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QIBA Newsletter

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

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In My Opinion

Conformance to QIBA Profiles for Practical Implementation of Quantitative Imaging Biomarkers: What Can We Learn from Pathology and Laboratory Medicine?

By SCOTT REEDER, MD, PhD

It has been a great pleasure to work as co-Chair of the QIBA Proton Density Fat Fraction (PDFF) Biomarker Committee as part of the larger QIBA Initiative. Through the energy and enthusiasm of my co-Chair, Takeshi Yokoo, MD, PhD, and the PDFF committee's membership, we have made excellent strides towards completing the technical performance specifications for PDFF as a biomarker of hepatic steatosis.

As we draw closer to completion of the technical Profile, many important questions arise, including, "What is the appropriate procedure for demonstrating compliance of a new MRI method to quantify PDFF?" The committee is actively working on guidelines for establishing procedures to collect the necessary data to demonstrate conformance. Regulatory-related questions have also arisen in this process. For example, for a method with sufficient data to demonstrate conformance, who, exactly, will be responsible for confirming that compliance? What regulatory imprimatur does that certification provide for the research and clinical use of PDFF as a biomarker of liver fat? Should certification be available only for commercially or vendor-developed work in progress (WIP) methods, or should it also apply to methods developed by individual investigators at academic institutions? Who will enforce conformance on an ongoing basis, for example, with MRI system software upgrades?

In my opinion, we should look to our colleagues in Pathology and Laboratory Medicine who live with considerable regulatory oversight for serum biomarkers used in everyday clinical care and research. There are a great number of lessons to be learned on how the imaging community might think about quantitative imaging biomarkers from Pathology and Laboratory Medicine. How might we, as an imaging community, approach

oversight of quantitative imaging biomarkers for clinical care and research? In the U.S., pathologists are familiar with the Clinical Laboratory Improvement Amendment of 1988 (CLIA ‘88) legislation establishing federal regulatory oversight and standards for Pathology and Laboratory Medicine. The CLIA legislation was instituted largely in response to scandals reported in the mid-1980s regarding inappropriate and unethical handling of the Papanicolaou (Pap) test for detection of precancerous and cancerous cervical cancer lesions. As a result of these scandals, regulatory oversight was imposed on Pathology and Laboratory Medicine by the U.S. government.

CLIA is administered by the Centers for Medicare and Medicaid Services (CMS) who rely on independent accreditation committees such as the Joint Commission on Accreditation of Healthcare Organizations (JCAHO). The CLIA legislation sets standards for quality assurance programs, proficiency testing and periodic accreditation inspections for clinical laboratories that perform laboratory testing on specimens obtained from humans for the purpose of diagnosis, prevention, or treatment of disease. Regulations that guide the enforcement of these standards can be accessed in the Code of Federal Regulations 42 CFR Part 493. A major objective of CLIA is to ensure the accuracy, reliability, and timely reporting of test results. Such tests include FDA-approved clinical lab tests as well as laboratory developed tests (LDT) that are commonly developed by individual clinical labs. The level of oversight is considerable and applies to almost every serum lab test ordered by physicians in the U.S. Similar regulatory oversight is present in other Western countries as well.

In closely examining the experience of Pathology and Laboratory Medicine and the impact of the CLIA ‘88 legislation, the imaging community can move closer to answering this question: What regulatory oversight, if any, should apply to quantitative imaging biomarkers? This is an open and important question that we, as experts in quantitative imaging biomarkers, are well qualified to address. Should organizations such as QIBA, RSNA, ACR, or other comparable societies be involved in the regulatory oversight of quantitative imaging biomarkers? As leaders in the imaging community, we should facilitate this discussion to understand what is in the best interest

of our patients and research subjects. If we are not at the table and actively engaged in this process, it is likely someone else will do it for us.

Scott B Reeder, MD, PhD

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Analysis Tools and Techniques

Keeping up with Technological Advances on Established Quantitative Imaging Biomarkers: Thoughts from QIBA's Proton Density Fat Fraction Biomarker Committee

By TAKESHI YOKOO, MD, PhD

Proton Density Fat Fraction (PDFF) is an established quantitative imaging biomarker (QIB) of liver fat content, measurable by MRI or spectroscopy. PDFF is increasingly used in clinical care, clinical trials, and other research contexts[1]. The initial technical validation studies were conducted in academic research laboratories using clinical MRI systems, with unmodified or modified-versions of the vendor's standard spoiled gradient recalled echo (SGRE) sequences and a dedicated multi-peak spectral reconstruction algorithm for PDFF mapping[2–4]. These initial research studies led to several

commercial implementations of PDFF in the early 2010s and approval by U.S. Food and Drug Administration (FDA) for clinical use.

Over the past decade, MR technology has continued to evolve with the release of new hardware and software, as well as updates and upgrades of existing system components. Because clinical MR systems are the instruments of PDFF measurement, any deviation from the original configuration under which PDFF was validated (e.g., gradient, coil, and noise performance, calibration/reconstruction algorithms) could alter the performance of the QIB. Currently, the need or the method of re-testing, if any, is left to the vendor's own internal Quality Assurance (QA) process. Therefore, it would be important for QIBA to partner with the vendors to develop testing recommendations, including how to measure QIB performance metrics (e.g., linearity, bias, repeatability) and standardize "pass vs. fail" criteria to permit assessment of QIBA Profile conformance.

Along with MR technology, the PDFF technology itself has continued to evolve, with integration of innovations such as motion-robust radial k-space acquisitions[5,6], compressed SENSE[7], and convolutional neural network PDFF reconstruction[8]. Extensive modifications in the acquisition and/or reconstruction paradigm like these could require more rigorous performance re-testing than after a routine system update. But what is considered "extensive" and what level of scientific scrutiny should be required remain unclear. What is clear, though, is that the exact replication of the original validation studies (e.g., multicenter human studies, with or without reference standard liver biopsy) for every new PDFF product would not be practical. An abbreviated pathway to technical validation might be considered for incremental modification of an established QIB like PDFF, and QIBA could be instrumental in providing such guidance.

Lastly, some academic laboratories and imaging CROs (contract research organizations) have been providing PDFF services without using commercial products (as done in the original development of PDFF) to support large-scale clinical trials. Historically, this was necessary because commercial PDFF products were not always available at clinical performance sites. Since PDFF maps can be retrospectively reconstructed from the source images acquired

using vendor's standard SGRE sequences, experienced laboratories could provide central PDFF reconstruction from locally acquired imaging data. While this process is not regulated by FDA (therefore not for clinical use), such laboratory based PDFF could be scientifically valid if the site met some performance standards needed for PDFF. Therefore, QIBA could play another important role by providing methods and criteria for site-qualification and maintenance testing, rigorous enough to ensure Profile conformance but sufficiently easy and practical for sites to comply.

QIBA has an excellent framework for initial QIB qualification and validation, which has guided our PDFF Biomarker Committee in the groundwork studies to define Profile Claims. As we look into the future, however, we are faced with more questions than answers. Issues such as conformance testing under evolving technology, and FDA-approved vs. non-regulated QIB processes, are likely universal issues impacting multiple QIBs. We may benefit from inter-committee dialogues to develop a framework to ensure relevance of QIBA Profiles in the future.

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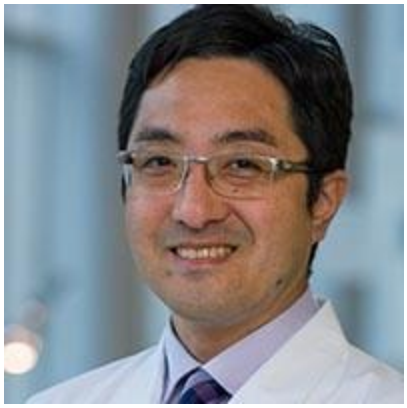

Takeshi Yokoo, MD, PhD

Takeshi Yokoo, MD, PhD, is an Associate Professor of the Department of Radiology and Advanced Imaging Research Center at the University of Texas Southwestern in Dallas, Texas. His research interests are centered around MRI of the liver, including diffuse liver disease such as fatty liver disease and iron overload. He is a co-chair of QIBA's Proton Density Fat Fraction (PDFF) Biomarker Committee.

QIBA Activities

QIBA Biomarker Committees are open to all interested persons. Meeting summaries, the *QIBA Newsletter* and other documents are available on the QIBA website RSNA.ORG/QIBA and wiki http://qibawiki.rsna.org/.

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Please contact QIBA@rsna.org for more information. We welcome your participation.

QIBA and QI/Imaging Biomarkers in the Literature

***Please note that the list of references has been migrated to EndNote. *To obtain access to the RSNA EndNote citations, please send an email request to: qiba@rsna.org.**

The list of references showcases articles that mention QIBA, quantitative imaging, or quantitative imaging biomarkers. In most cases, these are articles published by QIBA members or relate to a research project undertaken by QIBA members that may have received special recognition.

New submissions are welcome and may be directed to QIBA@rsna.org.

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