcare. And at this rapid pace, is there a concern that having NIST decided what methods or standards may increase the costs of providing medical care?

Dr. BAER. I think, again, NIST won't make the decision. NIST will lead a discussion which will result in a consensus. And quite the contrary. The lead toward personalized medicine, and quantitative tests that will enable that, will reduce the number of tests that are done. As it was mentioned, tests for PSA and TSH, thyroid stimulating hormone, which are done tens of millions of times a year, and they are repetitive tests that need to be done, because of the lack of reproducibility and accuracy.

Personalized medicine will allow the most effective therapies to be prescribed to patients, based on their personal molecular diagnosis. I firmly believe that this will substantially reduce the cost of medical, and it is a critical part of the overall program to do so.

Ms. BIGGERT. Well, that is good, because obviously, if we eliminate competition or disallow some forms of testing, then this would be in the opposite direction. Or, if there is picking winners or losers. We have had that in the banking, we don't want to get this into the scientific——

Ms. TERRY. I think, in fact, we will have better, cleaner, clearer competition in the sense of innovation and competition if we have standards. Because innovation will build on standards very, very rapidly. We are starting to see that in the health information technology field, and I think we would see it in other fields as well.

Dr. SULLIVAN. Yes, I would endorse that. Two points.

One is I also agree it would help to reduce duplication in the medical imaging area. We don't have good data on this, but it is

estimated maybe 20 or 25 percent of scans are just duplicate scans, because they can't compare them. And they are very expensive, so that would be a huge cost.

In terms of competition, in our work with the medical device manufacturers, and these are all of the large companies, GE, Phillips, Siemens, Toshiba, they view standards as an opportunity for competitiveness. That is, they can work to claim that their device is more compliant than their competitors with these standards.

Ms. BIGGERT. Thank you very much. I yield back.

Chairman WU. Thank you very much, Ms. Biggert. Thank you all very, very much for this very helpful testimony. We do have additional questions, which will be submitted in writing. I appreciate the distance that you all have come. I appreciate the work that you have done in your respective fields, and look forward to hearing more about that work as well.

Unless there are any other additional questions from the panel. Thank you all very, very much for appearing this afternoon. The record will remain open for two weeks for additional statements from the Members, and for answers to any follow-up questions the Committee may ask of the witnesses.

The witnesses are excused with the panel's great gratitude, and the hearing is now adjourned.

[Whereupon, at 2:45 p.m., the Subcommittee was adjourned.]

Appendix 1:

Additional Material for the Record

TESTIMONY OF DR. KAREN MANN, PHD, PRESIDENT OF THE ASSOCIATION FOR MOLECULAR PATHOLOGY

Chairman Wu and Members of the Subcommittee—thank you for the opportunity to provide written testimony on *How Can NIST Better Serve the Needs of the Biomedical Research Community in the 21st Century*.

My name is Karen Mann and I am the current President of the Association for Molecular Pathology (AMP), an international medical and professional association representing approximately 1,800 physicians, doctoral scientists, and medical technologists who perform laboratory testing based on knowledge derived from molecular biology, genetics and genomics.

The modern healthcare system offers great potential for personalized and effective medical care. However, the recognition and implementation of advances in medical research will be hindered by a lack of certified reference materials. Molecular assays provide the cutting edge diagnostics for many individualized therapies in oncology, transplantation, infectious disease and genetics, but the production of certified reference materials has fallen far behind the technical capabilities of these assays. Reference materials are important to ensure the necessary sensitivity, specificity and level of reproducibility of intra- and inter-laboratory test results. The best approach to achieve consistent and comparable quantitative data amongst laboratories is by the use of internationally established reference reagents.[1]

To illustrate the challenges of the dearth of reference materials, I will provide you with examples from four areas of active innovation in molecular diagnostics.

Example 1: Targeted therapeutics and tumor markers

Targeted therapeutics are drugs that directly target genes or genetic pathways involved in disease. Molecular testing is used to identify patients with these mutations in order to direct therapy to the appropriate patients, and, in some cases, to monitor response to therapy. Reference materials are necessary to ensure that these tests have appropriate sensitivity, specificity, and reproducibility. Chronic myeloid leukemia (CML) is a paradigm for molecular diagnosis and targeted therapy. Historically, the only definitive treatment was bone marrow transplant, a treatment with high morbidity and mortality and limited utility. A recently developed novel class of medicines, tyrosine kinase inhibitors (TKIs), has revolutionized the treatment of CML.

TKIs specifically target the oncogenic BCR–ABL fusion protein seen in CML, resulting in effective control of the tumor cells with relatively few side effects. The standard of care for monitoring the effectiveness of CML therapy is the quantitative molecular assessment of the level of the *BCR–ABL* fusion transcript in the patient's blood. Response to therapy is measured

by transcript level and rising levels of the fusion transcript indicate early relapse, development of resistance mutations, and the need to alter therapy. Accurate assessment of the level of *BCR–ABL* is, therefore, essential for both the individual patient and to accurately compare results between centers in clinical trials for improvement of leukemia therapy.

These advances have obviated the need for transplant in most CML patients, but the lack of standardized reagents has limited the reproducibility of these assays within and between laboratories. Therefore, if a patient has samples sent to different laboratories, as happens if they switch healthcare providers, it is impossible to accurately monitor the response to therapy. Therefore, quantitative standards for monitoring *BCR–ABL* are urgently needed. Furthermore, the model provided by CML may become the standard for other genes with molecularly targetable mutations or mutations suitable for minimal residual disease monitoring; e.g. *PML–RARA* and variants, *FLT3, cKIT*, *PDGFRA*, *PDGFRB*, *NPM1*, *ETO–AML1*, *JAK2*, *MLL*-mutation variants, etc.

Example 2: Companion diagnostic tests

Molecularly targeted therapies are frequently expensive and sometimes have significant side effects. Molecular pharmacogenomic assays (also called companion diagnostics) are used to identify patients likely or unlikely to benefit from these therapies, providing a method for optimizing the cost-effective delivery of healthcare. This is exemplified by the recent recognition of the role of *KRAS* mutations in colorectal cancer to identify patients unlikely to benefit from monoclonal antibody therapy (Cetuximab/Erbitux) that inhibit the epidermal growth

[1] Robertson JS. "International standardization of gene amplification technology." *Biologicals* 26:111–3, 1998.

factor receptor (EGFR). Mutations in *KRAS* preclude response to this therapy. However, the sensitivity and specificity of different molecular assays for identification of *KRAS* mutations varies with technique. Additional activating mutations of *KRAS* have been identified which need further study in order to understand whether they also cause resistance to anti-EFGR therapy. Standardized reagents are urgently needed to allow comparative analysis between clinical protocols. Mutations in the *EGFR* gene itself also appear to predict responsiveness to EGFR small molecule tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC). However, *EGFR* mutations are considerably more varied than *KRAS* mutations, demonstrating the need not only for standardized reagents but also for an up-to-date *EGFR* somatic mutation database that can predict TKI response in NSCLC for individual mutations.

Example 3: Transplant follow-up care and quantitative standards

Standardized molecular reagents are also urgently needed in the transplant setting. At the end of 2006, over 170,000 people in the U.S. were living with a functioning solid organ transplant; 27,578 solid organ transplants were performed in 2007.[2] From its founding in 1986 through 2004, the National Marrow Donor Program® coordinated more than 20,000 bone marrow and peripheral blood stem cell transplants.[3] All patients who have undergone transplants are given immune-suppressive drug therapy and are as a result more susceptible to viral and fungal diseases. Viral diseases can result via transmission from the donor tissue, exposure to the environment or more typically, reactivation of the patient's own latent viruses, held for years within their own body.

Several common viruses represent recognized and severe complications of organ and bone marrow transplantation, which adds excessive costs to US healthcare systems. Quantitative testing for viruses (viral load testing, e.g. for CMV, EBV, and BK viruses) is considered standard of care for perpetual monitoring of transplant patients. Current laboratory tests, however, show marked variability among commonly used methods because there are no established quantitative virus standards. Because of the variability among laboratory tests, repeat testing is often required when a patient switches health insurance or travels to a different hospital or city. Therefore, quantitative virus standards are urgently needed by the clinical laboratory community in order to provide accurate, reproducible, and comparable results and to reduce errors and repeat testing, all of which add to overall healthcare costs for this already costly group of patients.

Example 4: Reference gene sequence database

Currently, clinical sequencing methods rely either on the use of public sequence databases for sequence comparisons or on the use of annotated databases owned by commercial companies, which require high proprietary fees. Genetic sequence banks such as GenBank are unacceptable for use in clinical laboratories because of the open platform for those who enter sequences and the limited sequence verification for GenBank submission. Clinical laboratories performing gene analyses need a "certified" reference sequence that is locked and annotated.

Clinical laboratories rely on accurate genotypic bacterial identification based on the 16S rRNA gene for many fastidious microbes and fungi. The use of the 16S rRNA gene for identification of bacteria and fungi provides a faster method to identify slow growing organisms. Traditional methods may take up to 3 weeks to identify the microbe and delays in adequate treatment can occur, causing mortality and increasing hospital costs and in some cases, like tuberculosis, a risk to the public health. Two databases services, freely available on the Internet, offer an improved scenario, with some level of verification: 1) The Ribosomal Differentiation of Medical Microorganisms (RIDOM), and 2) the Ribosomal Database project (RDP) from the University of Michigan. These databases offer improvements in secondary-structure based alignment that provides better support for short partial sequences and improves handling of certain sequencing artifacts. However, limitations exist with these databases including, but not limited to, limited species representation and research use only disclaimers.

While improved over GenBank, experience in the clinical laboratory with analysis of the 16S rRNA gene of patient strains has shown that clear-cut results are not

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[2] Wolfe RA, *et al*. "Trends in organ donation and transplantation in the United States, 1998–2007." *American Journal of Transplantation* 2009;9(Part 2):869–878.

[3] U.S. Department of Health & Human Services Health Resources and Services Administration (HRSA). *2004 Biennial Report of the National Bone Marrow Donor Registry*. Available online at *http://wuvw.marrow.org/ABOUT/Who_We_Are/Publications/2004_Biennial_Report/PDF/biennial_report_2004_l.pdf*

the rule as the existing databases are not always well annotated and taxonomic changes are not regularly and rapidly updated. Commercial databases, such as MicroSeq (Applied Biosciences), and databases from reference laboratories such as Mayo Clinic and ARUP Laboratories offer better coordination with clinical laboratories, yet still rely on the subset of microbes submitted to them for identification to populate their databases.

As many clinical, research, and environmental laboratories currently use 16S-based identification of bacteria, including mycobacteria, a widely available quality-controlled database that interfaces freely and seeks to populate it with medically identified microbes from across the globe is long overdue. It is essential to accurately identify species or detect true sequence variations leading to the discovery of new species, with data validation protocols akin to that of 21 CFR Part 11 compliance. Ideally, such a database would provide ribosome related data and services to the clinical community, including online data analysis and aligned and annotated Bacterial and Archaeal small-subunit 16S rRNA sequences, as well as fungal rRNA sequences, and genetic sequences related to antimicrobial resistance. In terms of "personalized medicine" this resource would be valuable as sequence analysis of resistance mutations will be integral to initiatives such as personalized anti-tuberculosis (TB) therapy so that clinical laboratories could quickly identify drug resistant TB (MDR and XDR TB), a priority identified by the NIH.

The need for certified reference sequences extends to human genes, for both inherited diseases and acquired disorders (cancers). For example, the *RET* proto-oncogene is associated with Multiple Endocrine Neoplasia Type 2 (MEN2). From GenBank, two isoforms are given as well as alternative assemblies. One reference sequence lists a known minor allele as the wildtype allele. Reference sequences differ as some only include the coding region, whereas others include the entire genomic sequence. In addition, sequences may include the 5' untranslated region or begin with the first base of the transcribed mRNA. All these differences can cause confusion between reports from different laboratories testing for the same disease, based on which reference sequence is used. A clinically certified reference sequence would be checked to determine that the most common sequence is listed as the reference, and document known benign SNPs. The reference sequence would ideally have the chromosome, locus and sequence numbering so that results from different laboratories will be consistent. Annotating positions of the SNPs could help in designing assays thereby reducing the potential of false negative or positive results. A list of known benign SNPs can also help in interpretation when these variants are detected.

PRIORITIES: STANDARDS ARE URGENTLY NEEDED

While in the end, we hope to have standardized reference materials for all diagnostics targets and certified reference databases for all clinically relevant gene sequences, some are more urgently needed than others. Specifically,

1. **Immediate**
    a. Cytomegalovirus (CMV), quantitative assay standard, a recognized complication of organ transplantation
    b. BCR/ABL Adelaide standard; BCR/ABL tests are used to diagnose patients with a specific leukemia and to monitor their response to treatment
    c. KRAS mutation standards; KRAS mutation analysis testing is used to select patients for a specific chemotherapeutic drug
    d. EGFR mutation standards; EGFR mutation analysis testing is used to select patients for a specific chemotherapeutic drug
2. **Short term (one year)**—all quantitative assay standards.
    a. BK virus (BKV), a recognized complication of kidney transplantation
    b. Epstein Barr Virus (EBV), a recognized complication of organ transplantation
3. **Medium term** (1–3 years)

Below is a list of infectious agents, the diagnostic tests for which require standardized reference materials as well as note of the Certified Gene Sequence Databases (CGSDs). In addition, there is a significant need for reference standards for a number of oncology tests. AMP recommends that an ongoing program be established at NIST to create certified reference standards for molecular diagnostic tests and that NIST consult with molecular pathology experts to identify and prioritize standardized reference material development.

    a. Adenovirus, quantitative assay standard; important for directing antiviral treatment in immunosuppressed patients

b. Enterovirus, qualitative assay standard
c. Hepatitis B virus (important for liver transplants and also in the general population), quantitative assay standard
d. Herpes simplex (HSV), types 1 and 2, qualitative assay standard, recognized complications of organ transplantation
e. HHV–6, HHV–7, and HHV–8, increasingly common complications of organ transplantation, which may add severity to the more common CMV infections
f. HTLV 1 and 2, qualitative assay standard, important for transfusion services
g. Human metapneumovirus (HMPV), qualitative assay standard
h. Influenza virus, qualitative assay standard
i. JC virus, quantitative assay standard, closely related to BKV
j. Parainfluenza virus, qualitative assay standard
k. Parvovirus B19, quantitative assay standard
l. Respiratory syncytial virus (RSV), both qualitative and quantitative assay standards; quantitative assays are used as prognostic markers for patient care
m. Varicella zoster virus (VZV), recognized complication of organ transplantation
n. Certified Gene Sequence Databases (CGSDs)
   (1) Gene mutation sequence database, suitable for clinical test reference
   (2) Infectious agent (bacteria, viruses) sequence database, suitable for clinical test reference
o. Scientific advisory committee to identify and prioritize areas of needed references materials and to direct resources and the work of the CGSDs

AMP's Ongoing Efforts

AMP professional committees have collaborated with NIST and the CDC previously to identify, characterize and make available reference material. For example, characterized cell lines and a NIST standard are now available for Fragile X pre-mutation sizing. These can be used for test validation, proficiency testing, and controls or calibrators.[4] In addition, AMP provided a detailed list of critical needs gathered from the experience of AMP members to NIST in June 2009.

A focus of AMP's Clinical Practice Committee is on increasing the speed with which the National Institute for Standards and Technology (NIST) can prepare quantitative standards, which is critical to the national and international laboratory community and their ability to deliver accurate test results. The deliverable would be purchasable standardized reference materials that would ideally be available for inter-laboratory comparison studies and purchase by commercial and clinical laboratory communities. AMP estimates that it will cost approximately $500,000 to develop each set of reference materials and encourages Congress to consider funding this much needed initiative at NIST. With some of the costs being offset by the purchasing of materials, this is an innovative way for government to not only advance biomedical science but generate funds.

AMP stands ready to collaborate with NIST and work with Congress to do its part to hasten the process to achieve available certified reference materials for all clinical tests. Thank you very much for your attention and continued efforts to advance biomedical research through programs at NIST.

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[4] Amos Wilson J, et al. *J Mol Diagn*. 2008 Jan;10(1):2–12 Consensus characterization of 16 FMR1 reference materials: a consortium study.