QIN

Quantitative Imaging Network

Volume 1, Issue 3   **March 17, 2011**

The Interagency Oncology Task Force of NCI and FDA

By: Gary Kelloff, MD; Howard Higley, PhD; Caroline Sigman, PhD

In 2004, NCI and FDA formed the Interagency Oncology Task Force (IOTF) which in part was stimulated by needs identified in (the strategy leading to) the FDA's Critical Pathway Initiative. The interest in more efficient development of biomarkers, including imaging based biomarkers was viewed as a high priority and led to comprehensive overviews of FDG-PET [1] and promising new imaging probes [2].

In February 2006, FDA, NCI, and CMMS announced the Oncology Biomarker Qualification Initiative (OBQI)—an agreement to collaborate on improving the development of cancer therapies and the outcomes for cancer patients through biomarker development and evaluation (http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108597.htm).

The stated goal of OBQI was to validate and subsequently qualify particular biomarkers so that they can be used to evaluate promising new technologies in a manner that will shorten clinical trials, reduce time and resources spent during drug development, improve the linkage between drug approval and drug coverage, and increase the safety and appropriateness of drug choices for cancer patients. Formation of OBQI teams that could foster development of key information on biomarkers by working with academic and industry scientists, as well as professional organizations, was encouraged.

OBQI biomarker research was planned to focus in four key areas: standardizing and evaluating imaging technologies to see in more detail how treatments are working; developing scientific bases for diagnostic assays to enable personalized treatments; instituting new trial designs to utilize biomarkers; and pooling data to ensure that key lessons are shared from one trial to another.

Shortly thereafter, the NCI Cancer Imaging Program initiated a collaboration with the Foundation of the NIH (FNIH) Biomarkers Consortium to explore ways of carrying out the stated OBQI goal of standardizing and improving imaging technologies as biomarkers of response to cancer therapy. The Biomarkers Consortium is a major biomedical research public-private partnership (PPP) managed by FNIH with broad participation from stakeholders across the health enterprise, including government, industry, and academia, as well as patient advocacy and other non-profit private-sector organizations

Two new teams enter QIN

The Cancer Imaging Program of NCI announces that two sites have been added to the QIN network. The are Columbia University and the Massachusetts General Hospital. Dr. Larry Schwartz will lead the Columbia effort to apply quantitative CT imaging to sarcomas and to hepatocellular carcinoma. Two large clinical trials will be the source of data for building biomarkers from quantitative imaging. The first is a multicenter Phase II SARC 011 trial. The second will be a Phase III CALGB (80702) trial. Creation of new response assessment criteria along with other biochemical indicators will be made in order to offer clinically meaningful endpoints that will help guide future clinical trial design and patient care.

At the Massachusetts general Hospital (MGH), Dr. Greg Sorensen will use MRI to study microvascular properties of glioblastoma in order to measure therapy response. The team will use contrast enhanced and dynamic susceptibility MRI

Interagency Oncology Task Force (Continued from page 1)

"The stated goal of OBQI was to validate and subsequently qualify particular biomarkers"

(http://www.biomarkersconsortium.org/). The Biomarkers Consortium brings together the expertise and resources of various partners to rapidly identify, develop, and qualify potential high-impact biomarkers. The consortium was formally launched in late 2006 to identify and qualify new quantitative biomarkers for use by biomedical researchers, regulators, and health care providers. Effective identification and deployment of biomarkers, including those utilizing imaging technologies, is essential to achieve a new era of predictive, preventive, and personalized medicine. Several biomarkers based on the use of distinct imaging modalities, including FDG-PET, promise to accelerate basic and translational research, speed the development of safe and effective medicines and treatments for a wide range of diseases, and help guide clinical practice [1–3].

In 2007, FNIH Biomarker Consortium, NCI, and the Leukemia and Lymphoma Society sponsored a workshop focusing on a project to evaluate the use of FDG-PET as a tool to measure treatment response in non-Hodgkin's lymphoma (NHL) [4]. Attended by representatives of the FDA, CMMS, and scientists and clinical researchers from academia and the pharmaceutical and medical imaging industries, the workshop reviewed the etiology and current standards of care for NHL and proposed the development of a clinical trial to validate FDG-PET imaging techniques as a predictive biomarker for cancer therapy response. As organized under the auspices of the OBQI, the three federal health agencies and their private sector and nonprofit/advocacy group partners believe that FDG-PET not

only demonstrates the potential to be used for diagnosis and staging of many cancers, but in particular can provide an early indication of therapeutic response that is well correlated with clinical chemotherapy outcomes for this common form of lymphoma. Development of standardized criteria for FDG-PET imaging and establishment of procedures for transmission, storage, quality assurance, and analysis of PET images afforded by this demonstration project, could streamline clinical trials of new treatments for more intractable forms of lymphoma and other cancers, accelerating new drug approvals.

Later in 2007, a companion project plan was conceived by investigators from ACRIN to examine the utility and predictive value of FDG-PET in assessing response to chemotherapy in non-small cell lung cancer (NSCLC). Both the lung cancer and lymphoma trials (ACRIN 6678 and CALGB 50303) have been funded utilizing a PPP structure under the sponsorship of the FNIH Biomarkers Consortium and are currently in progress.

Project Teams for the lead FNIH FDG-PET Lung and Lymphoma studies consist of representatives from NCI, FDA, the FNIH Biomarkers Consortium Cancer Steering Committee, NCI grantees CALGB and ACRIN, and the private funders of the initiative, including Amgen, Inc, AstraZeneca, Bristol-Myers Squibb Company, Genentech BioOncology, GlaxoSmithKline, Johnson & Johnson, Inc., Merck Research Laboratories, and Pfizer Inc.

Recent discussions between members of the FNIH Biomarkers Consortium Oncology Imaging Project Teams and the Radiological Society of

North America/Quantitative Imaging Biomarker Alliance (RSNA/QIBA) have established common interests in promoting the technical validation and clinical qualification of the best-characterized imaging methodologies, FDG-PET and volumetric CT, as improved biomarkers of chemotherapy response in cancer. The joint FNIH/QIBA FDG-PET Working Groups are in the process of collecting and analyzing both prospective and retrospective data on FDG-PET reproducibility and performance in predicting patient outcomes in response to treatment with selected cytotoxic agents in a series of organ system cancers, with the objective of submitting a complete data package to the FDA Biomarker Qualification Review Team (BQRT). The expectation is that this initial review will identify a pathway to an eventual FDA determination that within the appropriate contexts of use, this biomarker may reliably support a specified manner of interpretation and application in drug development and cancer patient management. It is anticipated that QIN will serve as a research resource for the FNIH Biomarker Consortium.

1. Kelloff, G.J., Hoffman, J.M., Johnson, B., Scher, H.I., Siegel, B.A., Cheng, E.Y., Cheson, B.D., O'Shaughnessy, J., Guyton, K.Z., Mankoff, D.A., Shankar, L., Larson, S.M., Sigman, C.C., Schilsky, R.L., and Sullivan, D.C. Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development. *Clin Cancer Res* 11: 2785-2808, 2005.

2. El-Deiry, W.S., Sigman, C.C., and Kelloff, G.J. Imaging and oncologic drug development. *J Clin Oncol* 24: 3261-3273, 2006.

3. Shankar, L.K., Hoffman, J.M., Bacharach, S., Graham, M.M., Karp, J., Lammertsma, A.A., Larson, S., Mankoff, D.A., Siegel, B.A., Van den Abbeele, A., Yap, J., and Sullivan, D. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute Trials. *J Nucl Med* 47: 1059-1066, 2006.

4. Kelloff, G.J., Sullivan, D.M., Wilson, W., Cheson, B., Juweid, M., Mills, G.Q., Zelenetz, A.D., Horning, S.J., Weber, W., Sargent, D.J., Dodd, L., Korn, E., Armitage, J., Schilsky, R., Christian, M., O'Connor O, A., Wang, S.J., Farrell, A.T., Pazdur, R., Graham, M., Wahl, R.L., Larson, S.M., Kostakoglu, L., Daube-Witherspoon, M., Gastonis, C., Siegel, B.A., Shankar, L.K., Lee, D.B., Higley, H.R., Sigman, C.C., Carucci, D., Timko, D., deGennaro, L.J., Sigal, E., Barker, A., and Woodcock, J. FDG-PET lymphoma demonstration project invitational workshop. *Acad Radiol* 14: 330-339, 2007.

The Quantitative Imaging Biomarker Alliance (QIBA)

By: Daniel Sullivan, MD, RSNA

The Quantitative Imaging Biomarkers Alliance (QIBA) arose from a planning session at the 2007 annual RSNA meeting. Its first formal meeting was in May 2008. QIBA (http://www.rsna.org/Research/qiba_intro.cfm) engages the major equipment manufacturers in the process of improving the accuracy and precision of numbers that come from their scanners. QIBA's mission is to "Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time," that is, reduce variability due to non-biological factors, such that the measurements reflect true biological differences rather than technical artifacts. The initial focus is on imaging in clinical trials, with the intent to generalize to imaging in clinical care.

QIBA Technical Committees are resolving groundwork issues and developing quantitative imaging Profiles. A QIBA Profile is a document that includes claims and details (http://qibawiki.rsna.org/index.php?title=What_Are_Profiles%3F). The claims tell a user what can be accomplished by following the Profile. The details tell a vendor what must be implemented in their product before they can declare compliance with the Profile. The details may also define related user procedures necessary for the claims to be achieved. Profiles are developed through a four-step process that leads to the development and adoption of quantitative imaging biomarkers:

1. Identify sources of error and variation in quantitative results from imaging methods.
2. Specify potential solutions.
3. Test solutions.
4. Promulgate solutions.

There are now five QIBA Technical Committees: volumetric CT; FDG-PET SUV; DCE-MRI; COPD-asthma; and fMRI (for epilepsy surgery). There are in-person meetings in December and May of each year.

QIBA's intent is to facilitate useful standardization across the community. This will result in more consistency in image interpretation, which should create more efficient multi-center clinical trials and be useful as patients move among providers. While much of the initial focus has been on clinical trials, the results from clinical trials will disseminate into clinical practice.

We believe manufacturers will seek to comply with completed Profiles in response to the demand of clinical users for Profile-compliant equipment. Clinicians will be motivated to require Profile-compliant devices based on the result of clinical trials that used Profile-compliant equipment to improve their effectiveness. Over time, Profile-compliant equipment will become the standard of care. Strategic guidance supporting the development, qualification and deployment of quantitative imaging biomarkers will lead to improved standardization of imaging tests, proof of imaging test performance and greater use of imaging to predict tissue biologic behavior and monitoring therapy response.

QIBA includes liaisons to industry groups such as the Medical Imaging and Technology Alliance (MITA), the Pharmaceutical Research and Manufacturers of America (PhRMA), imaging societies, NCI, the QIN, and the FDA.

In May 2010, QIBA sent two letters to the FDA requesting that FDA begin the formal process to evaluate volumetric CT and FDG-PET as qualified biomarkers for drug development. In response, the FDA has created two internal Biomarker Qualification Review Teams (BQRTs), one for each request. Those teams will review the Briefing Documents, currently under development by a partnership of QIBA with the FNIH Biomarkers Consortium.

QIBA complements the QIN goals. Much of the necessary research on quantitative cancer imaging biomarkers will be accomplished in QIN. The QIBA Technical Committees can then incorporate the results of QIN research into the comprehensive Profiles, along with relevant work from other sources.

QIBA:
A Collaborative Enterprise for Multi-Stakeholder Participants in the advancement of quantitative imaging.

Two new teams enter QIN (Continued from page 1)

to improve quantification and decrease variability. Their application presented methods that will be applicable in the multicenter setting through a "bottom-up" approach of simulations, phantom studies, retrospective analysis and prospective analysis in patients undergoing treatment with anti-angiogenic therapies. The studies will be of benefit to QIN.

NCI Staff participating in the QIN:

Dr. Robert Nordstrom
QIN Program Director
nordstrr@mail.nih.gov

Dr. Laurence Clarke
Branch Chief
QIN Science Officer
lclarke@mail.nih.gov

Dr. Gary Kelloff
Special Advisor
QIN Science Officer
kelloffg@mail.nih.gov

Dr. Pushpa Tandon
Program Director
Cancer Imaging Program
tandonp@mail.nih.gov

Dr. Huiming Zhang
Program Director
Cancer Imaging Program
zhanghui@mail.nih.gov

Dr. Barbara Croft
Program Director
Cancer Imaging Program
croftb@mail.nih.gov

Dr. Keyvan Farahani
Program Director
Cancer Imaging Program
faranank@mail.nih.gov

Dr. James Deye
Program Director
Radiation Research Program
deyej@mail.nih.gov

Visit our web site
http://imaging.cancer.gov

QIN

The QIN: A Program Perspective of Its History and Goals

By Larry Clarke, PhD,
QIN Science Officer

Background: In 2000, NCI initiated its first public resources of image data, referred to as the Lung Image Database Consortium (LIDC). The intent was to compare the performance of CAD methods for detection and characterization of lung cancer using CT. In 2003, this database was expanded as the first science-based Public Private Partnership for NCI under the Foundation of NIH. This expanded database is referred to as the Image Database Resource Initiative (IDRI), and involved partnership with the device industry. Later in 2005, NCI expanded these public resources to address the physical measurement uncertainty within the context of the use of imaging as a biomarker, initially using CT images. Referred to as the Reference Image Database to Evaluate Response to therapy (RIDER), this database was later expanded in 2007 to cover full range of imaging modalities and organ systems that included both repeat and longitudinal measurements using physical and simulated phantoms in addition to patient studies. The results of related longitudinal measurements have been published as a reference method to stimulate the research community to design improved software tools. These initiatives were consistent with the aims of the Interagency Oncology Task Force described by Gary Kelloff in this edition of the QIN Newsletter.

In a parallel effort, NCI caBIG initiated a very comprehensive informatics program that included the development of an imaging archive and workspace that supported open source frameworks to permit the technical development and clinical deployment of image processing and clinical decision tools. These synergistic initiatives served to initiate an "open science" strategy to engage the research and industry communities to develop more standardized methods for both data collection and analysis for imaging as a biomarker. These efforts and the NCI OBQI initiatives stimulated the organization of a related a trans-NIH and trans-agency workshop at NIST in 2006, that energized all the imaging stakeholders, including scientific societies (RSNA (QIBA), AAPM, SNM, IMSRM), and industry to explore their collective role in developing and implementing physical imaging standards for imaging as a biomarker. However, despite this progress in engaging the research community, there was a critical need to provide public access to state-of-the-art databases, together with metadata (including clinical outcomes) to support the development and validation of more advanced methods for data collection and analysis as required the next generation of biomarker trials.

The Quantitative Imaging Network (QIN): The QIN initiative was first published in 2008 as a program announcement (PAR 08 225). The goal of QIN was to improve the role of quantitative imaging for clinical decision making in oncology by the development and validation of advanced data acquisition and analysis methods as applied to both prediction and response to drug or radiation therapy. To achieve this mission, multidisciplinary teams have been brought together in a network to share retrospective and prospective images and metadata, including outcome data, from targeted therapy trials as a public resource, and to use this resource to build consensus on validation and standardization methods. QIN is thus a unique research network, where the teams are funded to develop and validate innovative methods for data collection and analysis, while at the same time to develop resources and consensus methods for quantitative imaging.

NCI is also continuing to support a number of RIDER contracts that are addressing the critical problem of harmonization of data collection across the three major commercial imaging platforms that include PET CT, DWI and DCE MRI, important to achieve platform independent methods for data analysis and clinical decision making. QIN, through RIDER, is also collaborating with ACRIN cores to implement improved methods for monitoring longitudinal stability of imaging platforms, where the long term goal is to have these methods eventually incorporated into the accreditations of NCI funded cancer centers for advanced molecular imaging. Finally QIN is governed by a steering committee with representatives from each of the QIN teams, NCI program staff, NIH, FDA and NIST, and includes an external advisory committee that will have representatives of other imaging stakeholders. It is thus anticipated that QIN will serve as a critical research network to support the NCI FNIH Biomarker Consortium, ACRIN and other NCI clinical trial networks, and other initiatives supported by imaging societies such as the RSNA QIBA.