Report on the Quantitative Imaging Biomarkers Alliance Task Force

August 25, 2011

Overview and Charge:

The Radiological Society of North America (RSNA) commissioned a task force of experts from academia, industry, and government to addresss the role of quantitative imaging (QI) and imaging biomarkers (IB) in radiology and to provide recommendations to the RSNA Board of Directors regarding future directions for RSNA support of initiatives related to QI.

The formal charge to the ad hoc task force was:

- Assess the importance of and priorities for programs in QI and IB from the perspective of the RSNA and its members
- Make recommendations to the RSNA Board of Directors about future directions for and its most appropriate role in programs in quantitative imaging and imaging biomarkers.
- Evaluate the effectiveness and structure of the existing RSNA programs in quantitative imaging and imaging biomarkers and make recommendations for change if appropriate
- If the task force recommends continuance of the Quantitative Imaging Biomarkers Alliance, identify models for assuring its long-term functional and financial stability.

A 9-12 month window was established for completion of the task force duties, with the expectation of a report or “white paper”.

Process:

Carolyn C. Meltzer, M.D. was appointed as task force chair and engaged stakeholders from radiology, industry, and government to serve as members with key and complementary expertise (see Appendix 1 for full list of task force members). RSNA staff, Linda Bresolin, Ph.D. and Fiona Miller supported the process. Daniel Sullivan, MD, QIBA Chair, participated as an ex officio member. Reed Dunnick, M.D. served as liaison to the Board.

The task force carried out its activities through monthly conference calls and a one-day, in-person meeting held in Arlington, Virginia on May 26, 2011. Due to the scope of the charge and the diversity of expertise of the task force membership, it was felt that a face-to-face meeting relatively early in the proceedings would most efficiently and effectively serve the task force goals. Additional group and select individual follow-up conference calls were conducted to develop consensus and derive additional information from individuals with specific content knowledge.

The task force deliberated the overarching question of whether the current suite of RSNA QI/IB activities [Quantitative Imaging Biomarkers Alliance (QIBA), Toward Quantitative Imaging (TQI), CTSA Imaging Working Group (IWG), Imaging Biomarker Roundtable] were worthy and appropriate undertakings. Discussion further focused on

strategic evaluation of QIBA in terms of of: 1) scope and priorities among its component programs, 2) governance, and 3) funding sustainability.

Executive Summary:

The *RSNA 2011-2016 Strategic Plan* strives to advance the radiological sciences and foster the development of new technologies in part by promoting the "translation of radiologic science and quantification to clinical care." While there remain substantial barriers to the widespread use of quantitative measures in clinical radiology – including inherently large number of variables that impede validation of specific metrics, diversity of proprietary industry platforms, and lack of acceptance by radiologists – there was consensus among task force members that QIBA activities were both valuable and an appropriate investment by the RSNA. Indeed the added value of quantification in both the translational research and clinical environments is likely to increase as health care reform initiatives place increased pressure on radiologists to provide decision support for evidence-based care.

The Task Force believes that quantitative imaging and imaging biomarkers are critical to the future of radiology and should remain a priority for attention by the RSNA. Mechanisms to accelerate the development of QIBA-branded protocols and profiles should be pursued, and priority should be given to biomarkers that directly apply to patient care in addition to drug development and validation. Formal interaction with non-imaging medical societies (referring clinicians) may assist in identifying high priority biomarkers to address.

A re-distribution of current RSNA funding and efforts may be necessary to allocate limited resources to the most critical of the QI/IB initiatives. Selective simplification of the governance and structure of the RSNA QI/IB activities will facilitate this re-distribution. The task force recommends that the TQI program be mainstreamed into general RSNA program planning and that the activities of the CTSA Imaging Working Group should be reassigned to the Vice Chairs group of the Research Development Committee, with the exception of the UPICT program, which should remain with QIBA. Finally, the communication functions of the Imaging Biomarkers Roundtable, while important, should be pursued on an ad hoc activity held in conjunction with other QI/IB programs.

Leadership is critical to sustaining the QI/IB efforts. Each QIBA committee should be asked to develop a leadership succession plan. Additionally progress may be accelerated through RSNA hiring an additional staff member with content expertise appropriate to support and facilitate Profile development.

Background and History of QIBA

The RSNA has invested progressively more resources in QI since 2006, when the Board was approached by scientists from the pharmaceutical industry as an organization that had the resources and reputation to guide the standardization and implementation of QI in clinical trials. QIBA was officially launched in 2007 as a means to unite researchers, healthcare professionals, and industry stakeholders in the advancement of quantitative imaging and the use of biomarkers in both clinical trials and practice. For effective use in clinical trials, QI/IB needs to be standardized so that

imaging biomarkers can serve as a means for drug qualification. The clinical applications are sometimes distinct, but development of standard practices may yield advances in both the clinical and investigative arena (e.g., many biomarkers that are needed for drug discovery are likely to have further clinical relevance).

As the RSNA's efforts in QI have evolved, they have come to be structured into several interrelated entities, as described below and depicted in the schematic in Figure 1.

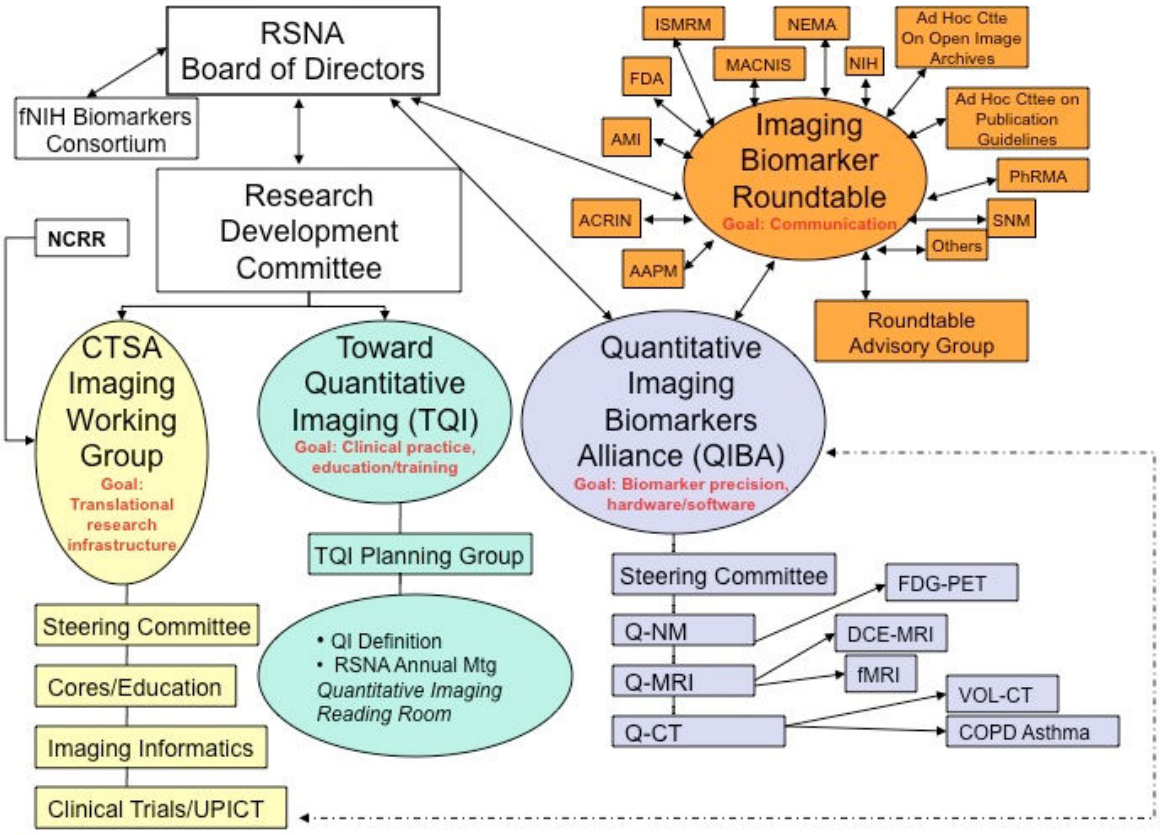

Figure 1. Schematic of the organizational structure of QIBA and related activities

The Quantitative Imaging Biomarkers Alliance (QIBA) - *This parent initiative, whose mission to: "*Improve the value and practicality of quantitative biomarkers by reducing variability across devices, patients and time" sets the tone for all of RSNA's QI activities. QIBA's five active technical committees (DCE-MRI, fMRI, FDG-PET, volumetric CT, COPD-Asthma) develop Profiles of standardized specifications for image acquisition, collection, and post-processing. Such Profiles must take into consideration technical (product-specific) standards, user activities, and relationship to a clinically meaningful metric such as therapeutic response or other patient outcome measure.

The Imaging Biomarker Roundtable (IBRT) - The Imaging Biomarkers Roundtable is a forum for stakeholders involved in quantitative imaging and imaging biomarkers to communicate on common challenges and solutions. For example, at a September 21/22, 2010 IBRT meeting, the 54 attendees heard presentations from 17 organizations and participated in breakout discussions on: 1) regulatory approach to combined products, 2) open image archives, 3) PET Profile and protocol writing, and 4) Alzheimer's Imaging biomarkers.

The CTSA Imaging Working Group (IWG) – Since a key aspect of the NIH Clinical and Translational Science Awards (CTSA) awards was the intent to form a national consortium through which multi-center trials and best practices in translational research were fostered, forming a working group to facilitate such efforts among imaging leaders at CTSA institutions was a logical role for the RSNA. In-person meetings held at the RSNA Annual Meetings were well attended, and over 250 members joined the IWG. Three subcommitees (Cores/Education, Informatics, and Clinical Trials,) communicate in monthly phone calls. The latter subcommittee has been instrumental in supporting the ***Uniform Protocols for Imaging in Clinical Trials (UPICT)*** project.

The Toward Quantitative Imaging (TQI) group - The ad hoc TQI group focuses on using RSNA channels to advance and promote QI and IB as part of the future of radiologic practice. A major aspect of the effort is educating practicing radiologists about strategies for and the importance of augmenting subjective image interpretation with quantitative measures. Its efforts have, to date, been focused on using the RSNA Annual Meeting as an educational forum.

Support for QI/BA activities has largely come through RSNA funding. More recently, a federal contract from the National Institute of Biomedical Imaging and Bioengineering (NIBIB) was awarded in support of QIBA and related activities. Taken from ARRA (American Recovery and Reinvestment Act of 2009) monies, the contract provides support of approximately $1.2 million for each of two years. Half the money will be used to offset RSNA costs, while the other half will subsidize subcontracts to support the activities of the technical committees. (See Appendix 2 for a list of the funded projects and investigators selected through a competitive process for the first year's funding cycle).

Barriers and Opportunities

In our evolving health care system in which standardization of evidence-based protocols is stressed, there is increasing incentive to transition from a largely qualitative practice paradigm to one with reproducible and meaningful quantitative elements. QI offers the promise of many improvements, including improved patient care through reduced variability in imaging test results reporting, greater efficiency and lower cost of radiological techniques, enabling of lowered radiation doses, and production of objective data that can be used for comparative effectiveness research and treatment trials. A move toward evidence of efficacy in the field of radiology is needed in the current landscape of health care evolution, and radiology lags behind the movement toward quantification that has become common among non-radiologic investigators in imaging research.

Yet not all radiology will become quantitative; some fields do not require QI and may not benefit from a move toward QI. Identification of disorders in which QI is likely to advance medicine is an important step toward determining the current state and needs of the field. While it is beyond the purview of the QIBA task force to answer questions about the needs of specific fields or which individual biomarkers to focus on, QIBA should have an effective means of prioritizing such measures going forward. The overarching themes of what will drive clinical medicine may be similar across the spectrum of radiology subspecialties. Indeed, as we better understand what is possible, we can develop predictions of how QI/IB will help clinicians and thereby determine the imperatives for QI in clinical radiology.

There are cultural barriers to the adoption of QI by radiologists, even in settings in which clear benefit has been validated and demonstrated. The major obstacles to overcome with practicing radiologists are a distrust of the reliability of QI and the fear of losing value of the radiologists' expertise through automation and commoditization. While the impact of QI on the business of radiology is uncertain, the attitude of radiologists toward QI's variability and inaccuracy may be subject to modification. One reason radiologists resist QI is because they believe their subjective impressions may be more valued in the clinical setting. Some of these impressions may be also influenced by a fear of the unknown—radiologists who are not trained in QI may feel uncomfortable with the change. There may also be a concern that QI may impede patient/clinician understanding by giving a false sense of exact knowledge.

Cultural change is needed among practicing radiologists and radiologists-in-training to overcome these preconceptions and reduce behavioral variations. Radiology needs to move toward practice that is clinically relevant and adds measurable predictive value.

An additional critical barrier to the implementation of QI in radiology is the lack of standardization among vendor platforms. Manufacturers strive for competitive differentiation in the marketplace, which often means distinct proprietary formats and technical specifications. Collaboration in the pre-competitive space is challenging yet crucial to address standardization, and integrating quantitative measurement into workflow will be necessary for wide adoption. However, regulatory issues in introducing new applications to support QI is a major hurdle for equipment manufacturers, especially when considering economic issues, healthcare reform, and the NIH budget drop.

The national investment in imaging research has fallen, and radiology as a field should be investing resources into technological development and research. RSNA funds are therefore critical. However, we need realistic expectations of what we can gain from QI. Radiology is in the business of providing information, and the precision with which we can do it adds value — QI may reduce variability, but it may not make imaging practice and science less dependent on human observers. Most important are data showing that quantitative measurements influence patient outcomes and thus provide specific clinical relevance.

This is particularly important in the evolving healthcare landscape. The payer community expects a demonstration of value to affect clinical decision-making. We need to show concrete benefit to the field in a patient environment. Simple and reliable QI/IB measures should enhance the value of radiology in the evolving healthcare field. The co-development of IBs for both clinical practice and trials may provide the best opportunity.

Discussion Points

While there has been progress in several areas of QIBA and its related activites, it has been slower than expected and some of the QI/IB component initiatives are considered more successful than others. Clearly the main QIBA initiative is the central effort and provides overall direction for the related QI/IB activities. The development of standardized Profiles was viewed as its most important metric of productivity. Two have been created and released for public comment so far. Barriers to success have included: differences of opinion on the exact format for the Profiles, how specific Profiles should be, and when and how to disseminate completed Profiles. The development of accepted Profiles is probably the greatest opportunity for impact.

The creation of meaningful QIBA-branded Profiles as the gold standard for adoption by industry and radiologists for research and eventual clinical quantification could transform the use of IB in an evidence-based health care system. Acceleration of the Profile standardization and production process would likely require augmentation of the volunteer efforts with additional expert staff.

While the CTSAs have been an excellent mechanism for bolstering the infrastructure to foster clinical and translational research at individual institutions or local/regional consortia of institutions, the diversity of structure among the CTSAs has made the CTSA National Consortium an undertaking that lacks a clear scientific focus. With the change in emphasis on CTSAs under NIH Director Francis Collins and their impending migration from NCRR to the new NIH entity NCATS (National Center for Advancing Translational Sciences), the priorities for coordinating national efforts are less clear. The CTSA IWG has also had limited productivity, and its future purpose is unclear. Some of the IWG functions could be transferred to other structures in the RSNA, such as the Research Development Committee and Radiology Informatics Committee. However, the UPICT function, which is relevant to the QI activities should be retained, potentially as a cross-cutting committee of QIBA.

The IBRT is a unique and useful forum for communication among stakeholder groups, including industry, government, and the radiology community. Indeed, continued interaction with pharmaceutical industry and regulatory groups is quite important. Yet the task force expressed concern that QIBA may benefit from IBRT having a more defined function and perhaps structure. Regarding the latter, one consideration would be for IBRT activities to be overseen and prioritized by subcommittee of the QIBA steering committee.

Given the ability of the RSNA to reach and influence such a large portion of the radiology community, the task force felt that the educational aspects of QIBA, including TQI, should be more seamlessly integrated into the educational activities of the RSNA.

There is clear interest among the membership, as evidenced by standing room-only participation in an RSNA 2010 special interest session providing an update on imaging biomarkers.

Recommendations:

Scope/Priorities:

1. **Quantitative imaging and imaging biomarkers (QI/IB) are critical to the future of radiology.** Support of QI research and implementation should remain a priority for the RSNA. The task force recommends continuing investment by the RSNA in QIBA, and increasing prioritization for integration into RSNA educational efforts.

A. Accelerated standardization and development of QIBA-branded UPICT Protocols and QIBA Profiles that can be used to compare quantification from images across sites and industry platforms and are relevant to patient outcomes should be the highest priority of QIBA. These QIBA standards should be accompanied by limited reference data sets, made available through a website, so that companies that wish to use the standard have a common way of validating their measures. With increasing demand from the RSNA membership, industry partners would see complying with QIBA standards as a marketing advantage. Additional expert staff may be needed to supplement volunteer efforts to achieve this goal.

A later phase might include the development of a compliance program to determine whether equipment is QIBA Profile-compliant, using QIBA-branded or recommended phantoms(test objects). In this scenario, companies would submit data for review by QIBA experts to determine if indeed acceptable compliance with QIBA Profiles has been achieved. QIBA accreditation of practice and/or facility adherence to QIBA Profiles and UPICT protocols would be a considerably greater commitment with large budgetary needs. While such accreditation programs could produce an income stream for sustainability of QIBA activities, they were viewed by the task force as requiring considerable additional resources, potentially competing with or adding complexity to existing accreditation programs, and outside the current scope of QIBA.

B. QIBA should also prioritize biomarkers that benefit direct patient care in addition to those that support drug development and validation. Prioritization should be given to developing Profiles that address priorities for the CMS Physician Quality Reporting System (taking advantage of motivation of the RSNA membership to seek these incentives) and other areas in which qualitiative imaging is inadequate. Suggestions for imaging biomarkers to be prioritized next include carotid stenosis, lung nodules (e.g., in lung cancer screening), ejection fraction for MR and CT, coronary stenosis, brain perfusion, breast MRI, endovascular aneurysm repair planning (characterization of abdominal and thoracic aortic aneurysms), and brain aneurysm characterization (key dimensions and ratios). Of note, current QIBA work on validation of tumor biomarkers, including volumetry and PET/CT SUV calculation, are substantial areas of need and warrant continued prioritization.

2. **The RSNA Board should consider developing a process to interact with non-imaging societies (e.g., ASCO) to identify driving clinical needs and priorities for biomarkers to address.** This could also be a function of a communication arm of QIBA.

Governance:

3. **Improvements to the QI/IB structure should be made.** The task force felt that selective changes to the governance and structure of the RSNA QI/IB activites could allow greater focus of resources on the largest and most important program, QIBA:

A. TQI should be transitioned in a phased way into the main program planning mechanisms for the RSNA Annual Meeting and Scientific Assembly.

B. The *CTSA Imaging Working Group* programs can be segmented out of the QI/IB map, with the probable exception of the Uniform Protocols for Imaging in Clinical Trials (UPICT) project. UPICT can be integrated into the QIBA governance structure. Some of the CTSA IWG interest areas might be integrated into other RSNA governance structures, such as the Research Development Committee and Radiology Informatics Committee.

C. Each QIBA committee should be asked to develop a leadership succession plan.

D. Communication and coordination among stakeholders involved in QI/IB is critical. However, the *Imaging Biomarkers Roundtable* does not need to serve as a standing group but rather may be most appropriate as an ad hoc, periodic event (perhaps tied to the QIBA annual meeting) that permits periodic two-way communication with a diverse group of external stakeholder groups.

E. While no immediate need for an external advisory board was identified, there may be a future time when such a group – small, focused and perhaps comprised of a subset of Roundtable participants – could be identified to serve in such a role.

A suggested simplified version of the current governance structure depicted in Figure 1 is proposed in Figure 2 below:

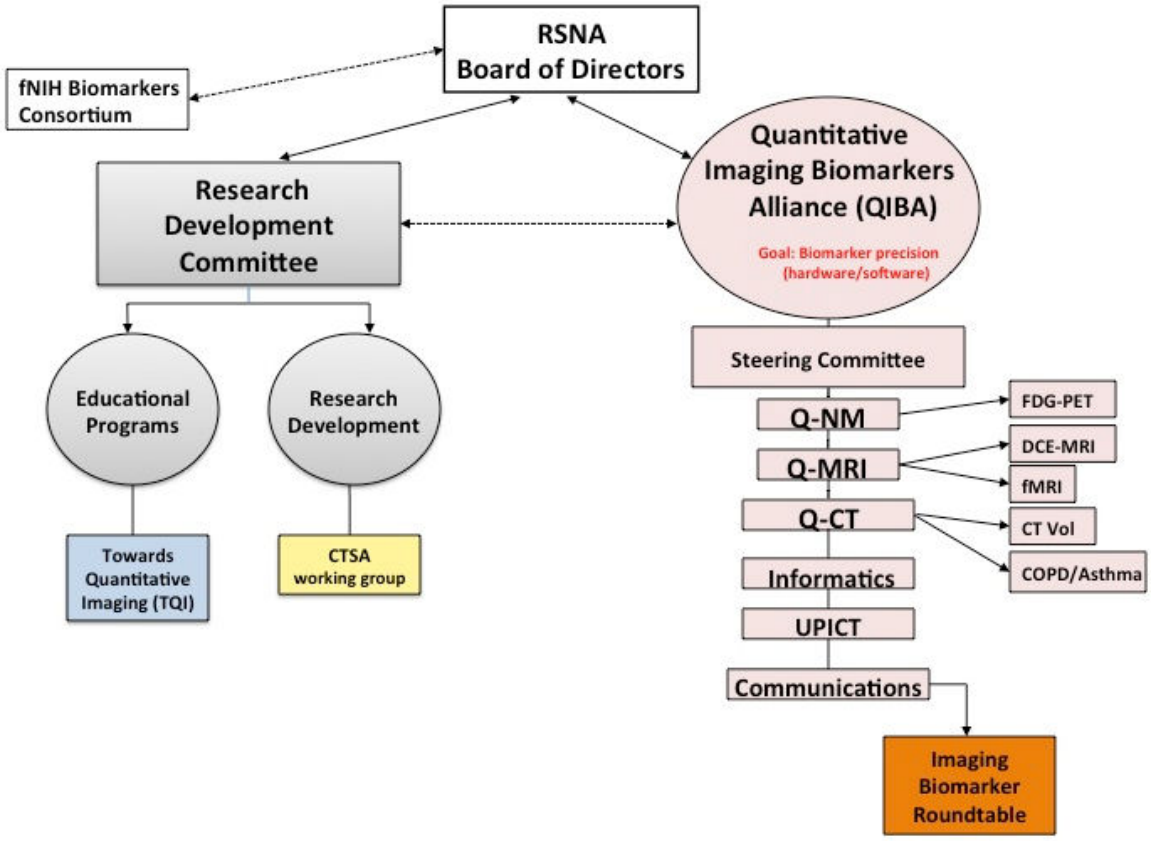

Figure 2. Schematic of the proposed organizational structure of QIBA and related activities

4. Leadership Sustainability: In consideration of the heavy administrative burden inherent in producing complex Profiles and the current predominent reliance on volunteer efforts, **an additional staff member with expertise appropriate to focus on program management of Profiles would be beneficial to the goals of QIBA**.

Appendix 1

Task Force Membership

Carolyn Meltzer, MD (Chair)	Emory University School of Medicine
Thomas M. Grist, MD	University of Wisconsin-Madison
David Jay Seidenwurm, MD	Radiological Associates of Sacramento
J. Anthony Seibert, PhD	University of California, Davis
Etta D. Pisano, MD	Medical University of South Carolina
Maureen White, MS, MD, MBA, FACR, FACPE	GE Healthcare Systems
Richard L. Ehman, MD	Mayo Clinic
Emily Rose White, MS	Science Writer
Max Wintermark, MD	University of Virginia
Jonathan S. Lewin, MD	Johns Hopkins University
Daniel C. Sullivan, MD	RSNA
Fiona Miller	RSNA
Linda Bresolin, PhD, MBA, CAE	RSNA
Gary S. Dorfman, MD	Weill Cornell Medical College
Jeffrey L. Evelhoch, PhD	Merck Research Laboratories
Robert Taylor, PhD	President & CEO, TeraRecon, Inc.
David A. Bluemke, MD, PhD	National Institutes of Health
Satoshi Minoshima, MD, PhD	University of Washington
N. Reed Dunnick, MD	University of Michigan
Bruce Rosen, MD, PhD	Harvard-Massachusetts General Hospital
Belinda Seto, PhD	National Institutes of Health
Paul E. Kinahan, PhD	University of Washington

Appendix 2

List of funded projects and investigators selected through a competitive process for NIBIB funding

Modality	PI	Institution	Project Title	Sub-award Amount
CT	Michael McNitt-Gray, PhD	University of California-Los Angeles	Inter-scanner/Inter-clinic Comparison of Reader Nodule Sizing in CT Imaging of a Phantom	$14,000
CT	David Clunie, MBBS	CoreLab Partners	Inter-scanner/Inter-clinic Comparison of Reader Nodule Sizing in CT Imaging of a Phantom	$11,000
CT	Michael McNitt-Gray, PhD	University of California-Los Angeles	Assessing Measurement Variability of Lung Lesions in Patient Data Sets	$13,185
CT	Binsheng Zhao, DSc	Columbia University	Validation of Volumetric CT as a Biomarker for Predicting Patient Survival	$124,990
CT	Ehsan Samei, PhD	Duke University	Development of Assessment and Predictive Metrics for Quantitative Imaging in Chest CT	$75,000
CT	Kavita Garg, MD	University of Colorado	Quantifying Variability in Measurement of Pulmonary Nodule (Solid, Part-solid and Ground glass) Volume, Longest Diameter and CT Attenuation Resulting from Differences in Reconstruction Thickness, Reconstruction Plane, and Reconstruction Algorithm.	$42,070
MR	Edward Jackson, PhD	MD Anderson Cancer Center	DCE-MRI Phantom Fabrication, Data Acquisition and Analysis, and Data Distribution	$60,347
MR	Edward Ashton, PhD	VirtualScopics	Software Development for Analysis of QIBA DCE-MRI Phantom Data	$29,975
MR	Daniel Barboriak, MD	Duke University	Digital Reference Object for DCE-MRI Analysis Software Verification	$57,763
MR	Edgar DeYoe, PhD	Medical College of Wisconsin	Quantitative Measures of fMRI Reproducibility for Pre-Surgical Planning	$19,411
MR	James Voyvodic	Duke University	Quantitative Measures of fMRI Reproducibility for Pre-Surgical Planning-Development of Reproducibility Metrics	$33,423
NM	Otto Hoekstra, PhD	VU Medical Center, The Netherlands	Meta-analysis to Analyze the Robustness of FDG-PET SUV Changes as a Response Marker, Post and during Systemic and Multimodality Therapy, for Various Types of Solid Extracerebral Tumors	$73,000

NM	Paul Kinahan, PhD	University of Washington	QIBA FDG-PET/CT Digital Reference Object Project	$68,240
NM	Richard Wahl, MD	Johns Hopkins	Analysis of SARC 11 Trial PET Data by PERCIST with Linkage to Clinical Outcomes	$57,500
Cross	Gudrun Zahlmann, PhD	Roche	Groundwork for QIBA image reference database - QIBA Image Reference	$10,250
Cross	Rick Avila, MS	Kitware	Groundwork for QIBA image reference database - QIBA Image Reference	$16,000
CT	Michael McNitt-Gray, PhD	University of California-Los Angeles	Extension of Assessing Measurement Variability of Lung Lesions in Patient Data Sets: Variability Under Clinical Workflow Conditions	$14,110
CT	David Clunie, MBBS	CoreLab Partners	Extension of Assessing Measurement Variability of Lung Lesions in Patient Data Sets: Variability Under Clinical Workflow Conditions (image reading services)	$13,125
CT	Grace Kim, PhD	University of California-Los Angeles	Comparative Study of Algorithms for the Measurement of the Volume of Lung Lesions: Assessing the Effects of Software Algorithms on Measurement Variability	$35,500
CT	Sean Fain, PhD	University of Wisconsin	Impact of Dose Saving Protocols on Quantitative CT Biomarkers of COPD and Asthma	$49,754
MR	Mark Rosen, MD, PhD	University of Pennsylvania	Test-Retest Evaluation of Repeatability of DCE-MRI and DWI in Human Subjects	$175,000
MR	Jay Pillai, MD	Johns Hopkins	Validation of Breath Hold Task for Assessment of Cerebrovascular Responsiveness and Calibration of Language Activation Maps to Optimize Reproducibility	$29,376
NM	Eric Perlman, MD	Perlman Advisory Group	Personnel Support for FDG-PET Profile Completion	$16,000