QIBA Newsletter

QIBA Newsletter May 2019 · Volume 11, Number 2: The Importance of QIBA Sustainability Efforts and the Engagement of Industry and Government

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QIBA MISSION

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

The Importance of QIBA Sustainability Efforts and the Engagement of Industry and Government

By ANNETTE SCHMID, PhD

I feel fortunate to work in the pharmaceutical industry during a time when patient-centered care is at the forefront of health care. Not only is helping patients a key reason most of us chose to work in this industry, but we are dedicated each day to determining what value our treatment provides patients.

According to Emil "Tom" Frei, MD,(1924-2013), an American physician and oncologist who served as director and physician-in-chief of the Dana-Farber Cancer Institute in Boston, the more rigorous clinical experimental design that was developed in the 1950s was the major watershed in bringing novel treatments to patients. In an interview in 1997, he stated, "In science you can make limited advances with qualitative observations, but to really advance, you need to have a quantitative fix."

Dr. Frei and his colleagues had a major impact on how we write protocols and think about clinical experimental design. However, in the context of the imaging biomarkers that are integral to so many trials, further work is needed to secure a reproducible, quantitative approach. The key challenge I observe in my work is often in the consistent application of an imaging acquisition, quality control and post-processing of the images — aspects of the imaging workflow that QIBA put at the center of their mission since its inception in 2007.

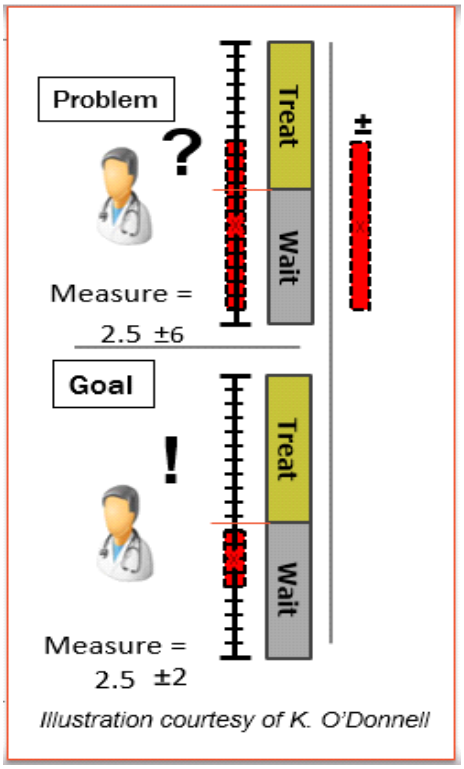


Figure 1: Illustration of challenges in applying results with increased variability to decision making in the treatment of patients

The process of bringing subject matter experts and key stakeholders from academia, industry, and government together to agree on minimum imaging standards and recommended approaches takes time but has the important advantage of creating an accepted standard. QIBA has also been critical in filling the gaps in documented/ published research that support the minimum performance requirements and claims of the selected quantitative imaging biomarkers. In this space, we have repeatedly shared the diagram on how variability in measures, including imaging biomarkers, impacts the clinician's ability to make a decision. (Figure 1)

Less frequently, however, do we discuss the challenges that variability in data presents to our understanding early in the process of drug development, and how it impacts the true value and promise of a potential new drug.

Considering the increasing variability of our quantitative imaging biomarkers, our decision making is either on shakier ground or we need larger patient numbers and longer trials to come to a well-founded conclusion. In the context of patients, this may mean that they are on an ineffective drug longer or need to wait for a new drug longer.

Much of the initial groundwork that QIBA performed was funded by multiple NIBIB contracts—a mechanism that has now expired. To allow QIBA to continue this important work, we need to find alternative sources of reliable funding ranging from payment schemes for certain services to direct contributions from industry, including pharma.

In addition, with the innovations and hopes in the industry, for example in the space of neurodegenerative diseases or immunotherapies, we will need to develop additional quantitative biomarkers, including novel predictors of patient outcomes. In this context, I foresee an important place for QIBA in these efforts, to the benefit of the industry, government and ultimately our patients.

Annette Schmid, PhD

Annette Schmid, PhD, is a Senior Scientific Director, Quantitative and Translational Sciences- Imaging at Takeda Pharmaceuticals in Cambridge, MA. At Takeda, she supports the translational and clinical oncology therapeutic area on imaging aspects and associated clinical trial endpoints. She holds a PhD in development and cell biology and has more than 20 years of experience in analyzing imaging data of various modalities ranging from PET to CT images, structural, functional and microimaging in MRI to MEG and various microscopic and radioisotope labeling techniques both in the academic and clinical trial setting. The views expressed in this piece are her personal opinion.

Analysis Tools and Techniques

Quantitative I-123 and Tc-99m SPECT Profiles

By ROBERT MIYAOKA, PhD, YUNI DEWARAJA, PhD, and JOHN DICKSON, PhD

With the advent of Single-photon emission computed tomography (SPECT/CT) and more powerful computers, quantitative SPECT has been translated from research facilities to clinical environments. All the manufacturers of modern SPECT/CT now offer the necessary corrections for quantitative reconstruction of SPECT data. SPECT imaging has established itself as a quantitative imaging modality and not just a tool for qualitative analysis.

Quantification improves the ability of SPECT imaging to influence medical decision making as well as enhances interpretability of the data. In addition, quantification promotes the use of SPECT imaging as a selection tool as well as a response biomarker for clinical trials. Image analysis is an essential component of the process for delivering consistent results that maximize the value of quantitative imaging.

As a result of the importance of image analysis, we have spent considerable effort in defining how data should be analyzed within our Profiles. The image analysis sections of the I-123 Ioflupane (i.e., DAT or dopamine transporter scan to diagnose Parkinson's Disease) and Tc-99m SPECT Profiles contain detailed text describing the input data to be analyzed and the methods for drawing volumes of interest (VOI) for data analysis in order to achieve the claims and quantitative measurands described in the Profile claims. The input data may be output images produced following the Profile's Image Reconstruction detailed instructions or digital reference objects (DRO) associated with each Profile.

The DRO is used to test the analysis workstation's software's ability to extract the known activity levels in the numerical phantom. Automated, semi-automated or manual VOI drawing tools may be used to extract the quantitative information from the DRO. Automated and semi-automated techniques may make use of anatomic images that clearly delineate the object boundaries or the emission image with an operator selected threshold (i.e., % maximum voxel value) to determine the VOI.

For DAT scan imaging, the analysis software may register the DAT image to a template and then use standardized VOI definitions/placement for analysis. DROs are useful to test and validate analysis software from different vendors in order to produce reliable quantitative results. For analysis packages that automatically draw VOIs, the quantitative measurand can vary significantly for different vendor software depending upon the technique used for determining the VOI definition. This was illustrated in a groundwork project for the Ioflupane DAT DRO Profile (see Table 1).

Table 1: SBR results from 6 different analysis packages

Analysis Software	Striatum SBR		Caudate SBR		Putamen SBR	
	Right	Left	Right	Left	Right	Left
Truth	4.5	4.5	4.5	4.5	4.5	2.25
Vendor 1 (no blur)	2.9	2.05	3.36	2.76	2.7	1.69
Vendor 2 (no blur)	3.19	1.87				
Vendor 3 (no blur)	2.53	1.81	2.4	2.33	2.56	1.43
Vendor 4 (no blur)	2.46	1.74	2.49	1.98	2.43	1.46
Vendor 5 (no blur)			3.6	3.05	2.76	1.7
Vendor 6 (no blur)	3.22	2.62	2.65	2.59	3.75	2.53
Vendor 1 (10 mm blur)	2.17	1.52	2.57	1.9	2	1.32
Vendor 2 (10 mm blur)	3.23	1.86				
Vendor 3 (10 mm blur)	1.72	1.21	1.92	1.61	1.66	0.91
Vendor 4 (10 mm blur)	1.92	1.29	2.07	1.47	1.74	1.07
Vendor 5 (10 mm blur)			2.67	2.11	1.71	1.12
Vendor 6 (10 mm blur)	2.71	2.19	2.6	2.3	2.83	2.04

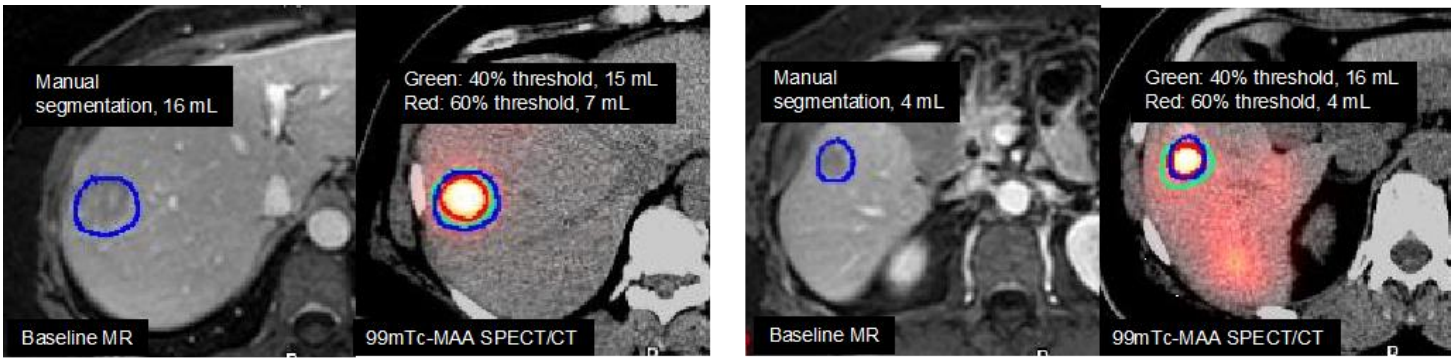
Results like these demonstrate two important findings:

1. the need for harmonization between vendor-specific analysis tools (i.e., vendor-specific tools need to deliver concordant results) to determine measurands such as specific binding ratio; and
2. the need for analysis results from DROs to validate different sites for quantitative and agnostic vendor harmonization so that sites can reliably participate in clinical trials.

While the SPECT Profiles have not tried to be too prescriptive on methods for VOI drawing and placement, it is important to understand the impact that VOI drawing and placement will have on a quantitative measurand. For measurands that are a ratio value, it is critical that the background VOI has been qualified for the measurement. Important characteristics of the background VOI include acceptable % bias that is significantly less than the acceptable variability in the quantitative ratio (or a bias that is linearly correlated with bias level). The average background value should also not vary much with VOI placement and should have high levels of inter- and intra-rater concordance. Factors that promote concordance include easily understandable rules for finding the region and defining its boundaries.

For patient imaging studies, automated, semi-automated, or manual VOI drawing tools may be used to extract the quantitative information from the object of interest. Automated and semi-automated techniques may make use of MRI or CT images with contrast that clearly delineate the object boundaries. When using a previously acquired MRI or CT image for organ, tumor or object delineation, the image registration tool for aligning the SPECT image with either the MRI or CT must be validated. The target VOI can also be based upon the emission image with an operator selected threshold (i.e., % maximum voxel value); however,

this methodology tends to be less consistent as the (optimal) threshold level that gives the best agreement with the true VOI is subject to many image and object properties (e.g., size, shape, contrast, etc.) as evident in the figure below.



Optimal SPECT threshold level that gives the best agreement with the true object depends on image and object factors. This example shows dependence on lesion size. For the lesion on the left, a 40% threshold gives good agreement with the contour defined by the radiologist while for the lesion on the right, a 60% threshold gives good agreement. Using the same (40% or 60%) threshold on both lesions of the same patient will lead to a substantial overestimation or underestimation of one of the volumes.

There are several other more advanced image segmentation methods that have been developed to address some of the limitations of thresholding the emission image and manual contouring on the anatomical image. They are briefly described in the SPECT Profiles and more fully in a recent review article [Hatt, *Med Phys*, 2017].

To reduce/eliminate the impact of partial volume effects on the quantitative measurand for the first version of the Tc-99m SPECT Profile, the QIBA workforce constrained the target and background objects to be at least 30 ml in size, with the recommendation that the background region be greater than 100 ml if feasible.

For the Iofupane SPECT Profile, the measurand is the specific binding ratio of the striatum or caudate/putamen to the background reference region (e.g., cerebellum or occipital region). VOIs are drawn on preprocessed images using automated, semi-automated or manual methods. Two VOI analysis strategies, one using a small VOI approach and the other using the whole striatum VOI approach are discussed.

Unlike positron emission tomography (PET), the quantitative measurand for SPECT is often not the maximum or peak standardized uptake value (SUV). For example, in the case of Ioflupane DAT scans, the measurand of interest is a ratio of the average specific uptake in a target region divided by non-specific uptake in a background region as opposed to an absolute quantitative voxel value. For some other quantitative SPECT studies (e.g., dosimetry applications), the measurand is the total activity uptake in a VOI. For SPECT, the absolute quantitative activity measures such as Bq/mL and %ID/mL require a scaling (calibration) factor to convert reconstructed image counts/sec to activity. This scaling factor, in units such as

cps/MBq, may be determined from a planar sensitivity measurement or from a reconstructed SPECT image of a uniform phantom and must be applied to the reconstructed (counts) images for absolute quantitative analysis. Some modern SPECT/CT systems come with "in-built" calibration procedures and the images are available in activity concentration units, as done in PET.

The tools for quantitative SPECT imaging are available. The goals of the QIBA SPECT Profiles are to provide practical guidelines to support consistent acquisition procedures, image reconstruction techniques and image analysis, so that the benefits of quantitative SPECT will be fully realized. In addition to the important role that quantitative SPECT is having for Tc-99m labelled compounds and I-123 Ioflupane, with the recent focus on theranostics, quantitative SPECT will also play an important role in personalizing therapies and may act as a biomarker for response to therapy. Thus, a key to expanding the role of SPECT in clinical diagnosis and clinical trials is to have established and consistent guidelines regarding quantitative imaging and analysis.

Robert Miyaoka, PhD

Robert Miyaoka, PhD, is a research professor of radiology in the Nuclear Medicine Section at the University of Washington. His research interests include quantitative SPECT/CT imaging including theranostics and PET instrumentation development. He is a member of the QIBA Nuclear Medicine Coordinating Committee and co-chair of the SPECT Tc-99m Biomarker Committee.

Yuni Dewaraja, PhD

Yuni Dewaraja, PhD, is a professor in the Division of Nuclear Medicine, Department of Radiology at University of Michigan. Her research focuses on quantitative imaging and patient-specific dosimetry in radionuclide therapy. Dr. Dewaraja is a member of the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine and Molecular Imaging (SNMMI), a member of the Report Committee on Treatment Planning for Radiopharmaceutical Therapy, the International Commission on Radiation Units and Measurements (ICRU) and a member of the Working Group on Radionuclide Therapy and the American Association of Physicists in Medicine (AAPM). She is a co-chair of the QIBA SPECT Tc-99m Biomarker Committee.

John Dickson, PhD

John Dickson, PhD, is head of Clinical Nuclear Medicine Physics at the Institute of Nuclear Medicine, University College London Hospital. His interests are in quantitative multimodality PET/CT, SPECT/CT and PET/MR imaging, with a particular focus in imaging neurodegenerative diseases. Dr. Dickson is a member of the QIBA SPECT Tc-99m Biomarker Committee and a co-chair of the SPECT I-123 Biomarker Committee.

QIBA Activities

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

QIBA Resources:

- QIBA Webpage
- QIBA Wiki
- QIBA Biomarker Committees
- QIBA Organization Chart
- QIBA LinkedIn page

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

QIBA and QI/Imaging Biomarkers in the Literature

This 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.