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.

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IN MY OPINION

Standardization of Clinical Trial Image Acquisition is Essential for Establishing Clinical Utility
By GARY S. DORFMAN, MD

In March of 2004, the U.S. Food and Drug Administration (FDA) issued a landmark white paper, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," providing an analysis of the "pipeline problem" defined as the slowdown in the delivery of innovative medical therapies to patients [1]. This slowdown in the availability of innovative biologic, pharmacologic, and device-based therapies is even more vexing as the magnitude of the National Institutes of Health (NIH) and industry investment per marketed product is skyrocketing and the number of potential new biologics, drugs, and medical devices undergoing development and investigation is also increasing, even as the annual number of new drugs continues to decrease.

That white paper suggested multiple contributing factors and potential solutions to remedy the failure of efficient translation from the bench to bedside by affecting three critical dimensions along the critical path from innovation to commercialization: 1) assessing safety, 2) demonstrating clinical utility, and 3) industrialization. One dimension not addressed by the Critical Path Initiative is facilitating availability to actual patients in the real world—a point I return to later in this paper.

With regard to safety, the FDA suggested that the development of biomarkers to define the best patient population to include in clinical trials (and therefore exclude subjects with lower chances of a clinically important response) would increase safety and decrease the size of clinical trials designed to demonstrate safety and/or efficacy. With regard to clinical utility, the agency suggested that the development of biomarkers that might be intermediate surrogates for clinically important outcomes would decrease duration of the clinical trial while still delivering an efficacy endpoint.

The document also suggests that *in vivo* biomarkers might be preferred in many circumstances as *in vitro* biomarkers might not be fully reflective of important aspects of pathophysiology related to the investigational intervention. In fact, several examples of imaging studies are included in the white paper.

Prior to use in the critical path, such biomarkers would have to be validated and found to be reflective of putative physiologically and/or clinically important endpoints. Such validation would demand multiple features, among them precision and accuracy. Specifically, variations in the measurement of the various biomarkers would need to be related to an actual variation in the underlying endpoint itself rather than some artifact of the biomarker measurement process.

The National Cancer Institute's Translational Research Working Group (TRWG) suggested four pathways for the development of various cancer interventions (drug or biologic agents, immune-response modifiers, interventive devices, and lifestyle alterations). For each of these intervention flow charts, the TRWG embedded the co-development of two types of biomarkers—one for identifying the appropriate cohort of subjects (or patients) to whom the intervention would be targeted; and a second for assessing the effect of the intervention on the purported target (see Figure 1) [2]. The TRWG hypothesized that either *in vitro* (biospecimen-based risk assessment devices) or *in vivo* (image-based risk assessment agents or techniques) biomarkers might fulfill either or both of these roles. Quantitative imaging biomarkers would be the archetypical *in vivo* biomarker for either cohort identification or response assessment. The developmental pathway for image-based risk assessment agents or techniques is of particular interest to this discussion [3]. In fact, the QIBA Profiles workflow is congruous with this particular developmental pathway [4].
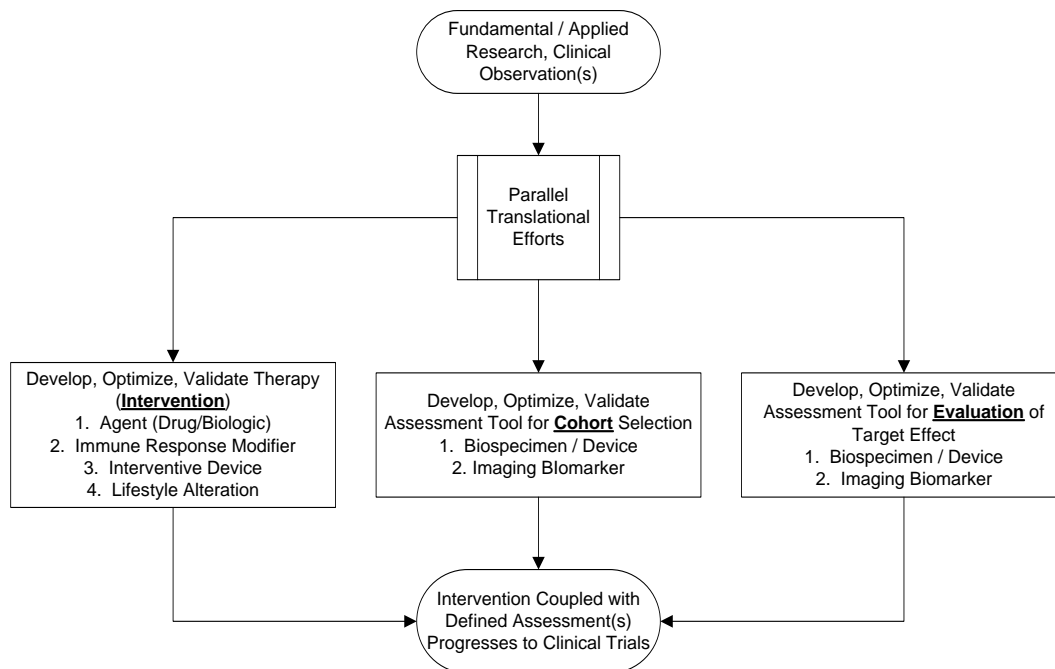
Figure 1: Diagrammatic Representation of the TRWG Developmental Pathways

Quantitative imaging biomarkers would be particularly useful along the critical path from bench to bedside. And as stated previously, variations in the quantitative output of such imaging biomarkers would need to be reliably related to the underlying biology or physiology of the disease and/or intervention rather than an artifact of the manner in which the quantitative imaging test was performed. Specifically, this would demand standardization of image acquisition and analysis of the data resulting from the acquisition. This standardization would need to transcend the various manufacturers' proprietary equipment and software models and versions as well as idiosyncratic behaviors with physician practices that are engaged in the conduct of imaging during clinical trials.

Hence, as the title of this opinion piece suggests, standardization of clinical trial image acquisition and analysis is essential to establishing clinical utility of innovative drug, biologic, and device-based interventions.

But what of the clinical utility of the imaging tests per se, rather than the interventions brought to market in part by the availability of those quantitative imaging tests? As mentioned above, a vital part of the "pipeline" is the actual availability of the commercialized innovative interventions to patients in the real world. It is entirely reasonable to assume that the very tests that were used to identify the proper cohort in the clinical trials will be required to establish appropriateness of patient selection in clinical practice. In addition, the very tests that were used to make early determinations of treatment effect during the clinical trials will likely be required to assess clinical impact in practice. Therefore, it is quite likely that the same degree of standardization in image acquisition and analysis will be required in clinical practice (for patient triage and follow-up) as will be used in the conduct of clinical trials (for assignment to the treatment cohort and for endpoint determination). Thus, standardization in acquisition and analysis will be essential in clinical practice to establish the clinical utility of these imaging tests in everyday use.

The current QIBA initiatives coupled with the implementation of Uniform Protocols for Imaging in Clinical Trials (UPICT) are on the Critical Path for imaging biomarker development, validation, and qualification. Promulgating these standardization programs into widespread clinical adoption is vital to establishing standardized quantitative imaging in clinical practice. The QIBA Technical Committee profiles focus on establishing performance claims for imaging platforms that result from standardized technical characteristics of those platforms when operated under standardized specified conditions for specific clinical conditions. The UPICT protocols are prescriptions to standardize image acquisition and analysis during the conduct of clinical trials. A description of the UPICT process and the elements that constitute these protocols may be found here: [5].

The majority of *in vitro* biospecimen-based tests include standardized methods for 1) managing the subject/patient prior to obtaining the sample for testing, 2) extracting the biospecimen from the human subject/patient, 3) handling the sample after extraction but prior to the actual test, 4) performing various steps during the actual test, 5) analyzing the data that result from the test, and 6) reporting the results often including comparison to normative benchmarks. The UPICT protocol elements similarly provide guidance for the standardization of acquisition and analysis inherent in imaging tests inclusive of pre-test subject management through and including reporting of results in the clinical trial setting. In addition, there is guidance within the UPICT protocol for the incorporation of the imaging tests within the clinical trial protocol itself. While some of the elements integral to the UPICT protocol will be unnecessary to the translation of these imaging protocols from the research setting into the clinical practice setting, the retention of other elements will be critical to the demonstration of clinical utility.

The combination of imaging platforms compliant with QIBA Profiles and implemented by practicing radiologists in a manner consistent with UPICT protocols will help transform imaging tests into reliable and necessary quantitative tools for patient triage and therapeutic monitoring i.e., the paradigm of personalized medicine.

Biomarker Roadmap (7/20/10)

		Statement of Value to stakeholders: patients, manufacturers, Pharma, etc. What are alternatives?	Discovery of potential imaging biomarker	Do tools exist or do new assays or other supporting tools need to be developed?*	Test / refine imaging performance, PK/PD, toxicology, etc. in preclinical setting			Optimize acquisition and analytic parameters in preclinical or Phase 0 setting	Test / refine imaging performance, PK/PD, toxicology, etc. in Phase I/II setting	Phase II+ trials for specific clinical utilities
Column headings in these first three rows are from TRWG Imaging Modality (IM) Pathway	*Column headings in this row are from TRWG IM, specific to imaging agents*			Current scanners can perform desired function?	Establish GMP production for agent if necessary	Submit IND if necessary		Establish GMP manufacturing if necessary		
	Column headings in this row are from TRWG IM, specific to devices			Develop necessary new imaging platform or function? (iterative with development of technique)	Pre-IDE meeting for platform if necessary	separate image acquisition and image analysis?	File IDE if necessary; If optimized platform available for clinical testing, file 510(k) if necessary			

	Technical Characteristics and Standards Groundwork (systems engineering analysis of sources of variability)			Clinical Performance Groundwork (Sensitivity and specificity for expert readers)		Clinical Efficacy Groundwork ("real world" imaging conditions)		
Define and iteratively refine acquistion, analysis, interpretation, QC, etc. (UPICT) for specific clinical utility (also define "gaps")	Phantom development	Assessment of intrinsic scanner variability / minimum detectable change	Assessment of intra- and inter-reader (human and/or computer) bias and variance across scanners and centers	intra-reader	Inter-reader (Multiple image analysts)	Correlation between new biomarker and "accepted-as-standard" method	Value from new imaging biomarker in clinical trials	Value from new imaging biomarker in clinical practice

Column headings in this row are from QIBA Pathway — *Pre-QIBA (though IB Roundtable may address these)*

Iterative refinement of UPICT during the row 4 and 5 activities for the specific clinical utilities

Implement the refined UPICT protocols during these Phase II+ trials and develop / merge databases from the trials to support validation and qualification of imaging biomarkers
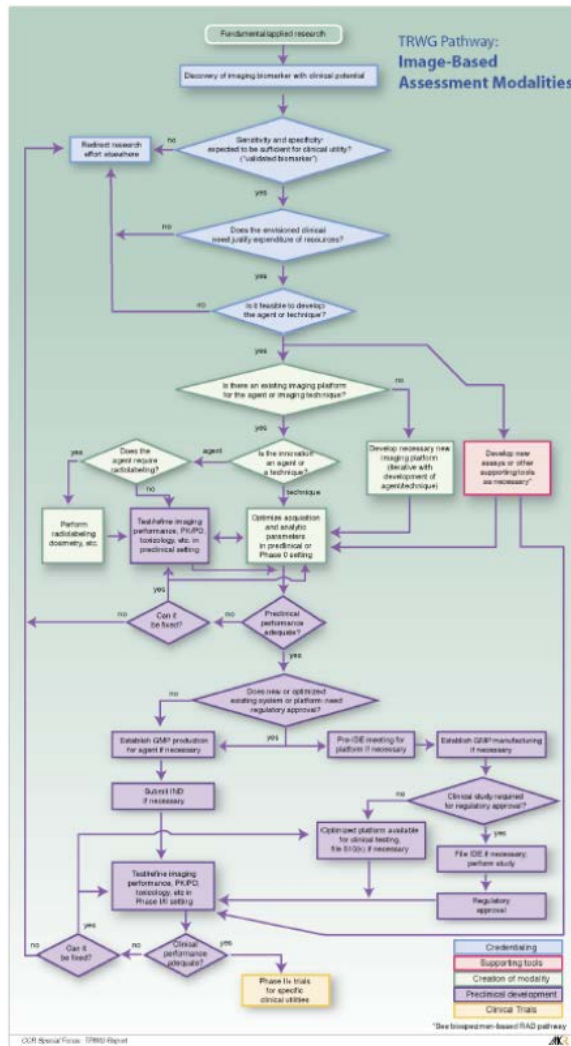
Figure 2: QIBA Biomarker Roadmap

Figure 3: https://www.cancer.gov

References:

[1] U.S. Food and Drug Administration, Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products

[2] National Cancer Institute (NCI), Introduction to the Translational Research Working Group (TRWG) Developmental Pathways

[3] NCI TRWG Image Assessment Model

[4] QIBA Biomarker Roadmap

[5] UPICT Template

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Challenges in Tackling Quantitative DCE-MRI

By: ALEXANDER GUIMARAES, MD, PhD

New blood vessel formation is a prominent feature in cancer. The malignant neovascular angiogenic phenotype is disorganized, nonuniform in size, and has been shown to be hyperpermeable to small molecules. The ability to quantify angiogenesis in tumors is thus important for prognosis, for planning treatment and assessing the therapeutic efficacy of angiogenesis inhibitors. In addition to serum and tissue markers, imaging parameters have demonstrated efficacy as surrogate biomarkers of anti-angiogenic therapy. Given the hyperpermeability of tumor neovasculature, dynamic contrast-enhanced MR imaging (DCE-MRI) has become an important tool for preclinical and clinical evaluation of microvascular changes associated with anti-angiogenic therapies. However, the introduction of DCE-MRI into clinical trials and clinical and drug development research has highlighted many challenges—namely, the relatively high variance of the technique.

Why is the variance so high? A short description of the DCE-MRI experiment may shed some light on the question. DCE-MRI can be analyzed using quantitative models based on the rapid intravenous (i.v.) administration and distribution of low-molecular-weight extracellular gadolinium-based contrast agents. Dynamic imaging techniques that depend on T1 contrast mechanisms yield rapid brightening of the tissues of interest. For quantification we must derive or estimate a native T1, vascular input function (VIF), and model the signal changes associated with quantitative or semiquantitative (model-independent) methods. Analysis of these data allows estimation of microvessel permeability (Ktrans).
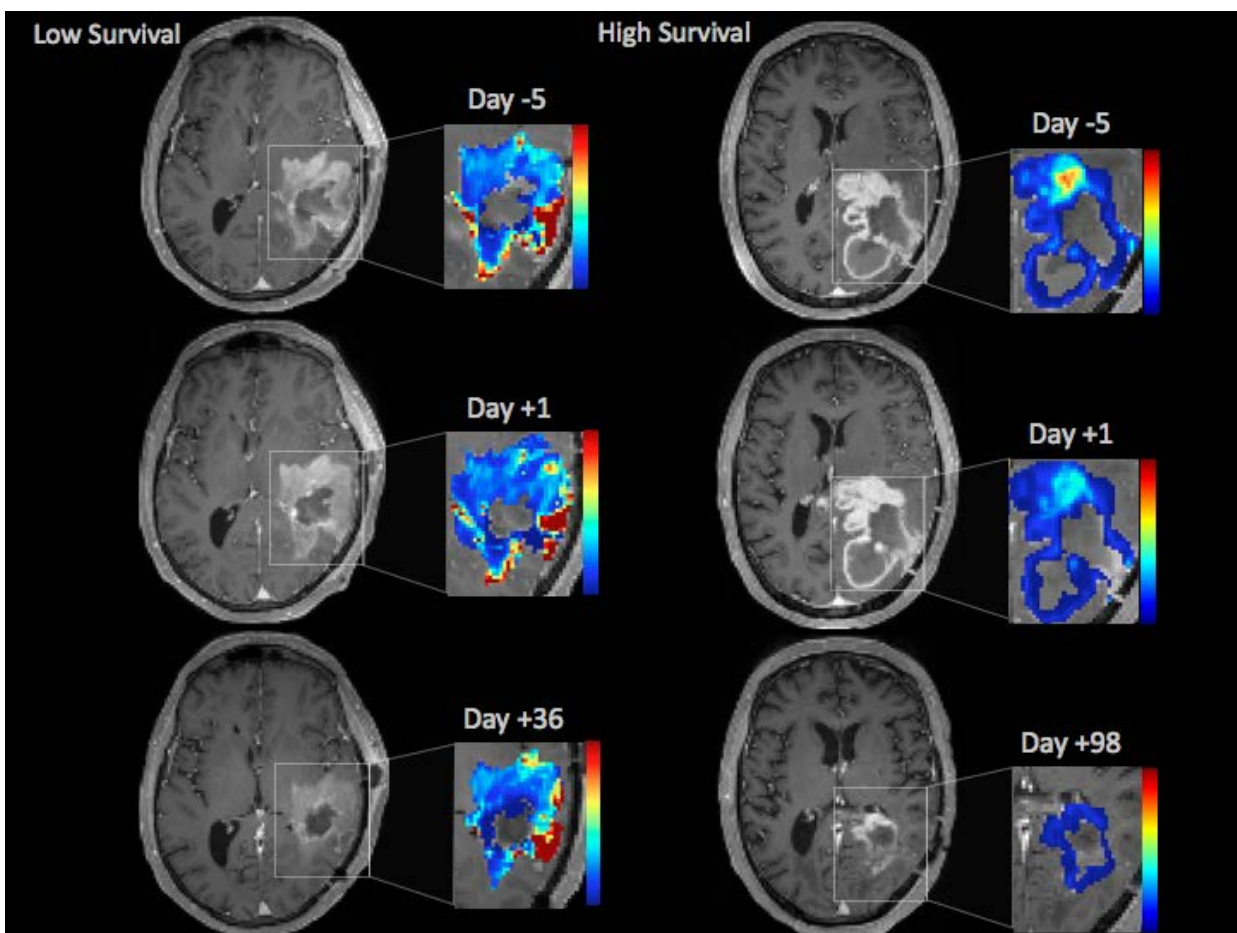
DCE-MRI Ktrans maps overlaid and zoomed up comparing two patients with glioblastoma multiforme (GBM) within the left parietal lobe, taken five days prior to, one day following, and 36 days following administration of a novel small molecule VEGF inhibitor. Note the areas of high permeability throughout the tumor in both the low and high survival patients. In the patient that demonstrated increased long-term survival benefit there was dramatic change in permeability as measured by Ktrans, which translated to tumor volume decrease and thus survival. (*Figure courtesy of Drs. Dominique Jennings and Elizabeth Gerstner*)

DCE-MRI requires the acquisition of parametric native T1 maps prior to dynamic instillation of contrast media, and all methods to date, including inversion recovery (IR) and variable flip angle (VFA) techniques, are B1-sensitive and a source of variance. The time-consuming nature of IR techniques also precludes their use for routine clinical or clinical research examination. Although also a source of variability, accurate estimation of VIF can compensate for changes related to rate of injection and cardiac output. Still, accurate estimation of VIF presents a significant hurdle secondary to in-flow pulsatility artifacts, and to accurately convert signal intensity (as measured by MR imaging) to relevant biomarkers, it is necessary to incorporate methods that can determine contrast agent concentration at each timepoint during the measurement period.

To overcome this variability, some groups have used population-based VIF, which removes some of these sources of variability but introduces others. Each of these variables has inherent high statistical variance; therefore, when input into a model, the combination begins to shed light on the high variance associated with quantitative estimates of Ktrans.

By inputting these spatially derived quantitative parameters into the Tofts' two-compartment kinetic model, based on the seminal Kety model, we can extract Ktrans. Although a widely accepted means of modeling tumor microvasculature, this generalized approach may not adequately reflect the microenvironment of different tumors (e.g., pancreatic cancer vs. glioblastoma) and, therefore, may not be spatially robust, potentially introducing errors that contribute to the approximate 20% variability inherent to the technique.

Quantitative approaches that demand less rigor (e.g., initial area under the gadolinium concentration curve [IAUGC]) are also included in routine analysis to reduce variance; however, such measures do not provide the same specific physiologic estimates of permeability as derived from the quantitative Tofts' model.

The combination of all of these sources of variance, therefore, illustrates the complex challenge for QIBA to create a Profile for vendors and sites to accurately perform DCE-MRI. For these reasons, QIBA has endorsed a literature-based claim (20% variance in baseline Ktrans and IAUGC measures) that is achievable when constrained to methods that reflect the peer-reviewed literature. Although exciting and provocative, DCE-MRI represents just one of many compelling and challenging opportunities for QIBA to tackle.

Alexander R. Guimaraes, MD, PhD, is medical director of the Martinos Center for Biomedical Imaging in the Department of Radiology at Massachusetts General Hospital, Boston. His clinical interests are in abdominal imaging with scientific interests in developing quantitative MR imaging methods for evaluating tumor response to targeted and non-targeted chemotherapeutic agents. He serves as the Profile editor for the DCE-MRI subcommittee.

QIBA AND QI/ IMAGING BIOMARKERS IN THE LITERATURE

This list of references showcases articles that mention QIBA, quantitative imaging, or quantitative imaging biomarkers. Most articles are published by QIBA members. New submissions are welcome and may be directed to QIBA@rsna.org