HHSN268201500021C
Quantitative Imaging Biomarkers Alliance (QIBA)

PROGRESS REPORT: AS OF MARCH 2017

This progress report is stated in terms given in the accepted Work Plan, and is organized in the following subsections:

A. Review of activities responsive to each objective.

B. Combined list of groundwork projects associated with the objectives approved by the Steering Committee.

C. Additional descriptions of general committee progress.

A. REVIEW OF ACTIVITIES RESPONSIVE TO EACH OBJECTIVE.

An update on Objectives 1-7 is given below. Note that, in general, the data from each of these efforts have been or will be uploaded to the Quantitative Imaging Data Warehouse (QIDW) identified in the methodology for Objective 6.

OBJECTIVE 1. CREATE AND DISSEMINATE NEW PROTOCOLS AND QIB PROFILES EACH YEAR THAT ADDRESS DISEASES OF SIGNIFICANT BURDEN TO THE US POPULATION.

Selected specifics:

CT Volumetry Biomarker Committee: The CT Volumetry Profile for volume change in advanced disease has achieved the Technically Confirmed stage. Feasibility tests have been conducted at a small group of clinical centers to assess its use in the field.

The Small Nodule CT Profile Task Force has made numerous revisions to all sections of the Profile to adhere to the evolving QIBA Profile template as well as to respond to outside reviewer comments. In addition, numerous refinements were made across all areas of the Profile to harmonize more closely with the organization and wording of the CT advanced disease Profile. A number of innovations have been proposed to facilitate the uptake and sustainability of this Profile in real world imaging settings, including providing an international CT image quality assessment support effort by means of a “cloud-based” image quality testing service. To allow for efficient and economical dissemination of this approach, a low cost phantom design was developed and a simple workflow approach for small lung nodule Profile conformance was defined. Using this system, CT scans were analyzed relative to their performance in characterizing the new QIBA CT Lung Nodule Profile phantom. Negotiations are underway to make these resources routinely available through QIBA and the first batch of these QIBA CT Lung Nodule Profile phantoms are being fabricated. Planning is ongoing for a more comprehensive international distribution and global crowd-sourced testing of the QIBA CT Lung Nodule Profile phantom. Feedback from several presentations to international clinical, engineering and scientific audiences regarding the QIBA Lung Nodule Profile and planned conformance testing methods has been positive and well received from an implementation perspective.

Groundwork projects focused on volumetry of liver masses have been undertaken for the purposes of extending the first version of the CT Volumetry Profile to include quantitative assessment of liver masses. It is anticipated that a Profile for CT Volumetry of liver masses will continue to develop, with a draft for public comment available in the latter part of 2017.

CT Lung Density Biomarker Committee: A Profile for the measurement of lung density based on quantitative CT measurements is in development and is expected to be released for public comment in 1Q2017. Multiple factors are under consideration for Profile development, including improved harmonization of density measures across CT scanner makes and models, CT dose reduction, and improved lung inflation volume correction (2015-16 Round-5 Project L) to improve repeatability of density measures.

Vendor harmonization, automatic exposure control (AEC) and iterative reconstruction (IR) remain open issues in the Lung Density Profile. A new groundwork project (2016-17 Round-6 Project U) supports the feasibility

testing of the CT dose reduction and harmonization approaches developed in previous cycles. In this ongoing project, the proposed methods for improving repeatability of density measures are implemented and tested in repeatability studies as part of the COPD-Gene Study, an ongoing multi-center longitudinal clinical research study of COPD disease severity and progression. This work will directly inform new versions of the Profile as results of repeatability studies become available.

fMRI Biomarker Committee: The QIBA BOLD fMRI Profile v1.0 titled "Mapping of Sensorimotor Brain Regions using Blood Oxygenation Level Dependent (BOLD) Functional MRI as a Pretreatment Assessment Tool" continues to develop. The current draft posted in GoogleDocs has undergone extensive discussion and revision by the committee. Current Profile efforts are focused on Conformance and Assessment procedures. For these projects, fMRI Digital Reference Objects (DROs) were used to investigate the potential effects of head motion on the Profile claims and to help characterize data quality control metrics (*e.g.*, minimum acceptable head motion) that will form the basis for subject image data QC and Profile conformance. Definition and standardization of means to measure activation "center of mass" (COM) has been identified as a potential issue since COM may not be readily measured by sites using their preferred fMRI analysis package(s). Even if software packages claim to report COM, the algorithm behind COM metrics may vary. Clear definition and technical steps to measure COM will be refined in Profile Activities (Section 3) and Conformance (Section 4) sections of the Profile. Completion of the Profile v1.0 by the fMRI BC for review/approval of the MR Coordinating Committee is anticipated 1Q2017, followed by release for public comment. While under public review, work can begin on language function mapping based on a Round-5 (2015-16) groundwork project, which will lead to a Profile draft later in 2017. The language mapping Profile development was supported by Round-5 (2015-16) Projects D1 and D2.

Perfusion/Diffusion/Flow (PDF)-MRI Biomarker Committee: The DCE-MRI Task Force has ported most elements of DCE Profile v1.0 into the new Profile template for revision into Dynamic Contrast Enhanced (DCE)-MRI Profile v2.0, which will extend the Profile to include 3.0T systems and parallel imaging techniques commonly used in DCE studies. Most Task Force efforts have been focused on an organ-specific systematic literature review process and groundwork projects. As with other biomarkers, the DCE TF has noted that despite a large volume of publications, there are relatively few good quality test-retest studies essential to development of the Profile claim(s). Candidate DCE organ sites being reviewed for development of claims include: brain; head and neck; prostate; and breast. The Profile Activities and Assessment Procedures sections (sections 3 and 4) are being redrafted for consistency with other QIBA Profiles. A PDF Biomarker Committee-approved version of DCE Profile v2.0 is anticipated 2Q2017.

Extensive rewrite of the Diffusion-Weighted Magnetic Resonance Imaging (DWI) Profile v1.0 was completed by the DWI Task Force in 4Q2016, and the claims were expanded to include prostate (along with brain and liver organ sites). A GoogleDocs version of the Profile is currently under internal review by the PDF Biomarker Committee. Response to and incorporation of comments and PDF Biomarker Committee ballot approval is targeted for March 2017, followed by review and vote by the MR Coordinating Committee and subsequent release for public comment soon thereafter.

Two additional PDF-MRI Biomarker Committee Task Forces are in earlier stages of Profile development. The Diffusion Tensor Imaging (DTI) Task Force, co-chaired by Drs. Provenzale (clinical lead) and Schneider (technical lead) are distilling a substantial volume of DTI publications to identify suitable biomarkers for the main target organ, which is brain. Standard fractional anisotropy (FA) and other scaler metrics, along with more advanced metrics derived from higher directional and multi-shell "DTI+" are being considered. Profile development for Dynamic Susceptibility Contrast (DSC) is led by Drs. Erickson and Wu. Elements of the DSC Profile have been drafted into the current QIBA Profile Template, and an extensive literature review is nearing completion. Technical assessment procedures are pending phantom development and multi-site/vendor measurements to inform the DSC Profile. A DSC Profile version ready for PDF Biomarker Committee and MR Coordinating Committee review is expected Q2-3 2017.

MR Elastography (MRE) Biomarker Committee: The MRE committee is refining its Profile v1.0 draft for quantitative MRE measurements in liver based on extensive meta-analysis of test-retest repeatability of hepatic MR elastography. Since substantive groundwork has already been performed and results previously published, Profile development is progressing rapidly and a draft Profile will be available for public comment by Q1-2 2017. The results of this meta-analysis form the objective basis for the quantitative cross-sectional claim

for the draft Profile. All elements of the Profile are essentially in place, although specific claim values are being evaluated for feasibility in demonstration of conformance at the "Clinically Confirmed" stage.

Proton Density Fat Fraction (PDFF) Biomarker Committee: The committee is actively developing a draft Profile v1.0 for quantitative proton density fat fraction measurements in liver. Since substantive groundwork has already been performed and results previously published, Profile development is progressing well. A robust literature search has been performed, which has informed the claim, and the Profile is in draft phase. Further, a meta-analysis that will be used to support cross-sectional and longitudinal claims is progressing. The meta-analysis has been written-up by the committee and accepted for presentation at the ISMRM 2017, and this will be expanded in manuscript form for publication. A first draft of the Profile is expected by 3Q2017.

FDG-PET/CT Biomarker Committee: The *FDG-PET/CT as an Imaging Biomarker Measuring Response to Cancer Therapy* Profile has advanced to the Technically Confirmed stage as of November 30, 2016. This is version 1.13, dated November 18, 2016, available at http://qibawiki.rsna.org/index.php/Profiles. To be a Technically Confirmed Profile, the Profile details have been implemented in more than one facility and each individual actor (system and person) successfully met the specifications. This was verified through two rounds of feasibility-testing across multiple sites and the FDG-PET/CT Biomarker Committee asserts that deployments will find the Profile requirements practical/feasible to understand and execute.

PET-Amyloid Biomarker Committee: A second-generation digital reference object (DRO) is being designed and created for the quantitative assessment of amyloid tracers. The committee is now revising their Profile claim based on current literature citations, as well as data from Round-5 (2015-16) Project E. Due to challenges in interpreting current literature, the release of the amyloid plaque neuroimaging Profile for public comment is now scheduled for 2Q2017.

SPECT Biomarker Committee: The first Profile (*Quantifying Dopamine Transporters with 123-Ioflupane in Neurodegenerative Disorders*) addresses Parkinson's disease (PD) and has advanced to the first stage of Version for Public Comment as of November 2016. The public comment phase continued until the end of February 2017, at which point the SPECT Biomarker Committee began the process of revising the Profile to respond to the public comments. It is worth noting that (1) this first draft of the Profile advanced to the Version for Public Comment stage in less than a year, and (2) substantive public comments have been received already. International enthusiasm for participation has been particularly strong from Japan and several European Union states. The second stage of a Publicly Reviewed Version is anticipated by end of 3Q2017.

The SPECT Biomarker Committee has also started a draft of a second Profile for 99m-Tc SPECT in Immunology/Oncology.

US SWS Biomarker Committee: The Profile *Ultrasound Measurement of Shear Wave Speed (SWS) for Estimation of Liver Fibrosis* continues to have broad support and strong effort from ultrasound system providers, basic and medical imaging scientists, and regulators. The literature review and results of studies of 20 patients, each with 3 different systems, has been incorporated into the draft. Mitigation strategies to reduce SWS-measuring system variance in clinical procedures have been characterized. Variances between measurements on ultrasound systems by 8 vendors at 13 sites on 9 models with 2 transducers each have been analyzed in 3 each of elastic and viscoelastic phantoms. Comparing these to MRE measurements on the same phantoms led to the decision to reference the ultrasound measures to those of MRE, after correction for the different shear wave frequencies in the different systems. Rather than an experimental correction for frequency, a model-based correction is being sought in simulations that might be more universally correct *in vivo.* Conformance will be monitored by completion of checklists that will be utilized in the planned, two-site feasibility study. The Profile is targeted for public review by June 2017 and has been informed by Round-5 (2015-16) Projects F1 and F2 and Round-6 (2016-17) Project BB.

US Volume Flow Biomarker Committee:

Work on the Profile continues, and a draft version is anticipated for release for internal review in September 2017.

CEUS Biomarker Committee:

The Contrast Enhanced Ultrasound Biomarker Committee is relatively new, has not started outlining the Profile and has no subcontract for groundwork projects. However, the Biomarker Committee is very active and volunteer efforts by industry, medical, medical support and biomedical researchers has been strong.

OBJECTIVE 2. PERFORM FIELD TESTS AND REVISE EXISTING QIB PROFILES AS NEEDED.

Selected specifics:

CT Volumetry Biomarker Committee: The advanced disease Profile has been tested at three sites. Feedback has been collected and is being used to revise the conformance procedures (Section 4) in the Profile.

fMRI Biomarker Committee: Discussion has centered upon planning staged multi-site human testing of the Profile (after receiving and incorporating public comments). The first stage will involve multiple sites within the Biomarker Committee's membership implementing Profile v1.0 and acquiring human subject motor mapping data. Testing will focus on identifying implementation issues, subject QC methods and agreement with claims in cases where multiple measurements are made in the same subject. The DROs will be used to find out if the performance plan is feasible. One scenario is to create a DRO of 20-30 cases known to surpass QC thresholds, and provide step-by-step assessment/procedure. This range of DROs are designed get the center of mass within Profile specifications. The next stage will likely involve extending such testing to additional sites that perform clinical fMRI motor mapping where site-generated datasets would undergo the same assessment procedure.

PDF-MRI Biomarker Committee: Overseen by the PDF-MRI Biomarker Committee, the DCE-MRI Task Force is awaiting analysis of the *DCE-MRI Quantification* Profile (v1.0) field test (design supported by a Round-2 groundwork project), implemented in the ACRIN 6701 prostate cancer patient test/retest study. This study also included site certification by scanning physical DWI and DCE (T1) phantoms. The ACRIN 6701 study was specifically designed to collect multi-site/multi-vendor DCE (and DWI) data, and will thus directly inform future QIBA Profiles involving MR for prostate imaging. Accrual for this study has been completed, and preliminary results are anticipated by Q1-2 2017. As DCE-MRI Profile v2.0 is recast into the new QIBA template, material related to 3T systems and parallel imaging techniques is being incorporated. Known B1 non-uniformity issues at high-field (3T) will be addressed in a recently awarded (2016-17 Round-6) groundwork project to build and test physical phantoms suitable for B1-and T1-mapping. Head- and torso-sized B1-uniformity phantoms are being scanned on multiple vendor platforms (2016-2017) to directly inform DCE Profile v2.0.

Beyond phantoms used in ACRIN 6701, a multi-site/multi-vendor study of a polyvinylpyrolidone (PVP) DWI phantom (supported by a Round-3 groundwork project) was performed with data acquisition completed mid-2016. Acquisition and analysis using a common DWI QA/QC software package (supported by 2013-14 Round-3 groundwork contract) directly informed technical Performance Assessment procedures and specifications contained in the DWI Profile.

The DTI task force is currently accumulating multi-site/platform DTI data using a novel phantom (supported outside of QIBA) based on "taxon" inserts to provide ground truth in anisotropy metrics. These physical phantom field tests will constitute base technical DTI performance to inform assessment procedures for the DTI Profile.

FDG-PET/CT Biomarker Committee: The Profile has completed two rounds of field-testing to examine its feasibility and practicality. The first round was at four academic imaging sites, while the second round was at 12 regional clinical sites across the USA. User-suggested changes to the Profile were made, as well as a revision of the checklists of conformance procedure steps. An updated version (Technically Confirmed Stage) of the FDG-PET/CT Profile was completed 4Q2016.

US SWS Biomarker Committee:

Redistribution within the Biomarker Committee is imminent with distribution to the US Coordinating Committee in March and expected release of the draft Profile for public comment in June 2017. A plan

has been refined for conduct of SWS acquisitions for the technical confirmation study at two sites, Massachusetts General Hospital and the Washington DC VA Medical Center (VAMC), as soon as the public comments have been addressed and incorporated into the draft Profile. The Profile will be used to test whether the protocols are practical in a clinical environment. The acquisitions are to be funded by internal funding from the two sites plus partial FDA funding for acquisition at the DC VAMC. In addition, a plan was developed to introduce deviations from the protocols outlined in the Profile into a subset of the acquisitions to study the effects of errors made during acquisition on the final SWS values. These data, plus manufacturers' results from their digital phantom tests, when analyzed, will be used to provide extrapolation to the reference MRE measurements. If the revisions are not substantial, we will attempt to not only reach the technical confirmation stage but also the "Claim Confirmed" stage of Profile development.

US Volume Blood Flow (VBF) Biomarker Committee:

Examination of Flow Phantom as Reference Standard for Validation of Ultrasound Volume Blood Flow Measurement, PI: Oliver Kripfgans, PhD - University of Michigan - Round-6 (2016-17) Project W. This project will include field tests with phantoms as described in other sections. Field tests on patients undergoing renal transplants are planned without support from this contract.

OBJECTIVE 3. PERFORM INDIVIDUAL GROUND WORK DATA COLLECTION AND ANALYSIS PROJECTS TO FILL GAPS IDENTIFIED DURING WORK DEVELOPING QIBA PROFILES COVERING THE FOUR MAJOR IMAGING MODALITIES, CT, MRI, RADIONUCLIDE, AND ULTRASOUND.

Selected specifics:

Each of the Round-6 (2016-17) groundwork projects are underway and will be completed by September 29, 2017.

Methodology and Reference Image Set for Lesion Characterization in terms of Texture and Morphology, PI: Ehsan Samei, PhD - Duke University (CT Volumetry Biomarker Committee) - Round-5 (2015-16) Project C

This is a two-part groundwork study: (1) Texture modeling and assessment: A lesion texture simulation platform has been developed to model internal lesion heterogeneity. By analyzing lesion images, lesion internal variances and structural inhomogeneities have been extracted from pathologically-confirmed clinical lesions. Texture features were assessed based on Haralick statistical features. Subsequently, the measured texture features were modeled in the framework of the Cluster Lumpy Background modeling method. A genetic algorithm has been employed to iteratively determine the closest association between modeled texture features and reference features. The imaging system's noise and blur were also accounted for in the texture modeling. (2) Morphological modeling: Phantom images containing lesions of varied but known morphology were acquired using a commercial CT system. Virtual lesions corresponding to physical lesions were modeled using a technique from the Round-4 (2014-15) Project. To assess morphological differences between the actual lesion and its CT system rendition, a 3D quantification technique based on the Hausdorff distance metric was used. The study is being used as a basis to ascertain the reproducibility of morphological features, enabling correction of the CT-measured morphological features for expected imaging distortions.

CT Lung Density Biomarker Committee:

Investigation of Methods of Volume Correction for Lung Density CT, PI: Sean Fain, PhD - University of Wisconsin (Lung Density Biomarker Committee) - Round-5 (2015-16) Project L

A reference library of CT lung density histograms has been created from test-retest scans in human subjects (from the COPD-Gene and NLST studies) to assess consequences of inconsistent breath-hold on CT density measures in the lungs. The performance of previously published statistical models for lung volume adjustment of CT density measures is now being tested using these histograms. In addition, several imaging phantoms, consisting of standardized reference material (lung equivalent density foams) ("QIBA-SRM" phantom) and a

piston system with shredded foam to enable controlled experiments at varied volume and density as a means to independently validate the different lung volume adjustment approaches in the literature, are being implemented.

CT Lung Density Biomarker: Translating Phantom Harmonization to Clinical Practice, PI: Stephen Humphries, PhD - National Jewish Hospital (Lung Density Biomarker Committee) - Round-6 (2016-17) Project U

This proposed multi-site, multi-vendor assessment will allow better definition of specifications for conventional and low-dose protocol conformity to support the claims. This will also be an important test of the technical feasibility of the draft Profile procedures in an ongoing clinical research trial. The proposed correction technique derived from phantom studies could potentially reduce or eliminate the variation due to scanner make and model in patient data, which would be a major advance in quantitative CT of the lung.

fMRI Biomarker Committee:

Quantitating Clinical fMRI Mapping of Language: Center, Spatial Extent, and Relative Strength of Active Areas, PI: James Voyvodic, PhD - Duke University (fMRI Biomarker Committee) - Round-5 (2015-16) Project D1 and D2

We identified and analyzed 775 fMRI scans of language function from 355 subjects (retrospective data regarding patients and healthy controls), each of whom underwent more than one language scan. Of these, 340 subjects had multiple scans within the same session and 15 subjects had language scans acquired in different sessions. Two different language tasks had been performed. All subjects had a "Sentences" task; 260 had multiple Sentences tasks whereas 95 subjects performed both a Sentences task and "Words" task. This allowed us to evaluate reproducibility of language mapping both within and across tasks. Affine registration transforms have been generated to register brain images from each session to a standard MNI reference brain and to other scan sessions of the same subject. Quantitative quality assessment measures have been generated for all scans. These include head motion indices, consistency indices for task performance, overall BOLD activation metrics (mean and peak amplitudes, spatial extent), regional activation statistics for multiple putative language ROIs, hemispheric lateralization indices, and subjective mapping assessments by multiple raters. AMPLE-normalized language fMRI maps were generated and resampled to the common MNI anatomical space so different language task maps could be overlaid and measured for reproducibility. Reproducibility metrics generated include 3-D location of activation peaks, spatial extent of activation, and hemispheric language lateralization indices. The final step will be to evaluate these reproducibility metrics as a function of the QA metrics in order to identify new Profile claims for reproducibility of language mapping and the data qualification necessary to achieve those claims.

PI: Jay Pillai, MD - Johns Hopkins University (fMRI Biomarker Committee) - Round-5 (2015-16) Project D2

Two commonly-used clinical language fMRI paradigms have been evaluated in a group of >50 patients over a course of 4 years to assess both reproducibility within a single scan session and effectiveness of hemispheric lateralization using threshold dependent and independent methods. In the reproducibility assessment, we have thus far evaluated holohemispheric laterality indices (LI) and plan to evaluate region-specific LIs as well as correlate the findings with QC metrics in the remainder of the project (under a 6-month NCE).

PDF-MRI Biomarker Committee:

DWI-DRO Development for ADC Analysis, PI: Dariya Malyarenko, PhD - University of Michigan (PDF-MRI Biomarker Committee / DWI Task Force) - Round-5 (2015-16) Project G

The goal of this project was to provide a DWI DRO containing “modeled ground truth” with realistic Rician noise conditions for evaluation of diverse software packages that purport to convert DWI into quantitative ADC. This DWI DRO was modeled after the DCE DRO (Round-1 groundwork project) and utilized diffusion DICOM attributes defined according to the standard (vendor-independent) DWI “macro” (http://dicom.nema.org/medical/dicom/current/output/chtml/part03/sect_C.8.13.5.9.html).

All stated project deliverables were met and include: a) definition of a wide tissue-relevant ADC/SNR parameter space, b) adherence to DICOM-compliant diffusion attributes, c) DWI generation based on the standard (mono-exponential diffusion model, though the framework is flexible for DRO extension to other tissue models in the future, d) trial of the DRO using a select set of DWI analysis software packages, and e)

delivery of DRO datasets with software performance analysis documentation to RSNA-QIBA for its distribution (on the Quantitative Imaging Data Warehouse, QIDW).

Dynamic Susceptibility Contrast MRI Phantom, PI: Ona Wu, PhD - Harvard University / Massachusetts General Hospital (PDF-MRI Biomarker Committee / DSC-MRI Task Force) - Round-5 (2015-16) Project H

The primary goal is to develop a prototype physical DSC phantom from which a gradient of susceptibility values can be measured. A secondary goal is to generate generic acquisition protocols by which one can assess the contrast-to-noise ratio of the susceptibility measurements, as well as stability across time and vendors. Finally, the third goal is to estimate reproducibility and feasibility of performing these measurements across multiple centers at multiple time points.

Two phantom prototypes to estimate reproducibility across imaging sites have been designed. A high-level generalized imaging protocol to be utilized with the phantoms has been developed. Candidate phantom components are being tested for stability and suitable magnetic properties such as susceptibility range and T1. Software tools are also being developed for analyzing data based on prior NIBIB-supported projects.

Measurements of Reproducibility of DTI Metrics on Clinical MR scanners using a DTI Phantom, PI: James Provenzale MD - Duke University (PDF-MRI Biomarker Committee / DTI Task Force) - Round-6 (2016-17) Project T

The goal of this proposal is to acquire the data needed to inform the QIBA DTI Profile using a novel phantom on representative multi-platform systems at a few medical centers. The phantom is stable over time and can provide “ground truth” measurements of DTI metrics, i.e., mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD). Data acquisition is ongoing (2016-2017), and subsequent analyses will determine variability, cross device/vendor match, and longitudinal stability of measurements (at least three measurements) of FA, ADC, RD, and AD.

Quantification of Reconstruction Method Impact on Measured Amyloid Load. PI: Dawn Matthews, MS, MBA - ADM Diagnostics, LLC - Round-6 (2016-17) Project DD

This project is quantifying the impact of reconstruction method on brain amyloid measurement, and developing recommendations for reconstruction method and region of interest definition based upon objectives for amyloid quantification. A comprehensive set of scans is being systematically reconstructed using variations of algorithms and parameters (Figure 1, below). In addition to ROI analyses, an advanced multivariate machine learning platform is being used to characterize differences between reconstruction methods.

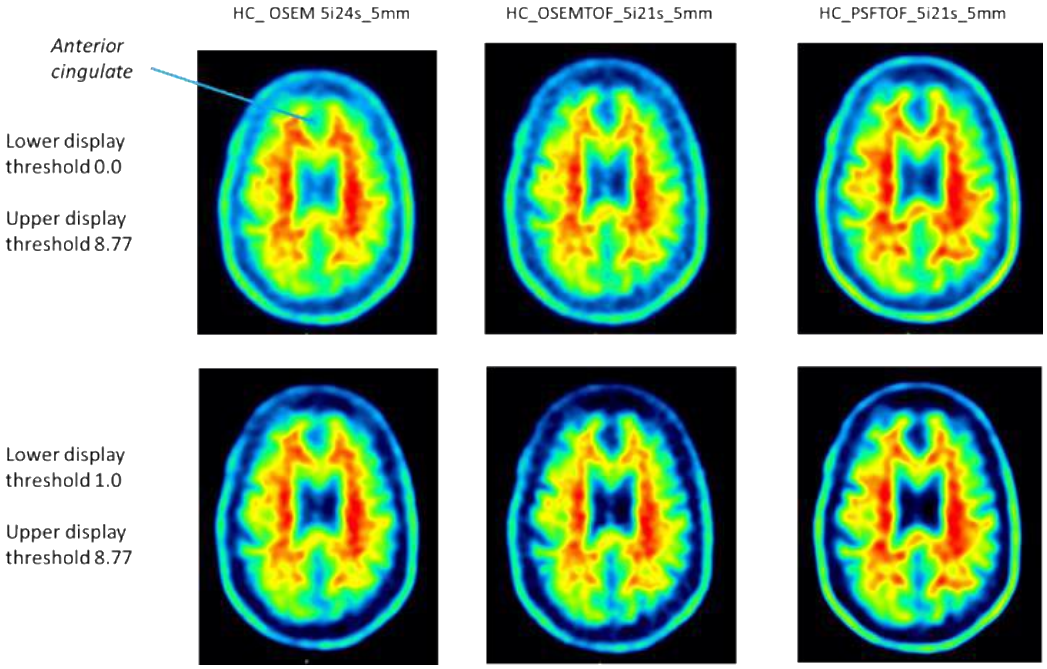
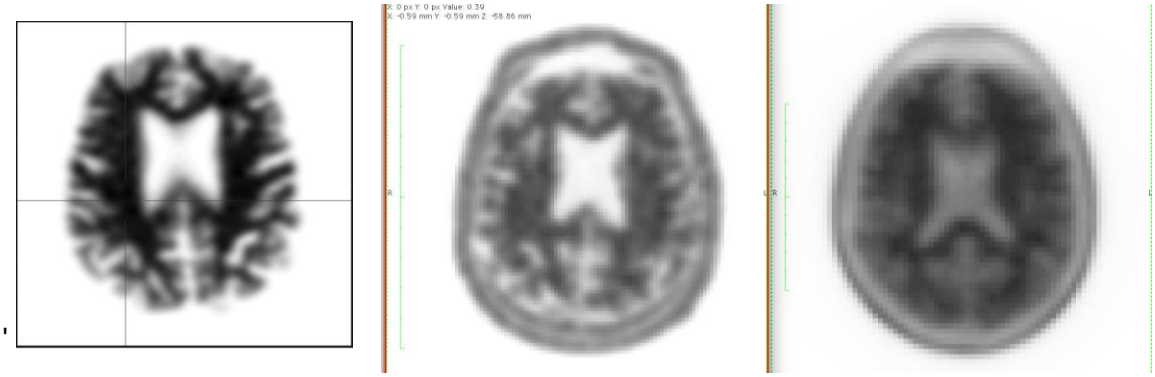


Figure 1. Comparison of three different reconstruction methods in amyloid negative HC. When probed for intensity, signal is approximately 25% lower in the PSFTOF than OSEM 5i24s at the lowest point (arrow), and 20% different adjacent to white matter; the differential lessens as the interior of the highest signal region in adjacent white matter is reached, where signal is approximately the same between the reconstructed scans.

Matched Digital and Physical Amyloid Phantom for Software and Scanner Validation, PI: Paul Kinahan, PhD - University of Washington - Round-6 (2016-17) Project AA

This project's goal is the creation of a digital amyloid phantom to support efforts to better characterize the quantitative measurement of amyloid imaging agents for PET. This is the second phase of a project where prototype digital and physical phantoms were constructed. Many suggestions for improvements were listed in the final report for the first project. In this second phase, lessons learned from the first project are being extended (Figure 2, below) in an implementation of a series of amyloid DROs simulating an range of anatomical variants, with an array of amyloid distributions.



Initial DRO Revised DRO patient Image

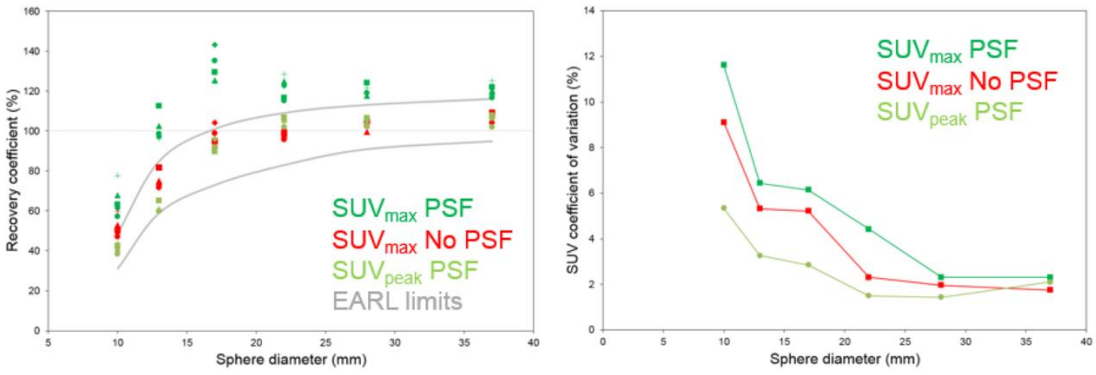
Figure 2.

FDG-PET/CT Biomarker Committee:

SUV Quantification with Point Spread Function PET Reconstruction, PIs: Martin Lodge, PhD, Johns Hopkins University and Ronald Boellard, PhD, University of Groningen - Round-6 (2016-17) Projects R1 and R2

The aim of the study is to investigate the effect of PET reconstruction with point spread function (PSF) modeling on tumor standardized uptake value (SUV). Initial work has involved phantom experiments using the NEMA image quality phantom, investigating the effect of image noise, voxel dimensions and phantom positioning on various SUV metrics including SUVmax, SUVpeak and SUVmean.

Preliminary data (below) suggest SUVpeak may be preferable to SUVmax when using PSF modelling, at least for tumors greater than around 17 mm diameter. SUVpeak improves the quantitative characteristics of PSF images, reducing positive bias and decreasing the variability of tumor SUVs.



Next steps include performing other phantom studies to further characterize the behavior of SUVpeak *versus* SUVmax and evaluating the feasibility of translating SUVmax derived from non-PSF reconstructions to

SUVpeak derived from PSF-reconstructed images. After that, patient studies are planned, including repeatability studies reconstructed with and without PSF, and will be used to assess the validity of phantom findings in a clinical setting.

Simple Variable Estimates in PET, PI: Timothy Turkington, PhD - Duke Univ - Round-6 (2016-17) Project CC

This project is developing and testing methodology for assessing the scanner noise component of test-retest variability so that future versions of PET Profiles can establish more specific and meaningful requirements for PET data acquisition and processing for individual imaging site. A key missing feature in the current FDG/PET Profile is a specification on image noise as it pertains to test-retest of SUV in hot lesions. Most if not all PET/CT systems built in the last 15 years are capable of producing PET images that support the Profile claim. However, the scan parameters necessary for each system are certain to be different. For example, a system with lower sensitivity or rejection of background will require a longer scan to achieve the same quality. Various benchmarks for image quality exist, but none is used routinely to assess test-retest variability. Many sites in the US are accredited by the ACR and therefore routinely image the ACR PET phantom. Repeat scans of this phantom are being used as the basis for a variability assessment.

The ultimate goal is an imaging site specification similar to the following: “Replicate images of the ACR PET phantom scanned and reconstructed according to the site’s standard protocols shall yield a coefficient of variation of less than X%, as measured over either of the two largest hot regions by SUVmax methodology.”

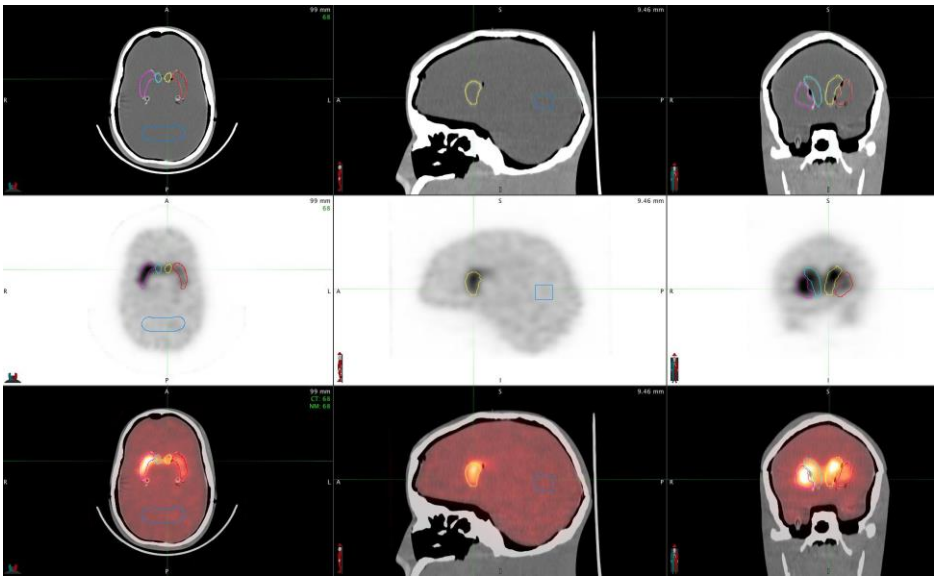
SPECT Biomarker Committee:

Multi-center Phantom Study to Characterize Bias and Precision of Quantitative I-123 SPECT. PIs: Yuni Dewaraja, PhD, University of Michigan and John Dickson, PhD, University College London Hospital - Round-6 (2016-17) Projects V1 and V2

The overall objective of this project is to determine the acquisition parameters and reconstruction methods for estimating the specific binding ratio (SBR) in 123-I ioflupane SPECT with higher precision and reduced bias.

A striatal phantom filled with the ratios suggested in the Profile was used to evaluate bias (relative to true SBR) and variance in SBR for different reconstruction methods with and without uniform (Chang) and non-uniform (CT-based) attenuation correction. Five acquisitions at 3 million counts each were performed on the Siemens Symbia SPECT/CT with the low energy collimator and each data set was reconstructed using 5 methods. No post-filtering was used with OSEM as recommended in the Profile when focus is on quantification.

Typical Images from the Michigan measurements are shown below, with the volumes of interest corresponding to the true boundaries defined on CT and applied to co-registered SPECT.



Summary of Results: The bias in SBR is high (60 – 70%), which can be attributed to partial volume effects. The bias is higher for the caudate, which is smaller in size. There is no substantial difference in bias between the different reconstruction methods, but in general FBP and OSEM without AC has slightly higher bias than with AC. The higher SBR (and lower bias) for a Chang AC compared with CT-based AC could be because the boundaries for Chang were determined by thresholding the SPECT image and hence did not include the skull (where there is no uptake). Further investigation on this is needed.

Studies evaluating impact of scatter correction and resolution recovery are ongoing. The data to evaluate the impact of varying the total number of counts (acquisition time) were acquired (one long scan of 12 million counts). A Poisson resampling algorithm, written in Matlab, was applied, followed by conversion to DICOM (to reconstruct with Siemens software) and sub-sampled data sets with 0.5 million, 1 million and 2 million counts will be evaluated in the next period.

I-123 DAT Scan Digital Reference Object Development. PI: Robert Miyaoka, PhD - University of Washington - Round-6 (2016-17) Project X

The primary goal is to design and construct a prototype brain Digital Reference Object (DRO) phantom with properties appropriate for testing software used to characterize I-123 ioflupane uptake in the striatum and the derivation of striatal specific binding ratio in a quantitative fashion. The results can be used to develop methods to be used in the SPECT DAT scan Profile and to test I-123 DAT scan analysis software in a consistent fashion. Based upon the initial results from other QIBA committees that have developed DRO phantoms, it is clear that consistent testing of vendor data analysis software is necessary to validate/confirm that given the same reference image all vendor software will return the same values given the same analysis task.

US SWS Biomarker Committee:

Establishing Acceptable Variance Limits for Healthy, F1 and ≥F2 Fibrosis Shear Wave Speed Values Across Systems and Between Operators for the QIBA Profile, PI: Manish Dhyani, MD - Mass Gen Hospital - Round-6 (2016-17) Project BB. Using existing data on 30 subjects at varying liver fibrosis stages, scanned with 5 scanners, analysis is performed to: 1) Characterize intraobserver and interobserver and intersystem variability of liver SWE in five commercially available systems using measurements; 2) Determine the effects on SWS of a subset of possible acquisition errors. Three meeting presentations with abstracts and one poster were presented this period.

Analysis of Sources of US SWS Measurement Inter-System Variability, PI: Mark Palmeri, MD, PhD. Round-5 (2015-16) Projects F1 and F2 produced one publication and one submitted in IEEE Trans UFFC, as well as 3 meeting presentations and 2 posters.

US Volume Blood Flow (VBF) Biomarker Committee:

Examination of Flow Phantom as Reference Standard for Validation of Ultrasound Volume Blood Flow Measurement, PI: Oliver Kripfgans, PhD - University of Michigan - Round-6 (2016-17) Project W

Testing of the groundwork protocol was performed on two separate company platforms on a prototype groundwork flow phantom developed in cooperation with an established ultrasound phantom company. Linear frequency shift and Doppler power image data extraction and partial volume corrections are in process for three other companies. Two phantoms (one supported by a professional/research society) will be shared for testing with groundwork protocol at 3 academic and 5 industry sites.

US SWS and MRE Biomarker Committees:

The Round-5 (2015-16) Project F1 and F2 teams performed further analysis of MRE and US SWS data on phantoms to show the level of corrections needed to provide the same results from the two modalities in the elastic and viscoelastic phantoms.

Cross-Modality:

Aggregated Measures of Agreement for QIB Validation: An Open Source Toolkit, PI: Daniel Barboriak, MD - Duke University - Round-5 (2015-16) Project K

The purpose of this project was develop open-source software to calculate aggregated measures of agreement in order to facilitate image analysis algorithm development, comparative analysis of algorithm output, and demonstrate technical conformance. This project also developed a toolkit that can calculate the following statistics: concordance correlation coefficient, root mean square deviation, total deviation index, Bland-Altman limits of agreement, and Sigma analysis based on estimates of allowable total error. An existing open-source package, QIBA DRO Evaluation Tool (QDET), developed by Hendrik Laue in a previous groundwork project, was used as a starting point. This package's source code was downloaded, and preliminary analysis of it was been conducted. The software required some Python modules, such as WxPython and Matplotlib, that are not part of the standard Python installation. These additional modules were obtained and installed. Python has several ways to package and release software as an executable application; these were investigated to determine which to use.

We have successfully continued updating the capabilities of the QDET program. The program now accepts text as input, and we have validated that the RMSD, CCC, TDI and Bland-Altman statistics obtained from text images are identical to those obtained from corresponding image data. These statistics have been verified against statistics obtained from the R software package. Scripts demonstrating how to use QDET to tune software parameters and to rank performance of competing algorithms have been completed.

OBJECTIVE 4. DEVELOP AND EMPLOY PHYSICAL AND/OR VIRTUAL (DIGITAL) REFERENCE OBJECTS NEEDED FOR ASSESSMENT OF IMAGING BIOMARKER VARIABILITY AND/OR TO DEMONSTRATE COMPLIANCE WITH QIBA PROFILES.

Selected specifics:

CT Volumetry Biomarker Committee:

Reference Image Set for Quantitation Conformance of Algorithmic Lesion Characterization, PI: Ehsan Samei, PhD - Duke University (CT Volumetry Biomarker Committee) - Round-5 (2015-16) Project C

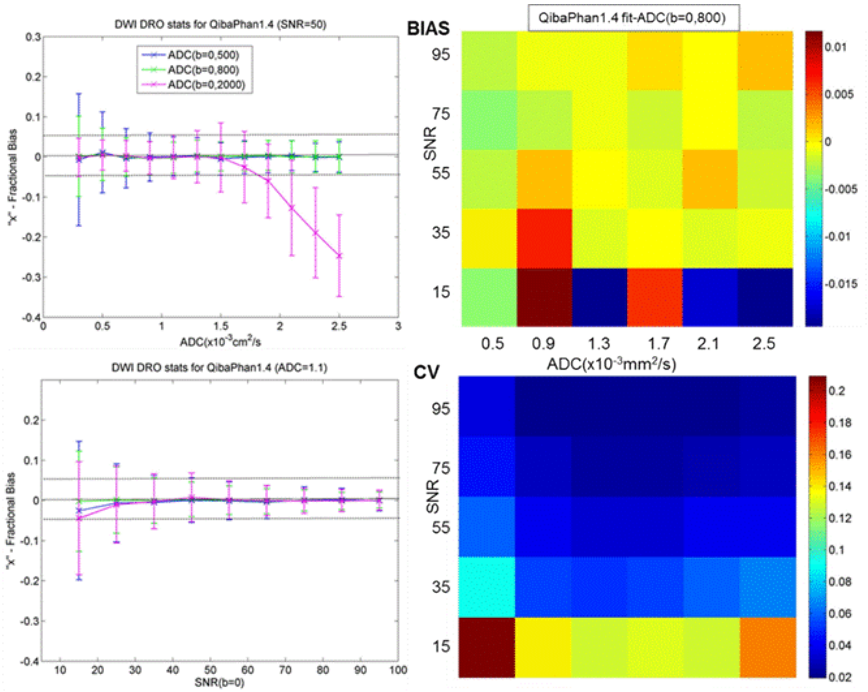
A library of realistic lung lesions with internal heterogeneity is being simulated to provide statistically relevant lesion texture ground truth. A database of patient cases has been identified and curated for virtual insertions of lesions with truth based texture synthesis. Clinical cases have been imaged under low noise conditions. A standard chest CT protocol has been used during acquisition of the reference image dataset. Virtual lesion insertion techniques previously used in a pilot study have been identified for application in the current framework. This process is building towards formation of a hybrid library with known lesion textural and morphological features.

PDF-MRI Biomarker Committee:

The DWI-MRI Task Force has completed its literature review and the development and dissemination of a NIST-traceable DWI MRI Phantom (along with associated data analysis software) funded by a NIBIB Round-3 project. The DWI-MRI Profile is currently being edited to incorporate suggestions of PDF Biomarker Committee members. Key aspects of the draft Profile have been implemented in collaborative studies with the EORTC / IMI and with a group of São Paulo neuroradiologists leading a multicenter, multivendor clinical trial of DWI in glioblastoma patients to allow initial field testing of Profile recommendations.

DWI-DRO Development for ADC Analysis, PI: Dariya Malyarenko, PhD – University of Michigan (PDF-MRI Biomarker Committee / DWI Task Force), Round-5 (2015-16) Project G.

Development of this DWI-DRO is completed and suitable to assess robustness of DWI analysis software packages used for quantitative ADC map generation. Modeled tissue properties span ADC = 0.1 to 3.5x10^{-3} mm^2/s and SNR = 0 to 100 (of *b*=0 image) within a DICOM-compliant DWI-DRO at *b*-values=0, 500, 800, 2000 s/mm^2 (see Objective 3). Analysis of the DRO was used to predict bias and variation metrics over relevant ADC and SNR ranges (illustrated in figure below) which led to technical specifications stated in the DWI Profile.



Dynamic Susceptibility Contrast MRI Phantom, PI: Ona Wu, PhD - Harvard University / Massachusetts General Hospital (PDF-MRI Biomarker Committee / DSC-MRI Task Force) - Round-5 (2015-16) Project H

Two phantom prototypes to estimate reproducibility across imaging sites have been designed. A high-level, generalized, cross-vendor imaging protocol usable on clinical MR scanners has been developed and will be utilized to characterize the DSC phantoms and assess repeatability on multiple scanner platforms. Phantom components are being tested for stability and suitable magnetic properties, such as susceptibility range and T1. Software tools are also being developed for analyzing data under a 12-month NCE.

fMRI Biomarker Committee:

Three different rounds of fMRI DROs were developed. A Round-3 (2013-14) groundwork project involved generating 20 empirically-derived DROs, which were then downloaded and analyzed at 8 QIBA fMRI Biomarker Committee sites; comparing results from different sites helped develop analysis standards for Profile v1.0. A Round-4 (2014-15) project generated synthetic DROs to model one of three major forces of variance: head motion, neurovascular uncoupling, or variable task performance. A third (unfunded) round of DRO development is ongoing to generate higher resolution DROs that combine empirically-derived head motion, neurovascular uncoupling, and task performance variability. Examples of Round-3 and -4 DROs are already available via the QIDW, and the next Round of DROs should be available early in 2017 for use in field tests. These DROs will be used to synthesize subject datasets (N=20-30) representative of adequate quality to pass subject QC review, thus measured COM location should be within Profile claims.

SPECT Biomarker Committee: The specifications for a “fillable” phantom were developed for deployment in multi-center environments. A concept for a solid phantom, with a traceable source of Tellurium-123 as a proxy for Iodine-123, was developed in collaboration with subject matter experts from the National Institute of Standards and Technology. A digital reference object (DRO) based on an anthropomorphic basal ganglia plus brain phantom is still being developed based on the successful prototype by the FDG PET/CT group.

US SWS Biomarker Committee:

See Round-5 (2015-16) Projects F1, F2 under Objective 3.

US Volume Flow Biomarker Committee:

Examination of Flow Phantom as Reference Standard for Validation of Ultrasound Volume Blood Flow Measurement, PI: Oliver Kripfgans, PhD - University of Michigan - Round-6 (2016-17) Project W

Two phantoms with more realistically complex flow patterns were constructed after the prototype testing and one has been delivered to the University of Michigan and successfully undergone initial testing. The groundwork protocol is designed to test the variability of single vessel volume flow measurements using a new scanning pattern and algorithm for much lower variance and bias. Results will be used to reduce those variances, particularly across vendors.

CEUS Biomarker Committee:

Parts for three basic flow phantoms for CEUS studies were acquired at the University of Washington. One phantom was assembled there and the other two were shipped to co-leaders at The Surgical Hospital at Southwoods, Boardman, OH and the University of Texas at Dallas. The intent is to evaluate the little-studied variability of results between contrast agents and ultrasound systems.

OBJECTIVE 5. DEVELOP PROCEDURES AND PROCESSES FOR HARDWARE AND SOFTWARE MANUFACTURERS TO DEMONSTRATE CONFORMANCE WITH QIBA PROFILES.

Selected specifics:

CT Volumetry Biomarker Committee:

The committee has prepared a checklist of actions for each "actor" to establish Profile conformance, divided into activities related to 1) patient handling activities, 2) scan acquisition and reconstruction, 3) image quality checks, and 4) segmentation and analysis. The actions are being reviewed based on feedback from the feasibility tests.

CT Lung Density Biomarker Committee:

Committee members are actively working with vendors to develop models for harmonizing CT lung density measures across different scanner manufacturers and models. This effort primarily uses the COPD-Gene Phantom modified to contain NIST-certified foam standards that fall within the ranges expected for CT density of lung parenchyma. A first round of scans was performed by the vendors and a preliminary correction model was developed to achieve consistent performance within 2 Hounsfield units across four vendors (GE, Siemens, Philips, and Toshiba). A second round of phantom scans with a greater number of scanner models and an updated anthropomorphic phantom has now been completed. Round 2 results support methods for harmonization of lung density measures across CT make and model using reduced dose (automated exposure control - AEC) and physical models developed in Round 1 with standardized reference materials (lung density equivalent foams). A Round-6 (2016-17) Project U is now testing these methods in an ongoing clinical research study, COPD-Gene.

PDF-MRI Biomarker Committee:

The conformance section of the DWI Profile has been completed according to the revised Profile template. Profile activities for the various "actors" are outlined in DWI Profile Section 3 along with assessment procedures in Section 4. Scanner platform-specific acquisition parameters, test procedures and target technical specifications are provided in Appendix E of the DWI Profile.

Analogous to other QIBA Profiles, such as DCE-MRI v1.0, conformance elements include scanner hardware, key personnel and image analysis procedures. The DTI and DSC efforts are fairly early in their Profile development, but conformance will be addressed as claims and protocols become more firm; scope and style will be consistent with the DWI and DCE Profiles.

fMRI Biomarker Committee:

The Round 1-5 groundwork projects on reproducibility and DROs identified reproducibility benchmarks for motor and language fMRI scanning that can be used as goals for conformance testing by manufacturers of fMRI task and analysis software. Currently there are no standards for such software, nor benchmarks for evaluating the quality of data produced by different tasks. Definitions and means to measure fMRI activation center of mass (COM), the target measurand, are not standardized and may not be readily available on standard fMRI analysis software packages, thus QIBA guidance and software tools may be required.

FDG-PET/CT Biomarker Committee:

The Profile has completed two rounds of feasibility-testing to examine its feasibility and practicality. The first round was at four academic imaging sites, while the second round was at a distribution of 12 regional clinical sites. At the completion of the first round feasibility test, representatives of each of the four vendors of PET/CT scanners systematically reviewed and commented upon their current and future ability to achieve conformance with the FDG-PET/CT Profile. Specific comments and suggestions from the vendors regarding feasibility and practicality were used to revise the Profile before the second round of feasibility-testing. After the second round of feasibility tests, checklists of conformance procedure steps for (1) manufacturers and (2) sites were added as appendices.

PET-Amyloid Biomarker Committee:

A revised draft version of the Profile provided to all Biomarker Committee members is undergoing final internal review with incorporation of the feedback in preparation for public comment.

SPECT Biomarker Committee:

As noted above, groundwork projects are being conducted on a multi-center phantom study to characterize the bias and precision of quantitative I-123 SPECT. Specifically, this will allow characterizing the linearity of the confidence intervals surrounding precision and bias, which are suspected of increasing with disease severity, i.e., increasing with decreasing signal-to-noise ratios as the signal becomes lost in patients with Parkinson's disease. In parallel, there is development of an I-123 DAT scan digital reference object. In addition to analyzing the phantom and DRO data, it is anticipated that the SPECT Biomarker Committee will assemble a test set from patients and matched controls with which all software vendors can test their analytical processes.

US SWS Biomarker Committee:

It is anticipated that phantom tests of shear wave speed estimation under various operating conditions will be an acceptable test for vendor conformance as claimed by the vendors. Round-6 (2016-17) Project BB will confirm or modify methods of archiving of acquired studies necessary for later site QA and/or conformance review that might also be useable for verification of ultrasound system performance in the field.

US Volume Flow Biomarker Committee:

It is anticipated that the phantom design from the groundwork project and modifications to the protocol will serve as a basis for demonstrating conformance.

OBJECTIVE 6. COLLECT IMAGES AND ASSOCIATED DATA FOR A QIB DATA WAREHOUSE OR OTHER PUBLIC DATA REPOSITORIES, AND PERFORM ANALYSIS ON THE DATA TO SERVE QIB COMMITTEES AND THE BROADER IMAGING COMMUNITY.

Note that in general the data from each all QIBA committee efforts have been, or will be uploaded to the Quantitative Imaging Data Warehouse (QIDW) identified in the Methodology for Objective 6.

Selected specifics:

CT Modality:

Reference Image Set for Quantitation Conformance of Algorithmic Lesion Characterization, PI: Ehsan Samei, PhD - Duke University (CT Volumetry Biomarker Committee) - Round-5 (2015-16) Project C

A collection of realistic lesion simulations that incorporate texture and morphology based on a range of clinically relevant protocols will be inserted into actual patient data. These images will be uploaded to the QIDW upon the completion of groundwork.

A prior reference image set (*Reference Image Set for Quantification Conformance of Algorithmic Lesion Characterization*) without internal lesion heterogeneity has already been formed and its associated metadata are expected to be uploaded into QIDW in the coming months.

Reference Image Set for Lung Density Analysis Software Challenge, PI's: Charles Hatt, PhD (Imbio LLC) and Miranda Kirby, PhD (University of British Columbia), CT Lung Density Biomarker Committee – In Approval Process. Reference human subject data from the COPD-Gene study for testing density analysis software performance and variability. The data set will include 20 cases, representing a range of COPD severity (GOLD 1-4) and including both low and conventional CT dose scans.

MR Modality:

Quantitating Clinical fMRI Mapping of Language: Center, Spatial Extent, and Relative Strength of Active Areas, PI: James Voyvodic, PhD - Duke University (fMRI Biomarker Committee) - Round-5 (2015-16) Projects D1 and D2

This Round-5 language fMRI project will allow the upload of representative human fMRI data sets (in deindentified form) to the QIDW to support our reproducibility findings. We will include examples of two language tasks from different subjects, representing different quantitative levels of reproducibility metrics.

DWI-DRO Development for ADC Analyses, PI: Dariya Malyarenko, PhD - University of Michigan (PDF-MRI Biomarker Committee) – Round-5 (2015-16) Project G

Initial compatibility of the DWI-DRO was performed by University of Michigan investigators in application of select DICOM readers and analysis packages (GE FuncTool, Philips, QIBA_Phan, Osirix, IDL, and MatLab). Currently, the DWI-DRO and User Manual reside on the QIDW, though greater use and visibility may be achieved via links on the QIBA-Wiki.

Multi-site/vendor scans of QIBA DWI phantom and DWI Phantom Analysis Software (QIBA_Phan), supported in prior year Groundwork Projects, also reside on the QIBA QIDW and serve as a resources for the broader quantitative imaging community.

Ultrasound Modality:

Analysis of Sources of US SWS Measurement Inter-System Variability, PI: Mark Palmeri, MD, PhD – Duke University (SWS Ultrasound Biomarker Committee) – Round-5 (2015-16) Projects F1 and F2

Elastic and viscoelastic digital phantom data (finite element simulation data) previously uploaded to QIDW continues to be downloaded by academic and industry members of the QIBA community.

OBJECTIVE 7. PROVIDE SUPPORT FOR THE QIB COLLABORATION PROGRAM STAFF (OUTSIDE ORGANIZATION STAKEHOLDERS AND QIB COALITION MEMBERS), PROJECT MANAGEMENT, MEETINGS, TRAVEL, AND CONFERENCE CALLS.

Support for all the above committee work, funded project management meetings, conference calls and travel continue to be administered and provided by the RSNA/QIBA staff, QIBA Chair / Vice-chair, and Scientific Liaisons. (Much of the administrative support for the US Volume Flow Biomarker Committee is provided by the American Institute of Ultrasound in Medicine in cooperation with the RSNA.)

B. COMBINED LIST OF GROUNDWORK PROJECTS APPROVED BY STEERING COMMITTEE ACROSS THE OBJECTIVES FOR ROUND-5 AND 6 (2015-2017) FUNDING.

Project Number	Biomarker Cmte	Round-5 & 6 Project Title	Investigator
A	PET Amyloid	**Analyses to Support Amyloid Imaging Profile Development**	Dawn Matthews, ADM Diagnostics, LLC
B	FDG-PET	**Biologic and Reader Repeatability of FDG and CT Volumetric Parameters (ACRIN 6678 & MERCK)**	Rathan Subramaniam, MD, PhD, MPH, Johns Hopkins University
C	CT Volumetry	**Reference Image Set for Quantitation Conformance of Algorithmic Lesion Characterization**	Ehsan Samei, PhD, Duke University
D1, D2	fMRI	**Quantitating Clinical fMRI Mapping of Language: Center, Spatial Extent, and Relative Strength of Active Areas**	James Voyvodic, PhD, Duke University Jay J. Pillai, MD, Johns Hopkins Univ
E	PET Amyloid	**Amyloid Brain PET Test-Retest Meta-Analysis**	Rathan Subramaniam, MD, PhD, MPH, Johns Hopkins University
F1, F2	SWS US	**Analysis of Sources of US SWS Measurement Inter-System Variability**	Mark Palmeri, MD, PhD, Duke Univ Shigao Chen, PhD, Mayo Clinic
G	PDF-MRI (DWI TF)	**DWI-DRO Development for ADC Analysis**	Dariya Malyarenko, PhD, University of Michigan
H	PDF-MRI	**Dynamic Susceptibility Contrast MRI Phantom**	Ona Wu, PhD, Harvard/Mass General Hospital
I	FDG-PET	**A PET Metabolic Tumor Volume Digital Reference Object (PET-MTV-DRO)**	Paul Kinahan, PhD, University of Washington
J	FDG-PET	**A Procedure to Facilitate Greater Standardization of PET Spatial Resolution**	Martin Lodge, PhD, Johns Hopkins University
K	Cross Modality	**Aggregated Measures of Agreement for QIB Validation: An Open Source Toolkit**	Daniel Barboriak, MD, Duke University
L	Lung Density	**Investigation of Methods of Volume Correction for Lung Density CT**	Sean Fain, PhD, University of Wisconsin-Madison
R1, R2	FDG-PET	**SUV Quantification with Point Spread Function PET Reconstruction**	Martin Lodge, PhD, Johns Hopkins University / Ronald Boellaard, PhD, University of Groningen
S	CT Vol	**Methodology and Reference Image Set for Lesion Characterization in Terms of Texture and Morphology**	Ehsan Samei, PhD, Duke University
T	PDF-MRI (DTI)	**Measurements of Reproducibility of DTI Metrics on Clinical MR Scanners using a DTI Phantom**	James Provenzale, MD, Duke University
U	Lung Density	**CT Lung Density Biomarker: Translating Phantom Harmonization to Clinical Practice**	Stephen Humphries, PhD, National Jewish Health

Project Number	Biomarker Cmte	Round-5 & 6 Project Title	Investigator
V1, V2	SPECT	**Multi-center Phantom Study to Characterize Bias and Precision of Quantitative ^{123}I SPECT**	Yuni Dewaraja, PhD, University of Michigan / John Dickson, PhD, University College – London Hospital
W	VBF	**Examination of Flow Phantom as Reference Standard for Validation of Ultrasound Volume Blood Flow Measurement**	Oliver Kripfgans, PhD, University of Michigan
X	SPECT	**^{123}I DAT Scan Digital Reference Object Development**	Robert Miyaoka, PhD, University of Washington
Y	PDF-MRI (DSC)	**A Web-based Tool for Creating DSC Digital Reference Objects**	Bradley Erickson, MD, PhD, Mayo Clinic
Z	PDF-MRI (DCE)	**Evaluation of RF Transmit Calibration Options for Quantitative DCE-MRI**	Krishna Nayak, PhD, University of Southern California
AA	PET Amyloid	**Matched Digital and Physical Amyloid Phantom for Software and Scanner Validation**	Paul Kinahan, PhD, University of Washington
BB	SWS	**Establishing Acceptable Variance Limits for Healthy, F1 and ≥F2 Fibrosis Shear Wave Speed Values Across Systems and Between Operators for the QIBA Profile**	Manish Dhyani, MD, Mass General Hospital
CC	FDG-PET	**Simple Variability Estimates in PET**	Timothy Turkington, PhD, Duke University
DD	PET Amyloid	**Quantification of Reconstruction Method Impact on Measured Amyloid Load**	Dawn Matthews, ADM Diagnostics, LLC

C. GENERAL PROGRESS ON ACTIVITIES BEYOND THE FUNDED PROJECTS

Additional updates from the committees are as follows.

CT Volumetry Biomarker Committee

The committee is forming a group to explore the standardization of analysis of morphological features beyond volume, such as texture and shape, as biomarkers.

A CT liver phantom has been designed and fabricated. Image data were acquired from two 64-detector scanners (GE and Siemens) per the designed imaging protocols. In total, we collected 384 image series (i.e., 2 scanners x 96 imaging settings x 2 repeats) and 34.4 GB of image data. All of the acquired image data were transferred to the FDA for analysis and are ready to be submitted to the Quantitative Imaging Data Warehouse (QIDW). This section briefly outlines the statistical analysis used to assess the volume estimation performance of the segmentation and matched-filter algorithms. The statistical assessment was based on the metrology recommendations outlined by the QIBA Metrology Working Group, which included the analysis of bias, variance, reproducibility, and repeatability. The results showed that the Vendor A scanner had smaller bias compared to the Vendor B scanner. Both scanners showed similar RMSE levels, suggesting that the added bias associated with the Vendor B scanner was offset by having a smaller variance (stdev) compared to the Vendor A scanner. The reproducibility and reproducibility results from the Vendor A scanner are similar to the Vendor B scanner except when mixed-density lesions are included. This is because the estimates for mixed-density lesions from the images obtained by Vendor A were not as accurate, compared to rest of the data.

This project is complete and a project report was given to QIBA. In addition, a manuscript entitled "Volumetry of low-contrast liver lesions with CT: Investigation of estimation uncertainties in a phantom study" has been published in *Medical Physics* describing the study and providing more detailed results and discussions.

The Lung Nodule Assessment in CT Screening Task Force has been working to ensure that the small nodule claims are consistent with the established claims of the advanced disease CT Volumetry Profile. Published results and unpublished data from members of the group have been used to inform development of claim details. The committee has collaborated with manufacturer representatives to obtain technical parameter guidance for individual scanner models for quantitative applications. The small nodule Profile will be released for public comment in 2017.

QIBA 3A Challenge: A new lesion quantitation challenge was designed and initiated by the QIBA CT 3A Group. The main objective of this challenge is to quantitatively benchmark the volume estimation performance of segmentation tools for lung lesions using phantom and clinical cases containing real and virtually-inserted lesions. The aim is to provide a quantitative understanding of the differences between segmentation approaches based on a reference data set, and further establish the statistical exchangeability between real and simulated lesions. Participants are asked to perform image-based segmentation on datasets generated using (1) an anthropomorphic phantom with synthetic and virtually inserted nodules and (2) clinical images containing real lung lesions and virtually inserted lesion models. Nodules were virtually inserted using three insertion methods: Techniques A, B, and C, where Technique A is a projection-domain insertion method, and Techniques B and C are image-domain insertion methods. Each participant is to use their segmentation algorithm to perform volume estimation on nodules with locations that are a priori provided. This Challenge remained open until March 1, 2017. The Challenge can be accessed at: http://qibachallenges.cloudapp.net. Once completed, the results will be analyzed and presented at RSNA and prepared for publication.

CT Lung Density Biomarker Committee

A draft Profile and Claim development are in progress, based on critical evaluation of literature for a lung density protocol. The acquisition and reconstruction specifications of CT images have been completed and are being evaluated by a working group of vendor scientists who are developing conformance procedures using the COPDGene Phantom. The image analysis section of the Profile is nearly completed.

The group has developed recommendations for reduced dose pulmonary quantitative CT (qCT) protocols to be used on multiple vendor scanners using automatic exposure control (AEC) and iterative reconstruction (IR). These protocols and guiding efforts to lower CT dose for ongoing and future clinical research studies and are currently being tested for feasibility in the ongoing multi-center longitudinal COPDGene study (Project L).

A Task Force of CT vendor scientists has been formed to develop a conformance checklist and to suggest changes to the acquisition and reconstruction parameter specifications in efforts to mitigate measurement bias. The Task Force has organized a project that involves scanning the same COPDGene Phantom using three radiation doses on two models of each vendor's CT scanners. The CT Vendor Task Force has completed two rounds of scanning and is using these data to further improve harmonization.

The Biomarker Committee has completed a meta-analysis of the CT lung density repeatability literature, thus finalizing their measurement repeatability claim for assessing emphysema progression. The meta-analysis may be the basis for a submission of a manuscript for publication in the peer-reviewed literature.

PDF-MRI Biomarker Committee

The majority of PDF-MRI activities are conducted within its respective Task Forces. Task Forces exist within the PDF-MRI Biomarker Committee for DCE-, DWI-, DTI-, and DSC-MRI. Single Task Force updates are presented to the full PDF-MRI Biomarker Committee on a rotating basis. Discussion with leaders in the Arterial Spin Labeling (ASL) perfusion field are also ongoing to develop a plan for forming an ASL Task Force in collaboration the European Society of Radiology's European Imaging Biomarkers Alliance (EIBALL). A formal proposal for an ASL-based biomarker in collaboration with QIBA was proposed by EIBALL members. The proposal was formally approved by the QIBA Steering Committee, and the ASL Task Force (within the PDF Biomarker Committee) will have primary logistical support for task force calls provided by EIBALL with the support of the European Institute for Biomedical Imaging Research (EIBIR).

The DCE-MRI Task Force is presently focused on defining systematic literature review procedures, and their application for select organ/tumor sites, to support the DCE-MRI v2.0 Profile claims. Even within a given organ site, the literature often reveals a broad range of key acquisition parameters (e.g., temporal sampling rate) with incomplete description of methodology. Relatively uniform multi-site/-platform DCE-MRI methodology was achieved in the ACRIN 6701 test/retest prostate clinical trial used to field-test the DCE v1.0 Profile. Moreover, an automated software analysis package was developed and applied to data acquired on the QIBA DCE-MRI Phantom for site qualification in the ACRIN 6701 study. The analysis software and user manual have been uploaded to the QIDW, along with example data from scanners from three major MR system vendors and the associated reports produced by the software. In addition, an open-source software package to facilitate comparison of parametric images generated by different DCE-MRI analysis packages when utilizing the DRO created as part of a previously funded groundwork project is also available on the QIDW. This software is capable of importing 2D and 3D DICOM images, or binary data formats, as well as imaging formats such as TIFF and PNG. It generates difference and ratio maps (exportable as PNG), scatter diagrams and box-plots, and ANOVA statistics to more easily compare analysis packages. These resources are available on the QIDW for future clinical trials and the broader quantitative imaging community.

In 2014-15 the DWI Task Force successfully completed scans of its physical “QIBA DWI phantom”, where all datasets were analyzed using the “QIBA_Phan” software developed as a prior groundwork project and available on the QIDW. In 2016, DWI Task Force members also completed development of a DWI DRO. Analogous to the DWI Task Force, the DSC Task Force is currently developing a physical phantom, protocol, and corresponding analysis software supported under QIBA groundwork project contracts. DTI Task Force leaders have previously developed a novel isotropic plus anisotropic physical diffusion phantom. This phantom allows ground-truth measurements of key DTI metrics: mean diffusivity (MD), fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (AD). Task Force members will be scanning this phantom in the coming year to evaluate intra-/inter-platform variance of these metrics.

fMRI Biomarker Committee

The fMRI Biomarker Committee is finalizing v1.0 of its Profile for pre-surgical mapping of eloquent brain tissue. Refinements to the clinical claims and context were made, particularly the acquisition guidelines, as well as accompanying appendices with detailed performance specifications. Likewise, members are in the process of completing Section 3, Profile Activities, specific to the mapping of motor cortex. To inform conformance procedures, members are conducting groundwork studies focused on software analysis specifications.

The fMRI Bias Task Force meets bi-weekly to focus on the issue of bias in the fMRI measureand. This activity informs the Profile claims definition and guides development of methodological sequences for image analysis that best achieve the claims.

fMRI-DRO testing was completed at 8 sites, all analyzing the same bilateral hand motion and language mapping DROs but with each site employing its own standard fMRI processing and analysis workflow. The activation map results accompanied by data analysis forms describing workflow were collected from each site. For the period through September 2015, generation and testing of advanced DROs for head motion in fMRI were performed. These include DROs from various combinations of selected empirical and synthetic datasets wherein amplitude and spatial distribution of task-related fMRI signals and associated fMRI noise were controlled. By fully specifying “ground truth” in this way, subsequent post-processing and display methods can be tested for the ability to accurately recover the original signal distributions and to quantify any inaccuracies that might be present. These DROs, containing realistic task signal and noise variability, including motion, performance, and neurovascular uncoupling (NVU) sources of variance, have been uploaded to the QIDW. These can be used for conformance testing and comparison of fMRI analysis and correction methods for coping with the variance of the BOLD signal in the primary motor cortex as a function of presence or absence of NVU.

Members of the fMRI Biomarker Committee contribute to the DICOM Working Group 16 fMRI Task Force. The proposed DICOM work item will build on recent quantitative imaging support added to the standard, with new elements created as necessary to represent fMRI acquisition, activation maps, and task paradigms. The functional requirements incorporated by WG-16 fMRI TF were drawn from work done in the QIBA fMRI Biomarker Committee.

FDG-PET/CT Biomarker Committee

With the Techically Confirmed status of the FDG-PET/CT Profile, the FDG-PET/CT Biomarker Committee is now looking at two main topics: (1) Revisions to the Profile to include technical advancements, such as the use of physics modeling of the PET scanner in the image reconstruction process, and (2) steps to advance to the next stage of Clinically Confirmed. For this stage, the Profile details have been implemented in more than one facility and each participating system and person successfully met the specifications. In addition, the overall performance was determined and the claim was achieved.

SPECT Biomarker Committee

With the Release for public comment of the SPECT Profile "123-Iodine labeled tropanes for quantifying dopaminergic degeneration in the basal ganglia", the SPECT Biomarker Committee is preparing for the next phase, which is addressing and responding to the public comments. It is anticipated that this will be completed 3Q2017.

US SWS Biomarker Committee

The original goal of the SWS US Biomarker Committee was to develop a QIBA Profile for a single biomarker: ultrasound shear wave speed (SWS) as a measure of liver stiffness, which correlates with the degree of liver fibrosis/cirrhosis present. Major efforts center on completing groundwork studies and publishing results, continuing to understand and account for sources of bias in SWS estimation with ultrasound imaging systems, continuing to determine sources of variance in these estimates, minimizing those contributions, and finalizing the draft Protocol and Profile documents.

Three recent areas of groundwork effort were: (1) Validation of simulations and phantoms mimicking elastic and viscoelastic properties of liver, (2) Comparison of SWS measurements in uniform liver-mimicking phantoms using ultrasound imaging systems, the established US non-imaging system, and, initially, MR elastography, and (3) Sources of measurement variability in shear-wave elasticity techniques. It is anticipated that the physical and digital phantoms will be part of these efforts, as well as of the conformance procedures.

Simulation data sets have been developed and posted on the QIDW for use by research groups and manufacturers. The goal is to find approaches that allow different ultrasound systems to achieve the same SWS results from data generated using appropriate simulated visco-elastic materials. Simulated data representing elastic (lossless) and viscoelastic (tissue-mimicking) media have been released for download by interested parties, and several manufacturers have begun to look at the materials to determine if it is technically and economically feasible to analyze test data using their proprietary software. A comprehensive comparison of simulation results obtained with two common commercial finite element modeling software packages has been performed, and the corresponding code to process the data are available on GitHub. If this plan is successful, use of digital reference objects (DROs) to analyze ways to achieve better agreement in SWS values will become possible.

Data have been acquired to investigate sources of variance from comorbidity, biological variability, and measurement methods that might affect SWS estimate correlation with fibrosis. Studies were based on a literature analysis of 1,548 publications, from which 102 SWS papers included a study of one or more confounding factors. A further analysis of the potential for steatosis and/or inflammation to affect the correlation of SWS with liver fibrosis was performed using results obtained for 242 subjects.

A standardized plan for archiving clinical and phantom data into the QIDW is being devised and will be included as an appendix to the QIBA Profile.

A first draft of the QIBA ultrasound Profile “SWS Estimation of Liver Fibrosis” has been created. Distribution within and approval by the Biomarker Committee is pending while the Profile document is converted to the new document template provided by the Process Committee and system-dependent methods descriptions are provided by the participating manufacturers. A standardized SWS data collection report form has been developed for inclusion in the Profile appendices.