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Before the House Science & Technology Committee Technology & Innovation Subcommittee
Hearing on
How Can NIST Better Serve the Needs of the Biomedical Research Community in the 21st Century?

February 24, 2010

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/qiba_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.

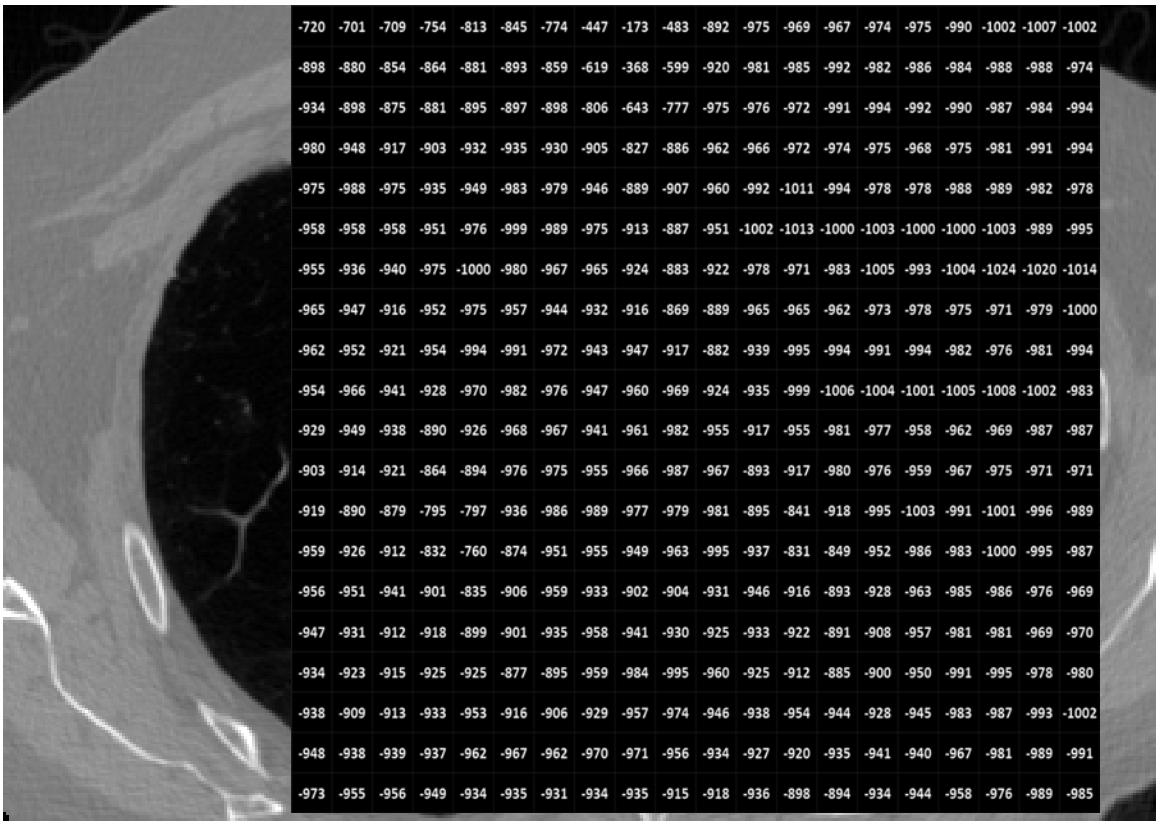

Figure 1. Pixel numbers superimposed on a chest CT scan.

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.

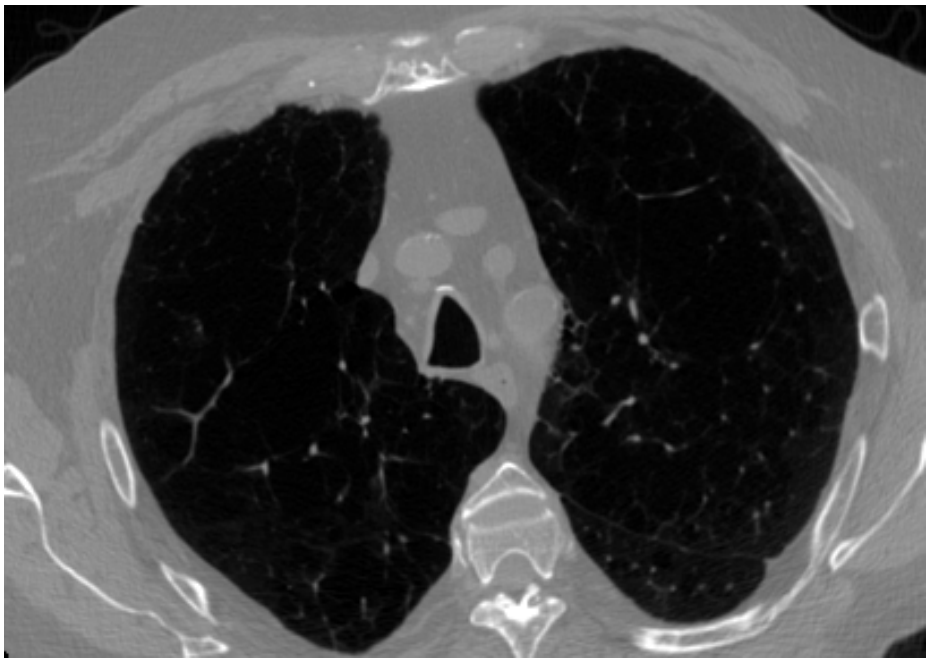

Figure 2. Chest CT scan of a patient with COPD.

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.

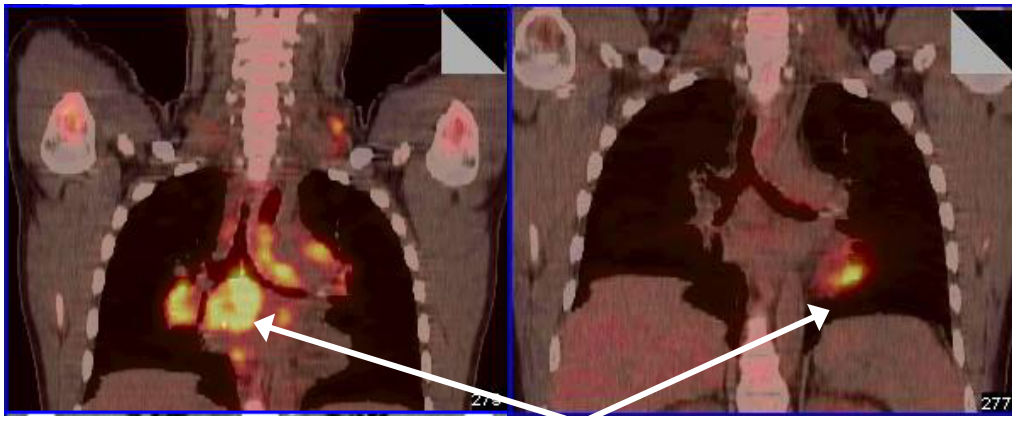

Figure 3. Combined PET/CT scans of lymphoma before and after therapy.

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.

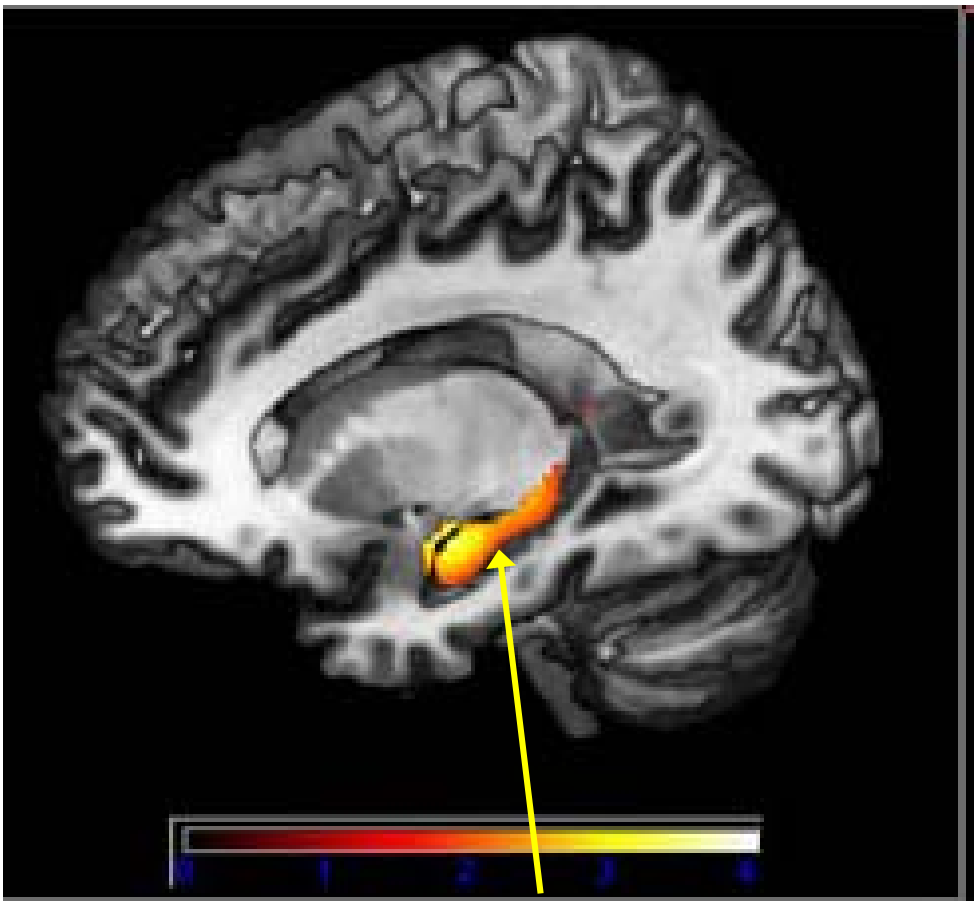

Figure 4 MRI scan of Alzheimer's Disease.

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 successful – 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 variance. 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)

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

"Build measuring devices, not just imaging devices."

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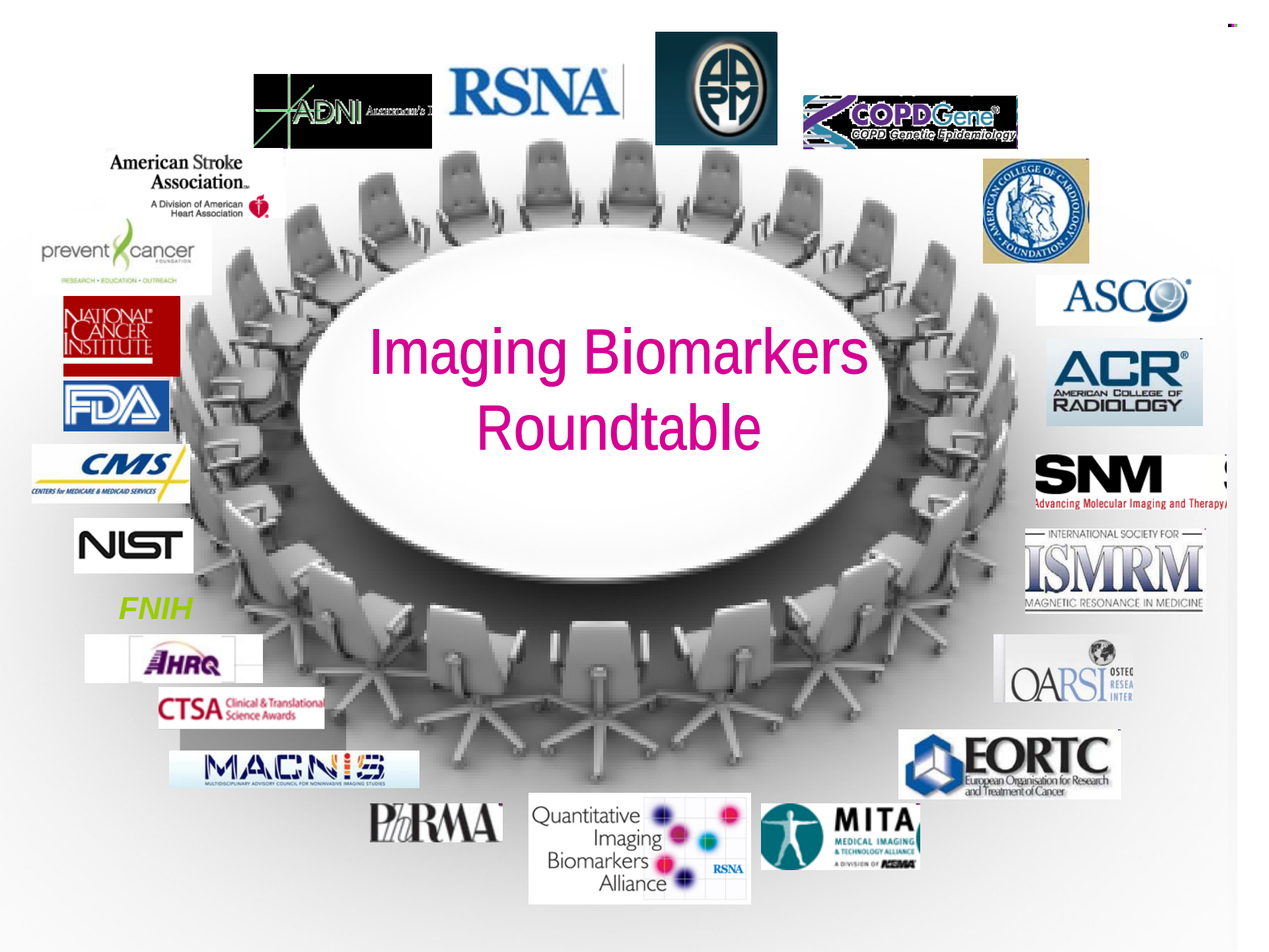
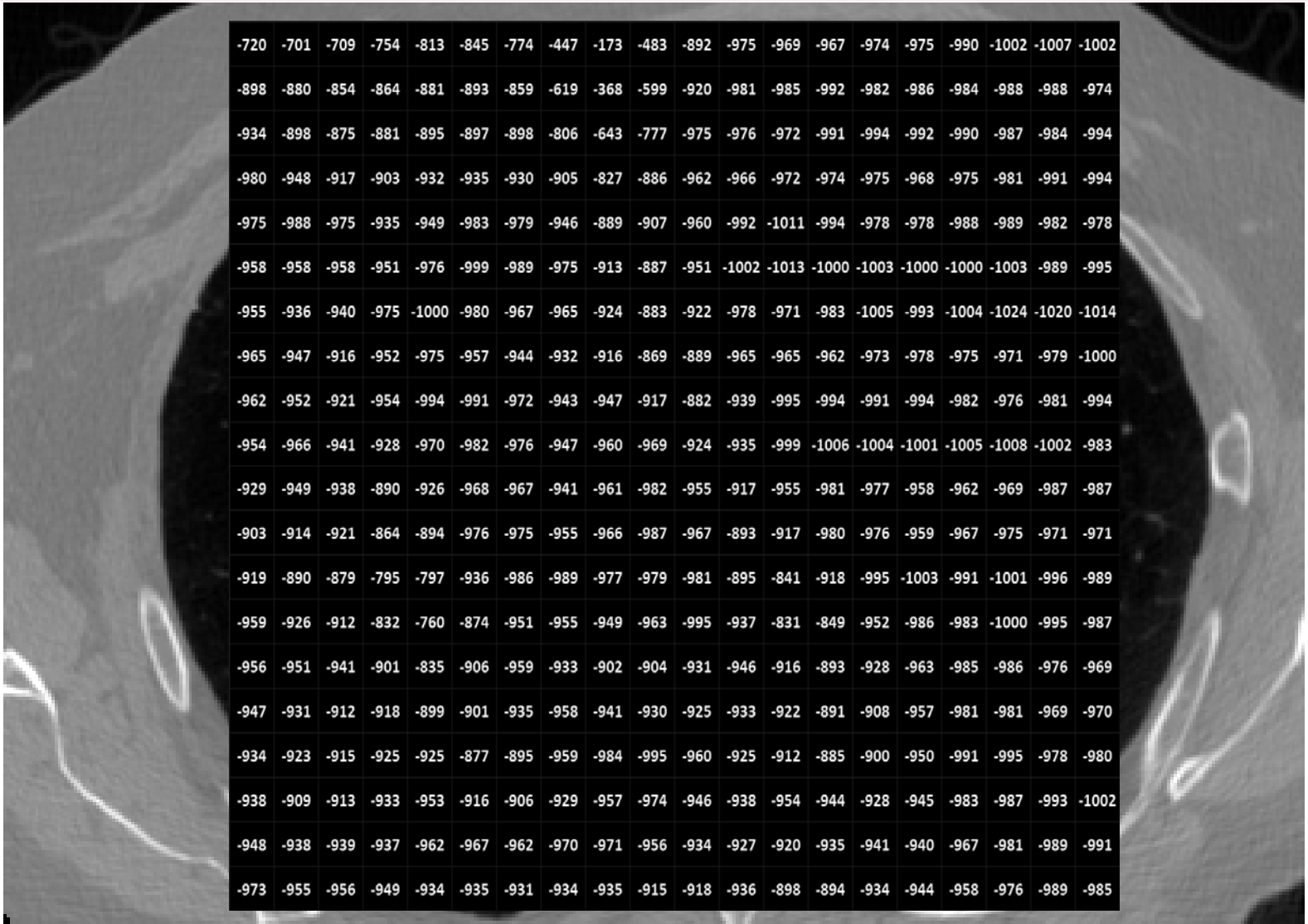
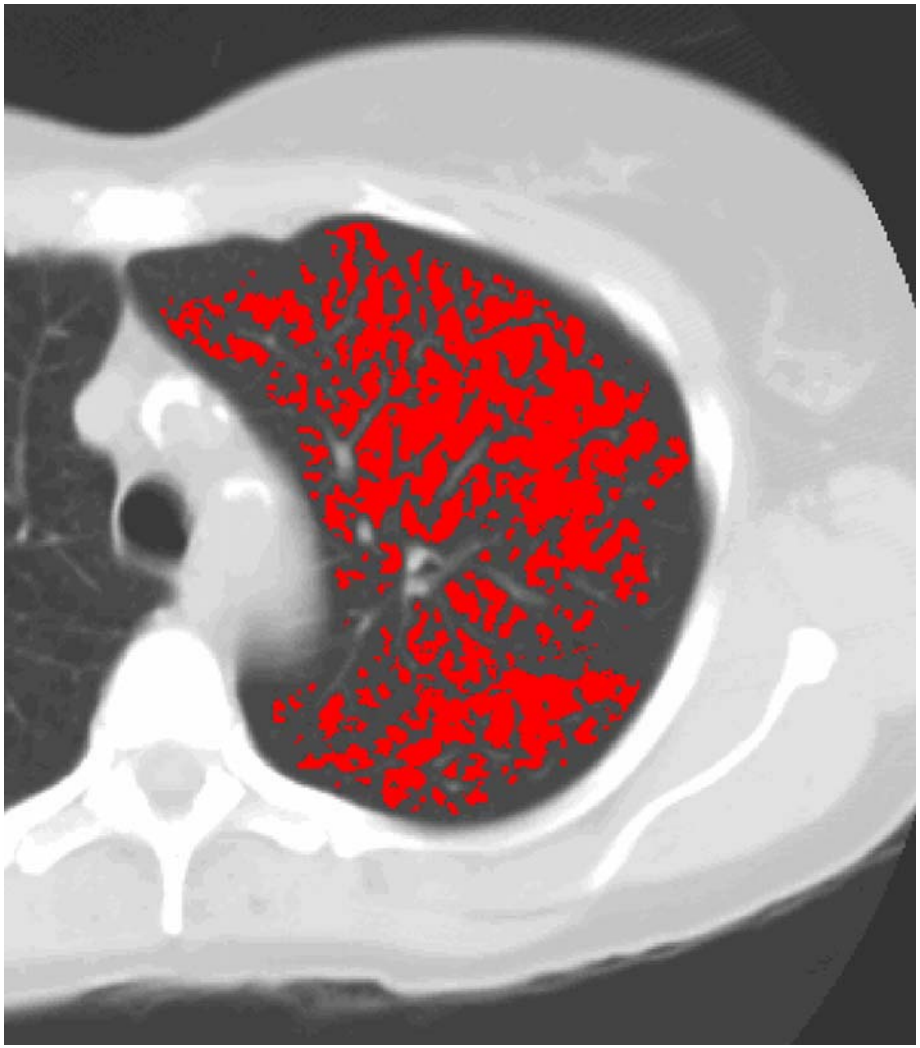
Radiological Society of North America (RSNA)


ADNI
RSNA
AAPM
COPDGene
COPD Genetic Epidemiology
American Stroke Association
A Division of American Heart Association
prevent cancer
RESEARCH • EDUCATION • OUTREACH
AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
ASCO
NATIONAL CANCER INSTITUTE
Imaging Biomarkers Roundtable
ACR
AMERICAN COLLEGE OF RADIOLOGY
FDA
CMS
CENTERS for MEDICARE & MEDICAID SERVICES
SNM
Advancing Molecular Imaging and Therapy
NIST
INTERNATIONAL SOCIETY FOR
ISMRM
MAGNETIC RESONANCE IN MEDICINE
FNIH
AHRQ
OARSI
CTSA Clinical & Translational Science Awards
MACNIS
MULTIDISCIPLINARY ADVISORY COUNCIL FOR NONINVASIVE IMAGING STUDIES
EORTC
European Organisation for Research and Treatment of Cancer
PhRMA
Quantitative Imaging Biomarkers Alliance
RSNA
MITA
MEDICAL IMAGING & TECHNOLOGY ALLIANCE
A DIVISION OF NEMA

Chronic Obstructive Pulmonary Disease (Chest CT Scan)



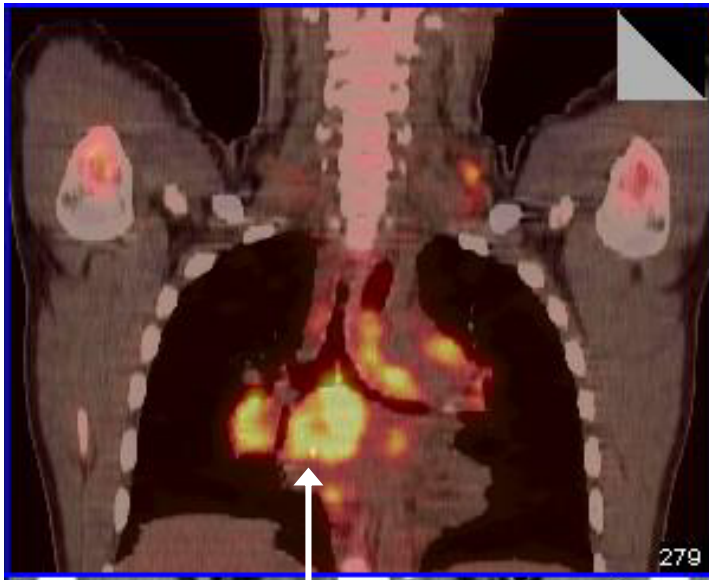
Chronic Obstructive Pulmonary Disease (Emphysema)



Red = Destroyed Lung tissue

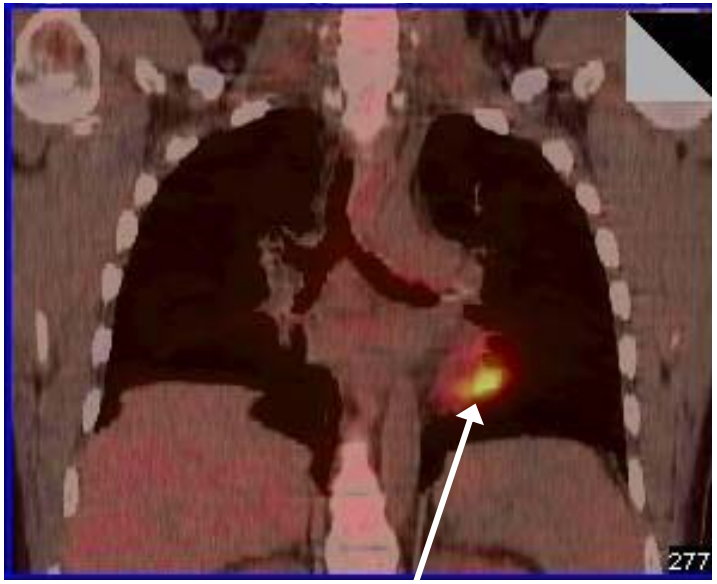
Lymphoma (Combined PET/CT Scan)

Before treatment



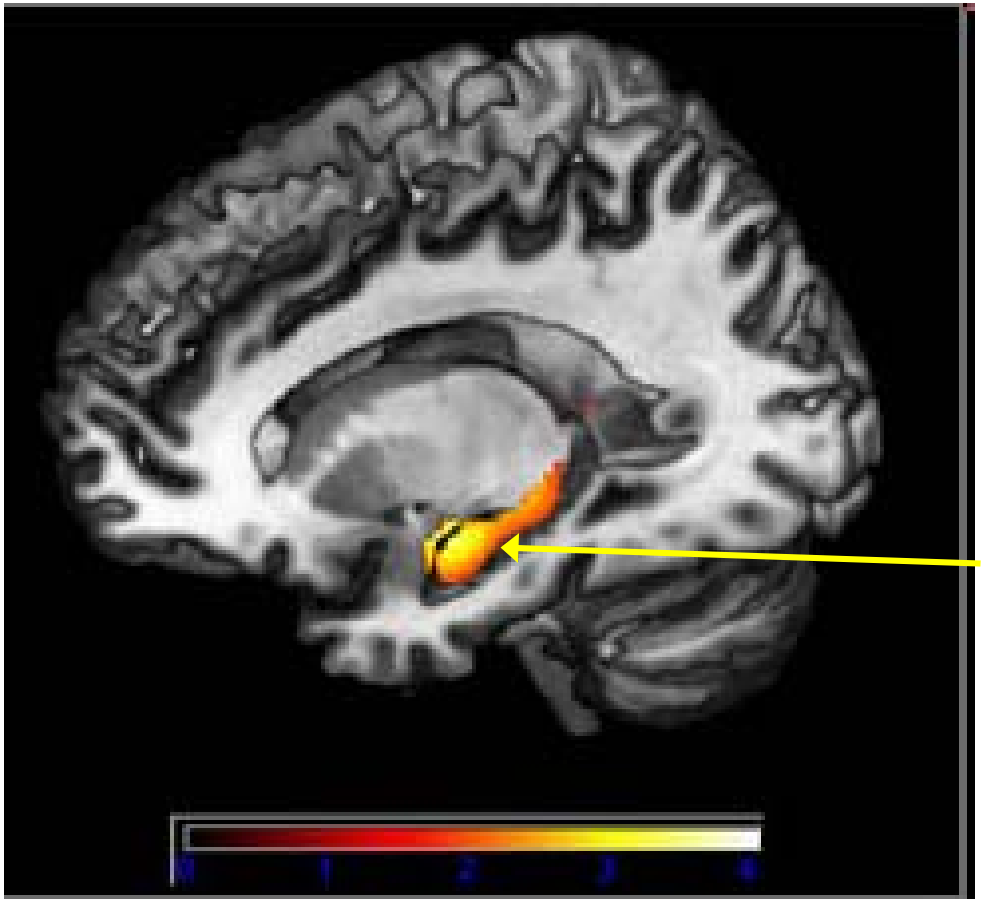
Tumor Uptake = 10.

During treatment



Tumor Uptake = 5.

Alzheimer's Disease (MRI Scan)



Conclusions

- **Develop reference materials, reference standards, and validation procedures in the biomedical imaging area**
- **Appoint an Advisory Board made up of industry experts and representatives of imaging device users**
- **Fund NIST-Academic Centers for Biomedical Research**
- **Create a User Facility for industry and academic developers**
- **Establish an Accreditation of Performance Level program**

Thank You