QIBA Quarterly

Quantitative Imaging Biomarkers Alliance RSNA

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In this issue:

QIBA MISSION
Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients and time.

QIBA CONNECTIONS

Quantitative Imaging Biomarkers Alliance (QIBA)

QIBA Wiki

Contact us
Comments & suggestions welcome

Daniel C. Sullivan, MD
RSNA Science Advisor

IN MY OPINION

Quantitative Imaging is Critical Part of COPD Diagnosis, Treatment Evaluation

By PHILIP F. JUDY, PhD

Through its work characterizing scanner inconsistencies, QIBA can play an important role in the quantitative evaluation of COPD using CT.

CT is considered useful in the diagnosis and evaluation of the treatment of chronic obstructive pulmonary disease (COPD), which is characterized by chronic inflammation and destruction of the airways and lung parenchyma. Quantitative changes in airway size and wall thicknesses and density of lung parenchyma measured by CT are considered primary efficacy endpoints.

Although this narrative has existed for 20 years, the potential of quantitative CT evaluation of COPD has not been fully realized—especially in the clinic—due to a lack of consistency. There is a premium on consistency (long-term precision and limited variations from scanner to scanner) because the progression of COPD is very slow.

Despite efforts to match tube potential, radiation dose, slice thickness, and reconstruction kernel across scanners, clinical studies have demonstrated systematic differences between scanners. Fortunately, specific CT scanners with standard calibrations and quality assurance are stable and scanner inconsistencies can be statistically modeled in studies involving a sufficient number of cases per scanner. However, standard calibration procedures are not sufficient to deal with inconsistencies in CT emphysema biomarkers. These scanner inconsistencies reduce the power of multi-institutional studies. More cases are required to achieve the required statistical power, increasing the cost of studies.

There is a tendency to deal with scanner inconsistency by specifying that the same scanner be used for COPD drug treatment clinical trials that follow up CT evaluation of cases. However, specifying the same scanner for each case becomes impractical for large clinical trials lasting several years. Statistical modeling corrections are not available for a clinical exam; the number of cases in such a study is one.

Evaluation of COPD is further complicated because the preferred emphysema CT biomarkers—percentage of lung pixels less than -950 and the 15th percentile—are histogram biomarkers. These biomarkers are lung density quantities that are intuitively and empirically related to histological quantitative measures. As CT biomarkers of bulk density (the central tendency of lung CT values), these preferred biomarkers are biased by image noise. Airway size measurements require super resolution techniques. While solutions for improving consistency are straightforward, they are demanding and costly. However, the savings for clinical trials in reducing the number of cases may lead to net savings for sponsors of clinical trials.

QIBA's Role

QIBA can aid in overcoming these obstacles by developing a calibration procedure to deal with scanner inconsistencies in CT emphysema biomarkers. I believe that a reference standard, or phantom, using a material with the attenuation and spatial characteristics of the lung parenchyma needs to be developed. Calibration procedures using the improved reference standard will be incorporated in the Profile being developed by QIBA's COPD/Asthma Committee. Ultimately, we

will need to demonstrate that these reference standard "biomarkers" track the differences caused by variations in scanners and protocols.

Because the preferred CT emphysema biomarkers are biased by image noise, the relationship between standard image quality metrics (spatial resolution, image noise, and CT number scale) and CT emphysema biomarkers must be carefully described in the QIBA Profiles.

QIBA members face interesting, challenging work in creating the QIBA Profiles for COPD and asthma.

Philip F. Judy, PhD, is an associate professor of radiology at Harvard Medical School and director of the Physics and Engineering Division, Department of Radiology, Brigham and Women's Hospital in Boston. Dr Judy is a co-chair of the QIBA COPD/Asthma Committee and a member of the Physics Committee of the National Lung Screening Trial.

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ANALYSIS TOOLS & TECHNIQUES

Merging CAD and Quantitative Imaging

By MARYELLEN L. GIGER, PhD

In 2009, the RSNA Toward Quantitative Imaging (TQI) Ad Hoc Committee developed a working definition of quantitative imaging: *"Quantitative imaging is the extraction of quantifiable features from medical images for the assessment of normal, or severity, degree of change or status of a disease, injury or chronic condition relative to normal."*

Such image-derived metrics may involve the extraction of lesions from normal anatomical background and the subsequent analysis of the extracted region over time (or another parameter) in order to yield a quantitative measure of some anatomical or physiologic characteristic.

Computational methods that will benefit these analyses are being developed by researchers in quantitative imaging, computer-aided detection (CADe) and computer-aided diagnosis (CADx) fields. Many times investigators in these areas of research may not be aware of each others' developments.

Computer-aided Detection and Diagnosis
CAD can be defined as a diagnosis made by a radiologist using a computer algorithm's output—obtained from an

automated analysis of medical images—in the interpretation of image data. With CAD, the radiologist makes the final diagnostic decision using the computer output as an aid. Currently, computer-aided *detection* (CADe), a localization task, provides a “second opinion” for the radiologist in locating suspicious regions within images, as in screening mammography, leaving diagnosis and patient management to the radiologist. However, the development of CAD methods is expanding beyond screening programs to include applications in diagnosis, risk assessment, and response to therapy. Computer-aided *diagnosis* (CADx) involves the characterization of a suspicious region or lesion, such that the computer output characterizes each suspicious region or lesion quantitatively and/or estimates its probability of disease (for example, malignancy), leaving patient management to the clinician.

For example, in breast cancer imaging, investigators are developing computer methods that automatically segment lesions from the background, extract mathematical descriptors of lesion characteristics, and merge these features into a “malignancy score.” It is important to note that these classifier outputs are based on the knowledge of diseased and non-diseased cases from a large database obtained from some population, which is used to train the classifier.

With a sufficiently large database that spans the population, it is expected that the output will yield a relative measure that is related to the likelihood of disease. Note that this differs from image-based metrics in quantitative imaging in which, for example, the image voxel value, after some specific corrections and standardizations, may be directly related to some underlying biological phenomenon.

Segmentation and feature extraction techniques from CAD may benefit quantitative imaging by delineating the lesion more objectively, by merging multiple quantitative values for a composite biomarker, or by yielding a relative value (for example, relative to a known population with similar lesion characteristics and/or response) that might be more robust that absolute measures of the underlying biology.

Computerized image analyses of the types used in CAD combined with quantitative imaging techniques are likely to yield improved methods of diagnosis and triaging for treatment.

Maryellen L. Giger, Ph.D. is a professor of radiology and chair of the Committee on Medical Physics at the University of Chicago. She is vice-chair of radiology for basic science research and director of the graduate programs in medical physics at the University. A pioneer in the development of CAD, Dr. Giger is a member of the RSNA’s Imaging Biomarkers Roundtable Advisory Group and Toward Quantitative Imaging

Planning Group.

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FOCUS ON

Mark your calendar

FDA/SNM/RSNA Workshop

April 13-14, 2010
Natcher Auditorium on the National Institutes of Health campus, Bethesda, MD

Registration is open for a two-day FDA/SNM/RSNA scientific workshop, "Two Topic Imaging Workshop: Day One - Standards for Imaging Endpoints in Clinical Trials, Day Two - Manufacturing of Positron Emission Tomography (PET) Radiopharmaceutical Products" to be held at Natcher Auditorium on the National Institutes of Health campus in Bethesda, MD. Free online registration and other information on the workshop is available here.

The 2007 Prescription Drug User Fee Act (PDUFA) IV called for the development of a guidance document to address *Imaging Standards for Use as an End Point in Clinical Trials.* As a step toward meeting the requirement under PDUFA, and its overall public health mission of working with stakeholders to facilitate the development of safe and effective medical products, FDA is stimulating discussion with stakeholder in the imaging community on key issues of standardization and optimization of imaging techniques and practices in clinical trials and drug development.

The workshop is expected to generate discussion and establish consensus on issues associated with using imaging to assess endpoints in clinical trials.

The first day of the workshop will focus on general issues of standardization to control variability and inconsistency in

acquisition, interpretation, and analysis of images in clinical trials.

The second day will focus on the regulatory framework for PET drugs, including the recently issued 21 CFR Part 212 regulations establishing the Current Good Manufacturing Practice (cGMP) for PET drugs, investigational new drugs applications (INDs), and new drug applications (NDAs) for PET drug products.

QIBA Third Annual Working Meeting

May 25-26, 2010
Hyatt Regency O'Hare, Rosemont, IL

QIBA was established late in 2007 with representation from pharmaceutical companies, imaging equipment manufacturers, imaging informatics companies, government agencies, imaging societies, RSNA leadership and clinical trialists. QIBA held working meetings in May 2008 and 2009.

This year's meeting will provide an opportunity for QIBA Quantitative PET, CT, MRI, fMRI and COPD/Asthma committees to report on the past year's progress and meet face-to-face to plan next steps and future activities.

Specifically, committees will define groundwork activities they plan to accomplish in the coming year (such as data collection from reference objects), identify Profile details they plan to work on, and determine how their activities align with emerging clarifications of FDA regulatory guidances and pathways.

Through its committee work, QIBA is engaged in understanding and reducing errors so that quantitative results are accurate and reproducible across patients, timepoints, sites, and imaging devices/software from vendors.

Summaries of the May 2009 and other QIBA meetings are posted on the QIBA Web site. Ongoing committee work is posted on the QIBA wiki.

QIBA always welcomes new committee participants. Contact QIBA@rsna.org for more information.

Testimony from February 24 House Committee on Science and Technology's Subcommittee on Technology and Innovation hearing

Dr. Daniel C. Sullivan was one of the witnesses who testified before the House Committee on Science and Technology's

Subcommittee on Technology and Innovation on February 24, 2010. Testimony from the hearing "How Can NIST Better Serve the Needs of the Biomedical Research Community in the 21st Century?" addressed ways the National Institute of Standards and Technology (NIST) could assist manufacturers, patients, academicians and regulators by supporting the development of reference objects, procedures and measurement standards for assessing the performance of biologics, drugs, and diagnostic tests and devices.

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QI/IMAGING BIOMARKERS IN THE LITERATURE

PubMed Search on Quantitative Imaging in COPD and Asthma

Each issue of *QIBA Quarterly* features a link to a dynamic search in PubMed, the National Library of Medicine's interface to its MEDLINE database. Click here to view a PubMed search on quantitative imaging in COPD and asthma.

Take advantage of the My NCBI feature of PubMed which allows you to save searches and results and includes an option to automatically update and e-mail search results from your saved searches. My NCBI includes additional features for highlighting search terms, storing an e-mail address, filtering search results and setting LinkOut, a document delivery service.

QIBA in the Literature

QIBA's efforts and accomplishments are the subject of a growing list of journal articles which is posted on the QIBA Web site.

As of March 2010, the list includes:

Biomedical Imaging/Disease Diagnosis: Quality and Standards: Making Bioimaging "Measure Up". Reiss, SM. *BioOptics World*. 2010 Jan 1. Online article.

The Use of Volumetric CT as an Imaging Biomarker in Lung Cancer. Buckler AJ, Mulshine JL, Gottlieb R, Zhao B, Mozley PD, Schwartz L. *Acad Radiol.* 2010 Jan; 17(1):100-6. PubMed citation.

Volumetric CT in Lung Cancer: An Example for the Qualification of Imaging as a Biomarker. Buckler AJ, Mozley PD, Schwartz L, Petrick N, McNitt-Gray M, Fenimore C, O'Donnell K, Hayes W, Kim HJ, Clarke L, Sullivan D. *Acad Radiol.* 2010 Jan; 17(1):107-15. PubMed citation.

Volume CT for Diagnosis of Nodules Found in Lung-Cancer Screening. Mulshine JL, Jablons DM. *N Engl J Med.* 2009 Dec 3; 361(23):2281-2. PubMed citation.

Quantitative Imaging Biomarkers Alliance FDG-PET/CT Working Group report. Frank R; FDG-PET/CT Working Group. *Mol Imaging Biol.* 2008 Nov-Dec; 10(6):305. PubMed citation.

Please contact QIBA@rsna.org with additions to the list.

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