Imaging as a Biomarker: Standards for Change Measurements in Therapy

A U.S. Measurement System Workshop

September 14-15, 2006
National Institute of Standards and Technology

Technical Co-Chairs: Ram D. Sriram (NIST) and Laurence Clarke (NCI)
General Coordinator: Linda Beth Schilling (NIST)

Executive Summary

Background: Biomarkers are biological indicators of disease or therapeutic effects that can be measured by *in vivo* biomedical imaging and molecular imaging in particular, as well as other *in vitro* or laboratory methods. Recent work has shown that biomedical imaging can provide an early indication of drug response by use of X-ray, computed tomography (CT), positron-emission tomography-CT (PET-CT), or magnetic resonance imaging (MRI). There are three primary sources of uncertainty in using imaging as a biomarker: (a) the biological variability, (b) the variability associated with the clinicians interpreting the images, and (c) the physical measurement variability associated with image data collection, analysis across the same or different imaging platforms. Although biological variability is a large source of error, the physical uncertainty often significantly reduces the robustness of the imaging methods and the clinical decision tools required for quantitative measurement of therapy response over time. Physical and biological measurement uncertainties may be addressed prior to designing a clinical trial and thus help in reducing the case size and cost of a clinical trial associated with a drug submission to the Food and Drug Administration (FDA).

The National Institute of Standards and Technology (NIST) has been approached over the last few years by several industry and medical stakeholders to address the physical sources of measurement uncertainty. NIST's initial research discovered that the characterization of measurement uncertainty poses many complex metrology and standardization problems on a scale that appears to need significant collaboration across the different medical imaging stakeholders. Many of the issues are similar to other scientific domains that NIST has addressed as part of its mission to provide metrology standards to enhance the competitiveness of U.S. industries. To better assess the measurement and standards needs for using imaging as a biomarker, NIST engaged leading representatives from many of the different imaging societies, the imaging, pharmaceutical and e-health and other healthcare stakeholders, as well as other key federal agencies (the National Institutes of Health Institutes and Centers (NIH ICs), and FDA) to organize and conduct a United States Measurement System (USMS) workshop: http://usms.nist.gov/workshops. The workshop entitled "*Imaging as a Biomarker: Standards for Change Measurements in Therapy,"* was thus held on September 14-15, 2006 at NIST in Gaithersburg, Maryland. (Workshop agenda, presentations and final workshop report will be available at http://usms.nist.gov/workshops/bioimaging.htm.)

Report: This meeting was the largest USMS workshop held by NIST. It was attended by more than 250 researchers from the medical imaging community including: academia, clinicians and research physicians, imaging and pharmaceutical companies, contract research organizations (CRO's) and trade organizations (NEMA, PhRMA Consortium), representatives from many different imaging societies (RSNA, ACR, AAPM, SNM, ISMRM) and key agencies of the federal government were represented (NIH: NCI, NIBIB, NIA, NIAMS, NIGM, NCRR; FDA: CDRH, CDER; and NIST: CSTL, EEEL, PL, MSEL, MEL, ITL).

The workshop was organized as follows: (a) presentations from current or planned public-private partnerships that included imaging as a biomarker and the need for associated metrology and standards

for Alzheimer's disease**,** osteoarthritis, and cancer, followed by an FDA discussion of these and related clinical trial issues associated with imaging; (b) presentations on the NIST U.S. Measurement System activity; (c) presentations from several of the key stakeholders that outlined their level of interest in supporting standards for biomedical imaging; and finally (d) presentations from the National Electronics Manufacturer's Association (NEMA) and three leading medical imaging companies outlining their interest in collaboration with other stakeholders. Six breakout sessions were organized over the two-day workshop to specifically address emerging imaging modalities being used in the clinical setting for drug or radiation therapy response, and related resources needed to meet the imaging metrology and standards needs for measuring change. Each breakout session was chaired by four representatives from the different stakeholder groups. The breakout session summaries are described in the NIST workshop report. The final workshop session summarized key points from all the speakers and breakout sessions and opened discussion with panel representatives from the stakeholder groups.

The physical measurement uncertainties for monitoring therapy response as applied to different diseases and the need for quantitative measurements were recognized as an important problem to be collectively addressed by the different agencies of the federal government, with NIST recognized as having an important role in the development of needed metrology. There was also very strong expression of interest by all the academic and industry stakeholders to become collectively engaged in finding solutions for these measurement and standards challenges, such as through the different scientific (volunteer) tasks groups within academic societies and industry trade organizations (PhRMA, NEMA). In addition it was recognized that there was an opportunity to collaborate in other interagency efforts that address the role of biomarkers for drug discovery and response, including potential FDA Critical Path, and NIH roadmap and partnership initiatives, which are described at:

http://www.fnih.org/Biomarkers%20Consortium/Biomarkers_home.shtml
http://www.fda.gov/oc/mous/domestic/FDA-NCI-CMS.html
http://www.fda.gov/cdrh/ocd/criticalpath.html
http://nihroadmap.nih.gov/

The workshop concluded with agreement to organize several follow-up meetings between the federal agencies and the academic/industry stakeholders to continue development of a roadmap of how to address both short-term and long-term challenges. One such stakeholders' meeting is planned by the leadership of the Radiological Society of North America (RSNA) on November 28, 2006.

Highlights, in no particular order, from key workshop findings are given below. Many of these opportunities can be addressed in the short term, and others on the longer term, depending on the complexity of the imaging modality, the particular measurement challenge and the value that the solution could bring to drug development.

- Identify and characterize the physical performance requirements of emerging imaging platforms that are required to measure therapy response, in order for the imaging industry to consider responding to these requirements during new platform introduction or system upgrades.
- Develop open architecture standards such as that initiated by NEMA-DICOM that permits the interoperability of software tools for both data collection and analysis, thus encouraging harmonization or ideally greater standardization for targeted imaging drug trials.
- Develop standardized imaging phantoms that are designed to better characterize time-related changes in the physical performance of imaging systems, and to include anatomical, functional and molecular-based measurements.
- Develop and share open-source tools to encourage more standardized methods for phantom data analysis.
- Encourage imaging companies to cross-license biomarker-specific software for data integration and clinical decision tools, as required for the measurement of drug and radiation therapy response.

- Develop public federated image database resources to help standardize image data acquisition, analysis, and related annotation and mark-up methods developed by academia and industry. One example is to permit standardization of methods to benchmark the performance of user-developed or commercial clinical decision tools for the measurement of drug or radiation therapy response. This resource should therefore permit accelerated FDA approval and/or usage of clinical decision change analysis tools and facilitate their broad dissemination and implementation in future clinical therapy trials.
- Develop comprehensive interoperability standards for both user-developed and commercial information technology solutions, such as research and clinical Picture Archiving and Communication Systems (PACS), knowledge-based or decision support systems that support clinical therapy trial data collections and meta-analysis as required for FDA drug submissions.

Workshop Sponsors:

NIST	National Institute of Standards and Technology
CSTL	Chemical Science & Technology Laboratory
EEEL	Electronics & Electrical Engineering Laboratory
PL	Physics Laboratory
MSEL	Materials Science & Engineering Laboratory
MEL	Manufacturing Engineering Laboratory
ITL	Information Technology Laboratory
NIH	National Institutes of Health
NCI	National Cancer Institute
NCRR	National Center for Research Resources
NIA	National Institute on Aging
NIAMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIBIB	National Institute of Biomedical Imaging and Bioengineering
NIGMS	National Institute of General Medical Sciences
FDA	Food and Drug Administration
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
AAPM	American Association of Physicists in Medicine
ACR	American College of Radiology
DICOM	Digital Imaging and Communications in Medicine
ISMRM	International Society for Magnetic Resonance in Medicine
NEMA	National Electronic Manufacturers Association
PhRMA	Pharmaceutical Research and Manufacturers of America
RSNA	Radiological Society of North America
SNM	Society for Nuclear Medicine
SPIE	The International Society for Optical Engineering