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# QIBA Newsletter

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

**QIBA CONNECTIONS:** [QIBA Wiki](#)

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Edward F. Jackson, PhD, QIBA Chair

## IN MY OPINION

*Editor's Note: This article is a response to the In My Opinion, "Why FDG-PET is a Useful Biomarker of Tumor Response," in the October 2012 QIBA Newsletter.*

### **18F-FDG PET— from Promise to Product: Action Needed in Response to Biomarker Validation**

Otto S. Hoekstra, MD

While 18F-FDG PET-CT has an accepted role in oncological staging and re-staging, its role in response evaluation hasn't matured as quickly, except in malignant lymphoma. Response Criteria in Solid Tumors (RECIST) 1.1 guidelines involved PET, but only to the extent that new 18F-FDG-positive lesions were considered to represent progression. International Conference on Malignant Lymphoma (ICML) guidelines also implemented visual PET-evaluation only, even though emerging evidence suggests that quantitative analysis may be superior. Unfortunately, awareness that standardizing quantitative procedures to measure tracer uptake is essential has emerged relatively late. Two decades of research provides strict criteria on how much tracer uptake represents true biological change [1], and abundant proof of principle that 18F-FDG uptake changes can stratify patients even early after therapy begins. The former is highly relevant in drug development. However, it is difficult to translate the accumulated evidence into a response classification system.

Taxonomies to categorize changing tracer uptake require validation. With neoadjuvant therapy, histopathological response often provides prognostic information. Non-invasive biomarkers to detect such response might help to guide patient management in practice and trials. Data heterogeneity might be partially balanced by studying individual patient data. Such meta-analysis (50 studies un to mid-2011, >1700 patients) on the ability of 18F-FDG-PET to predict histopathological response showed that 18F-FDG-PET uptake change, as a surrogate for histopathological response, had an accuracy of 75%-80% across tumors [2]. Accuracy was better with chemotherapy than with chemoradiotherapy and in tumors with higher baseline uptake rates.

It is also unclear whether response systems (including RECIST) need to be modified for targeted agents. Often, targeted drugs have cytostatic rather than cytotoxic effects which may affect the association between lesional change and patient outcome. Moreover, variable "target" presence among tumor sites within the same patient might require a different approach. In a study combining individual non-small cell lung cancer patient data PERCIST proved to be significantly predictive for patient outcomes with cisplatinum-containing as well as targeted therapy (sorafenib, erlotinib and/or bevacizumab) [3].

Current investigations suggest that besides tracer uptake, "metabolically active volume" or radiomic features may qualify as predictive biomarkers. The PET professional community and vendors should urgently agree on standardized methodology for these metrics, to avoid wasting time and resources. Vendors should realize that society demands generally applicable quantitative measures. These should be developed at a pre-competitive level, leaving ample room for selling points unique to each product. At the academic level, initiatives towards data-sharing with transparent policy rules should be encouraged to allow for statistically and biologically sound investigation of effect modifications and biases of the 18F-FDG- PET biomarker. The wealth of data in the RECIST CT warehouse shows that this is feasible. For quantitative PET, conditions may be more demanding than for CT so that such initiatives will require financial support.

Societal concerns about costs of new therapies are increasing. Cost-effective "diagnostic-therapy combinations" should reduce toxicities as well as costs of ineffective treatment. The surge of enthusiasm about immunotherapy may be a unique opportunity to show that the PET field has learned from its past,

seizing the opportunity for concerted research efforts to validate response biomarkers. Taken together, the years ahead may become excitingly productive once the medical community, developers and vendors of drugs and scanners agree on substantial common interest.

*Otto S. Hoekstra, MD, is a Professor of Nuclear Medicine at VU University Medical Center, Amsterdam. Areas of interest are technical and biological validation of oncological imaging biomarkers, standardization of quantitative PET procedures and education on both topics. Dr. Hoekstra's background is in internal medicine and clinical epidemiology.*



#### References:

1. de Langen AJ, Vincent A, Velasquez LM, van Tinteren H, Boellaard R, Shankar LK, Boers M, Smit EF, Stroobants S, Weber WA, Hoekstra OS. [Repeatability of 18F-FDG uptake measurements in tumors: a meta-analysis.](#) *J Nucl Med.* 2012 May;53(5):701-8.
2. Vincent A, Rizvi SN, van Tinteren H, Riphagen I, Hoekstra OS. Towards qualification of FDG PET as a biomarker of response to cancer therapy: A meta-analysis *J. Nucl Med.* May 2012; 53:1444.
3. [http://qibawiki.rsna.org/images/2/20/HHSN268201000050C\\_QIBA\\_Final\\_Report\\_29-March-2013.pdf](http://qibawiki.rsna.org/images/2/20/HHSN268201000050C_QIBA_Final_Report_29-March-2013.pdf).

## PUBMED

Each issue of *QIBA Newsletter* features a link to a dynamic search in PubMed, the National Library of Medicine's interface to its MEDLINE database. Link to articles on: "[FDG-PET is a Useful Biomarker of Tumor Response.](#)"

## ANALYSIS: TOOLS & TECHNIQUES

### Assessment of Reader and Software Variability

Michael McNitt-Gray, PhD and Grace Hyun Kim, PhD

The QIBA CT Volumetry Biomarker Committee's 1B Group performed a study on patient image datasets with two time points to investigate the effects of measurement method and reading paradigm on the variability in lesion size measurement, and specifically change in size [1]. This study used the same image datasets described by Zhao *et al.* [2] with a "no change" condition. All lesions were measured by five radiologists using 1D and 3D measurement methods. In addition, two different reading paradigms were employed. In the first paradigm, the image data set from each time point was assessed independently (that is, without the ability to review the other time point). In the second paradigm, a locked, sequential reading was performed in which readers made measurements on one time point and then the results of that reading were locked. The reader was then allowed to review (but not change) the measurements made on the first time point while making the assessment on the second time point.

For the locked sequential readings, 10 cases with actual changes were used in addition to the "no change" cases. These "change" cases served as distractor cases and were used to reduce the expectation that all cases had "no change," which allowed us to estimate percent differences across time points in a practical setting. This study showed the mean percent difference ( $\pm$ SD), when pooled across both readers and lesions for 1D and 3D measurements, was  $2.8 \pm 22.2\%$  and  $23.4 \pm 105.0\%$ , respectively, for the independent reads. For the

locked sequential reads, the mean percent differences ( $\pm$ SD) reduced to  $2.52 \pm 14.2\%$  and  $7.4 \pm 44.2\%$  for the 1D and 3D measurements, respectively.

Thus, the authors concluded that even under a “no change” condition between scans, there is variation in lesion size measurements due to repeat scans and variations in reader, lesion, and measurement method. This variation was reduced when using a locked, sequential reading paradigm compared to an independent reading paradigm. While this work demonstrated a larger difference in absolute mean difference values for the 3D measurements than the 1D measurement method, when using the normalization described by Petrick *et al.* [3] in which percent size change metrics are converted to a common scale to allow comparisons (by converting 3D size estimates to a 1D (mm) scale by taking the cube root of the size estimates), the normalized 3D (volumetric) mean percent change was 2.4%, which is quite comparable to the 1D mean percent change value. Therefore, this work’s conclusion was similar to that of Petrick *et al.*, which is volumetric measurements can provide small measurement variability, and especially so when the locked sequential read is used.

*Michael McNitt-Gray, PhD, is Professor of Radiological Sciences at the David Geffen School of Medicine at UCLA, Los Angeles. His research focus is on CT physics, acquisition and reconstruction, especially for quantitative imaging applications. He has over 15 years of experience working with clinical trials and imaging core labs. Dr. McNitt-Gray is a member of the QIBA CT Volumetry Biomarker Committee.*



*Grace Hyun Kim, PhD, is an Assistant Professor of Radiological Sciences at the David Geffen School of Medicine and Biostatistics at the Field School of Medicine at UCLA. Her research focus is on biostatistics, classification using texture features, study design, and statistical analysis, especially for quantitative imaging biomarkers. She has over 12 years of experience working with clinical trials and imaging core labs. Dr. Kim is a member of the QIBA CT Volumetry Biomarker Committee.*



## FOCUS ON

### **Tribute to Dr. Sullivan**

Edward F. Jackson, PhD

### **A Debt of Gratitude to Daniel C. Sullivan, MD, Founding Chair of QIBA**

As many members of QIBA know, Dan Sullivan recently retired from the Duke University School of Medicine, and also stepped down as chair of QIBA. The positive impact directly related to Dr. Sullivan’s dedication to initiate and develop QIBA cannot be overstated. Working with RSNA leadership and senior administration, he instigated the creation of QIBA in 2007 and provided remarkably effective leadership since that time.

All of us who are associated with QIBA clearly owe a debt of gratitude to Dr. Sullivan for his vision, commitment, and leadership since 2007, and we all wish him the very best in his retirement from Duke University. Fortunately, however, he has *not* retired from QIBA. We are very pleased to report Dr. Sullivan will remain actively involved with QIBA as the vice chair of the Process Committee, as a member of the QIDW Oversight Committee, and in a new role of External Relations Liaison.

Read the full letter [here](#)

Daniel C. Sullivan, MD, is the Chair Emeritus of QIBA and a retired Professor and Vice-Chair for Research for the Department of Radiology at Duke University Medical Center. Dr. Sullivan also served as RSNA Science Advisor from 2007 – 2015.



### RSNA Awarded Third NIBIB Contract to Support QIBA Activities

The RSNA has been awarded a new two-year contract for \$2.5 million, from the National Institute of Biomedical Imaging and Bioengineering (NIBIB), to support the Quantitative Imaging Biomarkers Alliance (QIBA) and its research activities. Imaging biomarkers are of considerable interest in evidence-based clinical decision making and for therapeutic development. A portion of this funding will support groundwork projects by QIBA members to help validate specific imaging metrics, improve reproducibility and standardization across vendor platforms. This multi-stakeholder collaboration will produce standards documents, informed by the groundwork activities, physical phantoms and digital reference objects to test the performance specifications in the documents, and data sets to assess compliance. QIBA will also continue to share outcomes to help educate imaging physicians about the reliability of Quantitative Imaging. The QIBA Biomarker Committees will hold working meetings during RSNA 2015.

## QIBA ACTIVITIES

### SAVE-THE-DATE

#### QIBA Biomarker Committee Working Meeting at RSNA 2015

Wednesday, Dec. 2, 2:30-5:00 p.m. – Lakeside Center

- Plenary Session: 2:30-3:00 p.m.
- Breakout Sessions: 3:00-5:00 p.m. (*Breakout rooms will be available until 6:00 p.m.*)

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](http://RSNA.ORG/QIBA) and wiki <http://qibawiki.rsna.org/>

Please contact [QIBA@rsna.org](mailto:QIBA@rsna.org) for more information.

### QIBA Kiosk

Located at the front of the Learning Center, Hall D, the QIBA kiosk provides an overview of the QIBA Biomarker Committees and the Profile process, and provides an area for QIBA members to meet and exchange ideas.