Certificate Course: Beyond Clinical Imaging – August 2, 2017
Session 2: Recent Advancement of Imaging Guidance in Clinical Trials
WE-DE-205-0

QIBA / Imaging Analysis in Clinical Trials

Edward F. Jackson, PhD
Professor and Chair, Department of Medical Physics
Professor of Radiology and Human Oncology

School of Medicine and Public Health
UNIVERSITY OF WISCONSIN-MADISON

Objectives

This presentation will address:

- the advantages of quantitative imaging biomarker (QIB) measurements in clinical trials,
- key challenges to the validation and qualification of QIB measurements, and
- examples of efforts to address such challenges

Biomarkers

Biomarkers are characteristics that are *objectively measured* and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1]

Quantitative imaging biomarkers (QIBs) are objective characteristics derived from *in vivo* images as indicators of normal biological processes, pathogenic processes, or response to a therapeutic intervention.[2]

[1]NIH Biomarkers Definitions Working Group, *Clin Pharmacol Therap* 69(3):89-95, 2001
[2]Sullivan *et al.*, *Radiology* 277(3):813-825, 2015 (www.rsna.org/qiba)

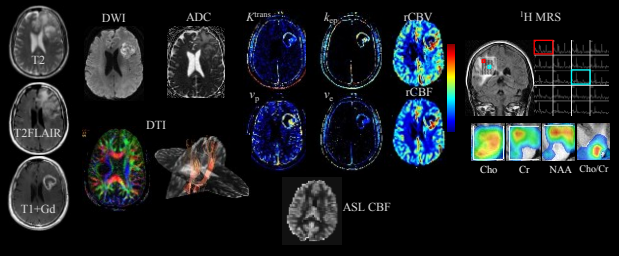
From Qualitative Findings to QIB Assay

- Validation: "assessing the assay and its measurement performance characteristics, and determining the range of conditions under which the assay will give reproducible and accurate data"
- Qualification: "'fit-for-purpose' evidentiary process linking a biomarker with biology and clinical endpoints"
- Surrogate: "a biomarker that can substitute for a clinical endpoint in a regulatory approval process"

Wagner JA, *et al.* Translational Medicine 81(1):104-7, 2007

Current MR QIB Applications

Existing MR QIBs in Glioma: Morphological to Functional



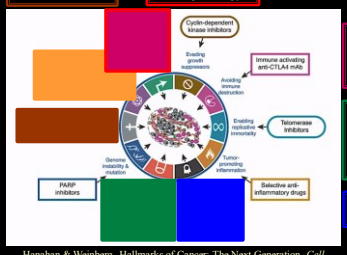
MR QIBs in Glioma

Modified version of Table 1 of Nelson, *NMR Biomed* 24:734-739, 2011

Imaging Applications in Precision Medicine

^{18}F/ ^{99m}Tc-Annexin V
Diffusion MRI

^{18}F-FLT PET
Diffusion MRI
^{1}H MR Spectroscopy



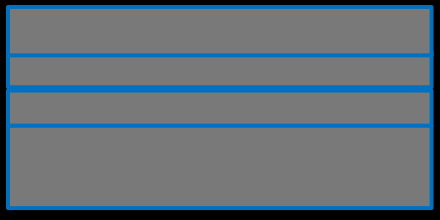
^{18}F-FDG PET
^{18}F-MISO PET
^{1}H & ^{13}C MR Spectroscopy
BOLD MRI

DCE-MRI / DCE-CT
DSC-MRI / ASL MRI
CE-US
^{68}Ga-/^{64}Cu-DOTA-cRGD PET
^{89}Zr-bevacizumab

^{18}F-FDG PET
Diffusion MRI

Hanahan & Weinberg, Hallmarks of Cancer: The Next Generation, *Cell* 144:646-674, 2011

QIBs in Precision Medicine



Buckler, *et al.*, A Collaborative Enterprise for Multi-Stakeholder Participation in the Advancement of Quantitative Imaging, *Radiology* 258:906-914, 2011

Objectives

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- examples of efforts to address such challenges

Problem: QIB Uncertainties

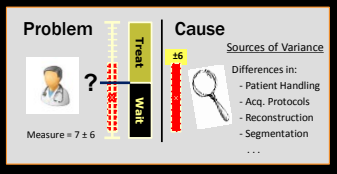


Image compliments of Kevin O'Donnell

2017 Fleischner Society Guidelines for Management of CT Pulmonary Nodules

Nodule Type				Comments
Single				
Low risk[1]	No routine follow-up	CT at 6–12 months, then consider CT at 18–24 months	Consider CT at 3 months, PET/CT, or tissue sampling	Nodules <6 mm do not require routine follow-up, but certain patients at high risk with suspicious nodule morphology, upper lobe location, or both may warrant 12-month follow-up (recommendation 1A).

MacMahon H, *et al.*, Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017.
Radiology 2017 Feb 23

QIB Challenges

Diagnostic Imaging System ≠ Measurement Device

- Measurement Device:
  - Specific measurand(s) with known bias and variance (confidence intervals)
  - Specific requirements for reproducible quantitative results
  - Example: a pulse oximeter
- Diagnostic Imaging Equipment:
  - Historically: best image quality in shortest time (*qualitative*)
  - No specific requirements for reproducible *quantitative* results (with few exceptions)

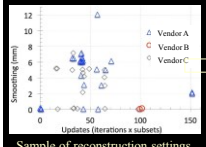
QIB Challenges

General QIB technical challenges:

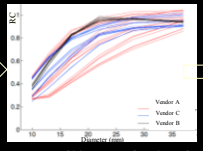
- Lack of detailed assessment of sources of bias and variance
- Lack of standards (acquisition and analysis)
- Highly variable quality control procedures
  - QC programs / phantoms, if any, typically not specific for *quantitative* imaging
- Little support (historically) from imaging equipment vendors
  - No documented competitive advantage of QIB (regulatory or payer)

All lead to varying measurement results across vendors, centers, and/or time

PET Reconstruction Harmonization

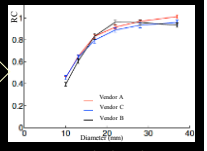


Sample of reconstruction settings from 68 academic imaging centers



Range of biases as a function of object size for different reconstruction settings

(1.0 = no bias)



Harmonized results

RC = Ratio of Observed Activity Concentration to Actual Activity Concentration

Source: Paul Kinahan, PhD

Adopting Metrology Principles in Imaging

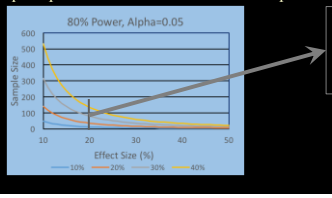
Sources of bias and variance in QIB measurands are identified and mitigated to the degree possible.

- Bias* (accuracy):
  - Often difficult to assess due to absence of reference standard ("ground truth") measures
  - Potential role for application-specific phantoms
- Precision* (variance):
  - Repeatability* – All conditions the same except short time separation ("test/retest")
    – Repeatability coefficient
  - Reproducibility* – Different operators, different days
    – Reproducibility coefficient

*Kessler, Barnhart, *et al.*, *Stat Meth Med Res* 24:9-26, 2015; Sullivan, Obuchowski, *et al. Radiology* 277:813-825, 2015 available at www.rsna.org/qiba

Adopting Metrology Principles in Imaging

- Levels of bias and variance remaining after mitigation are characterized => confidence intervals.
- Knowing these levels translates to statistically valid study designs with adequate power and the fewest number of patients.



Number of patients:	
10%	12
20%	35
30%	78
40%	133

Need for Data Sharing

- Clinical trials involving QIBs are expensive
  - Individual trials typically have small numbers of patients (Phase I / II)
- Standardization ➔ Pooled, quality data
  - Meta analysis studies
  - Algorithm development, validation, and comparison
  - Evidence-based medicine / comparative effectiveness studies
  - Radiomics / radiogenomics studies

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Selected QIB Initiatives

RSNA: Quantitative Imaging Biomarkers Alliance (QIBA) with support from NIBIB

NCI: Quantitative Imaging Network (QIN)

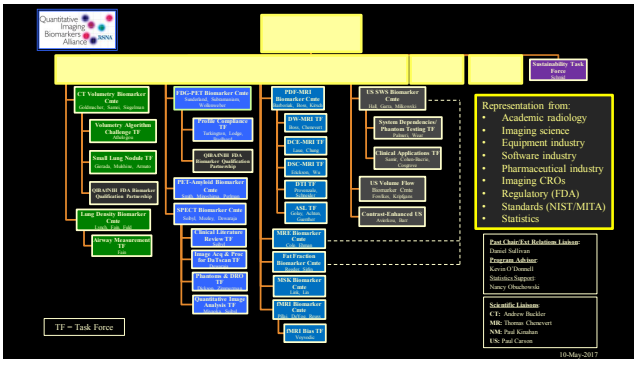
NIST: Quantitative Imaging Physical Phantoms / Metrology

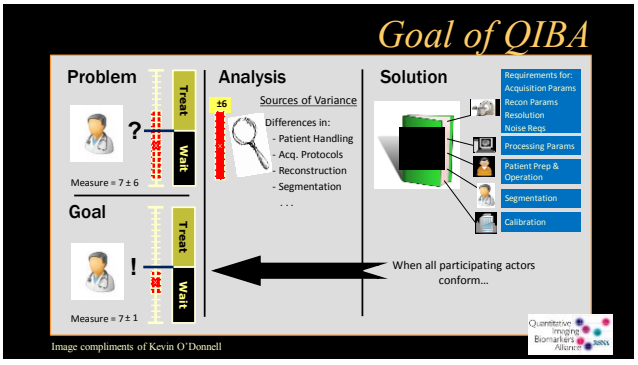
FDA: Quantitative Imaging Physical Phantoms & Regulations

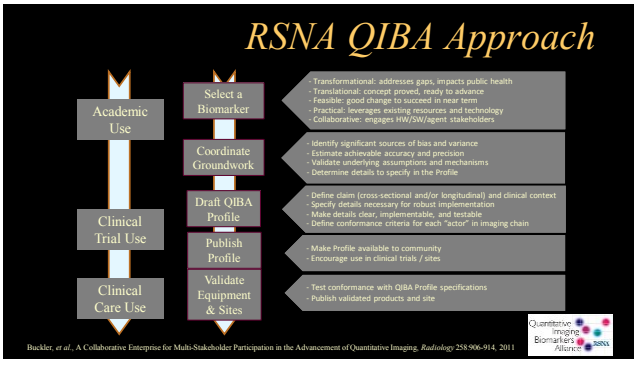
Scientific organization efforts

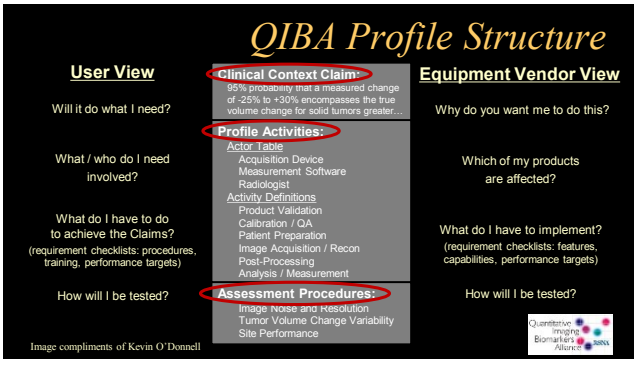
Quantitative Imaging Biomarkers Alliance

- QIBA was initiated in 2007
- RSNA Perspective: *One approach* to reducing variability in radiology is to extract objective, quantitative results from imaging studies.
- QIBA Mission
  - Improve the value and practicality of *quantitative imaging biomarkers* by reducing variability across devices, imaging centers, patients, and time.
  - "Industrialize imaging biomarkers"

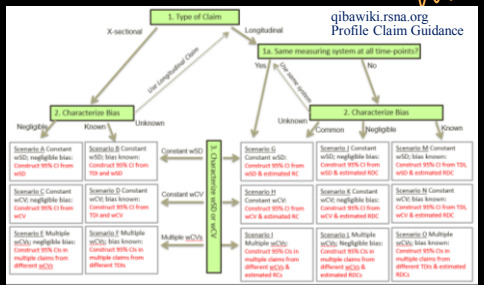



Goal of QIBA
Problem
Treat
Wait
Measure = 7 ± 6
Goal
Treat
Wait
Measure = 7 ± 1
Analysis
±6
Sources of Variance
Differences in:
- Patient Handling
- Acq. Protocols
- Reconstruction
- Segmentation
. . .
Solution
Requirements for:
Acquisition Params
Recon Params
Resolution
Noise Reqs
Processing Params
Patient Prep & Operation
Segmentation
Calibration
When all participating actors conform…
Image compliments of Kevin O'Donnell


RSNA QIBA Approach
Academic Use
Clinical Trial Use
Clinical Care Use
Select a Biomarker
Coordinate Groundwork
Draft QIBA Profile
Publish Profile
Validate Equipment & Sites
- Transformational: addresses gaps, impacts public health
- Translational: concept proved, ready to advance
- Feasible: good change to succeed in near term
- Practical: leverages existing resources and technology
- Collaborative: engages HW/SW/agent stakeholders
- Identify significant sources of bias and variance
- Estimate achievable accuracy and precision
- Validate underlying assumptions and mechanisms
- Determine details to specify in the Profile
- Define claim (cross-sectional and/or longitudinal) and clinical context
- Specify details necessary for robust implementation
- Make details clear, implementable, and testable
- Define conformance criteria for each "actor" in imaging chain
- Make Profile available to community
- Encourage use in clinical trials / sites
- Test conformance with QIBA Profile specifications
- Publish validated products and site
Buckler, et al., A Collaborative Enterprise for Multi-Stakeholder Participation in the Advancement of Quantitative Imaging, Radiology 258:906-914, 2011


QIBA Profile Structure
User View
Will it do what I need?
What / who do I need involved?
What do I have to do to achieve the Claims?
(requirement checklists: procedures, training, performance targets)
How will I be tested?
Clinical Context Claim:
95% probability that a measured change of -25% to +30% encompasses the true volume change for solid tumors greater…
Profile Activities:
Actor Table
Acquisition Device
Measurement Software
Radiologist
Activity Definitions
Product Validation
Calibration / QA
Patient Preparation
Image Acquisition / Recon
Post-Processing
Analysis / Measurement
Assessment Procedures:
Image Noise and Resolution
Tumor Volume Change Variability
Site Performance
Equipment Vendor View
Why do you want me to do this?
Which of my products are affected?
What do I have to implement?
(requirement checklists: features, capabilities, performance targets)
How will I be tested?
Image compliments of Kevin O'Donnell

QIBA Claim Template



qibawiki.rsna.org
Profile Claim Guidance

Current Profile Status *(As of 7/15/2017)*

- 20 Profiles (4 CT, 3 NM, 10 MR, 3 US)
- Technically Confirmed Stage:
  - *FDG-PET/CT SUV as an Imaging Biomarker for Measuring Response to Cancer Therapy* (v1.05)*
- Publicly Reviewed (Consensus) Stage and Posted:
  - *CT Tumor Volume Change* (v2.2) for tumor response (expected to be Technically Confirmed Spr 2017)*
  - *DCE-MRI Quantification* (v1.0) for tumor response
- In Public Comment Stage:
  - CT: *Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening Quantification*
  - SPECT: *Quantifying Dopamine Transporters with 123-Iodine labeled Ioflupane in Neurodegenerative Disease*
  - DW-MRI for tumor response

*Highlighted on Cancer Moonshot website

qibawiki.rsna.org

Current Profile Status *(As of 7/15/2017)*

- In Final Stage of Development for Public Comment Stage:
  - CT lung densitometry for COPD
  - PET amyloid for Alzheimer's Disease
  - fMRI for pre-surgical planning
  - Ultrasound shear wave speed for liver fibrosis
- In Development:
  - CT tumor volume change for liver lesions
  - MR elastography for liver fibrosis
  - Dynamic susceptibility contrast (DSC)-MRI for perfusion assessment in brain
  - MR proton density fat fraction (PDFF) for liver disease
  - MR diffusion tensor imaging (DTI) for traumatic brain injury
  - Revised DCE-MRI to address 3T and parallel imaging
  - Arterial spin labeling (ASL) MR – collaboration with EIBALL
  - T_2 and $T1_\rho$ MSK MR for degenerative joint disease
  - Ultrasound volume flow for perfusion studies – collaboration with AIUM
  - Contrast-enhanced ultrasound (CEUS) for perfusion studies

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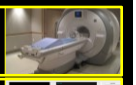
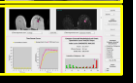
QIBA Groundwork Projects

QIB Implementation and Qualification

- Data acquisition => Physical phantoms & datasets
  - Application specific phantoms
  - Clinical trial datasets



- Data analysis => Synthetic phantoms & datasets
  - Application specific "digital reference objects" or DROs
  - Clinical trial datasets

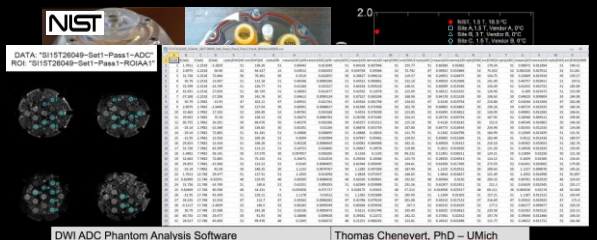


- Qualification => "Fit for purpose" <= clinical trials

QIBA groundwork projects funded by 3 contracts from NIH National Institute of Biomedical Imaging and Bioengineering

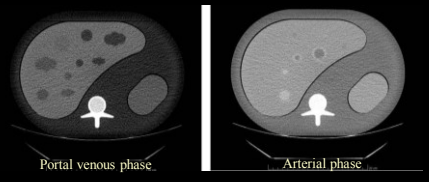
Quantitative Imaging Biomarkers Alliance RSNA

RSNA QIBA Groundwork Projects



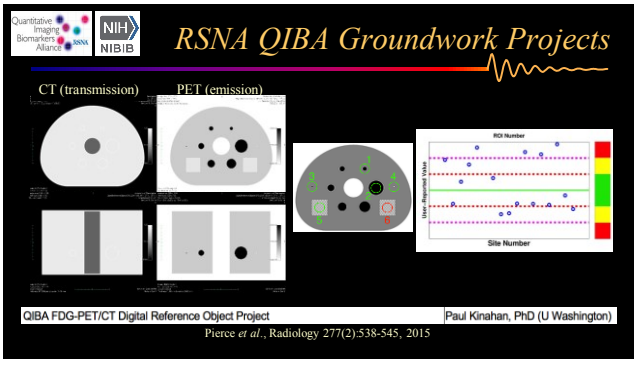
DWI ADC Phantom Analysis Software | Thomas Chenevert, PhD – UMich

RSNA QIBA Groundwork Projects



Phantoms for CT Volumetry of Hepatic and Nodal Metastasis | Binsheng Zhao, DSc – Columbia University

RSNA QIBA Groundwork Projects

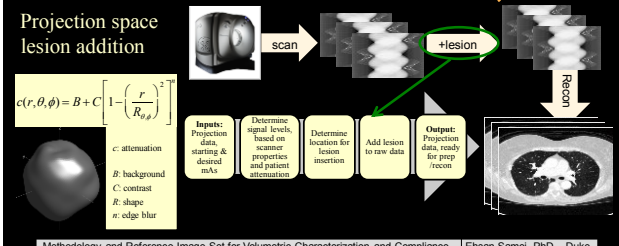


QIBA FDG-PET/CT Digital Reference Object Project | Paul Kinahan, PhD (U Washington)

Pierce *et al*., Radiology 277(2):538-545, 2015

RSNA QIBA Groundwork Projects

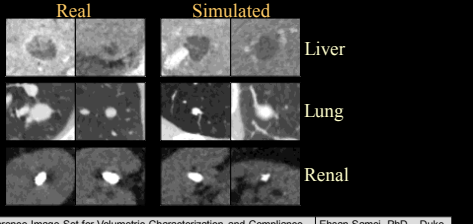
Projection space lesion addition



Methodology and Reference Image Set for Volumetric Characterization and Compliance | Ehsan Samei, PhD – Duke

RSNA QIBA Groundwork Projects

Which lesions are real?

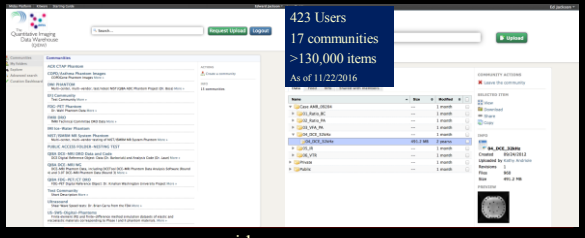


Methodology and Reference Image Set for Volumetric Characterization and Compliance | Ehsan Samei, PhD – Duke

QIBA Phantoms & Datasets

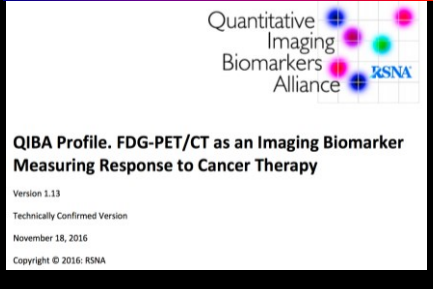
- Physical Phantoms
  - Volumetric CT Liver Phantom (arterial/portal venous phase)
  - DCE-MRI Phantom and analysis software
  - DWI ADC Phantom and analysis software
  - DSC-MRI Phantom (in development; target release Q4/2017)
  - Shear Wave Speed Phantoms (varying viscoelastic properties) – for both US SWS and MRE
- Digital Reference Objects (Synthetic Phantoms) – Publicly Available
  - Volumetric CT DRO (Liver, Lung, Kidney)
  - DCE-MRI DRO (T_1 mapping and K^{trans}, v_e) and analysis software
  - DWI ADC DRO
  - DSC-MRI DRO (in development; target release Q3/2017)
  - fMRI DROs (motor and language mapping)
  - PET SUV DRO
  - SPECT DRO (^{123}I dopamine transporter, DaTscan; in development; Q3/2017)

Quantitative Imaging Data Warehouse (QIDW)



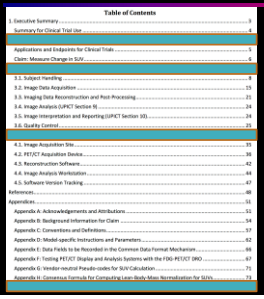
qidw.rsna.org

FDG-PET/CT SUV Profile



qibawiki.rsna.org
=> Profiles

FDG-PET/CT SUV Profile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Conformance to this Profile by all relevant staff and equipment supports the following claims:

Claim 1: Tumor glycolytic activity as reflected by the maximum standardized uptake value (SUVmax) is measureable from FDG-PET/CT with a within-subject coefficient of variation of 10-12%.

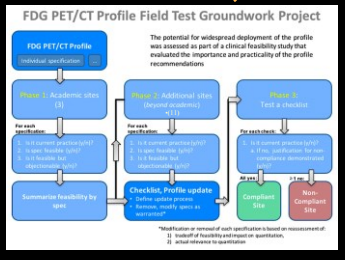
Claim 2: A measured increase in SUVmax of 39% or more, or a decrease of -28% or more, indicates that a true change has occurred with 95% confidence.

FDG-PET/CT SUV Profile

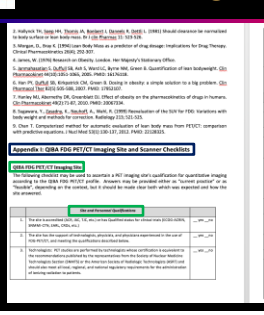
Conformance Checklists

Feasibility testing: academic sites and community sites

80 page profile => clinical site implementation and qualification checklists



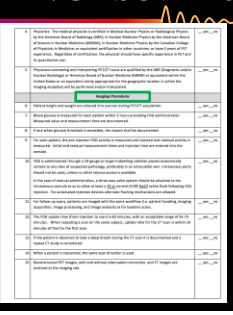
FDG-PET/CT SUV Profile

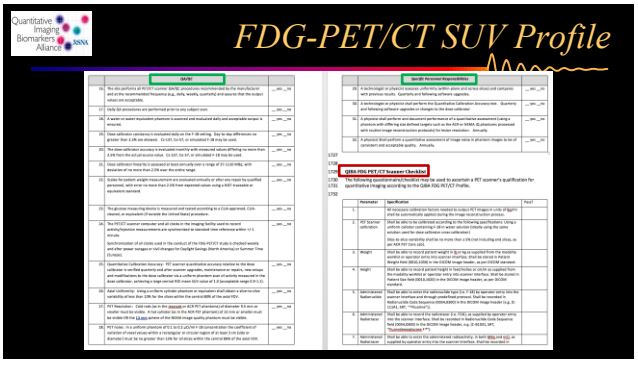

Appendix I: QIBA FDG PET/CT Imaging Site and Scanner Checklists

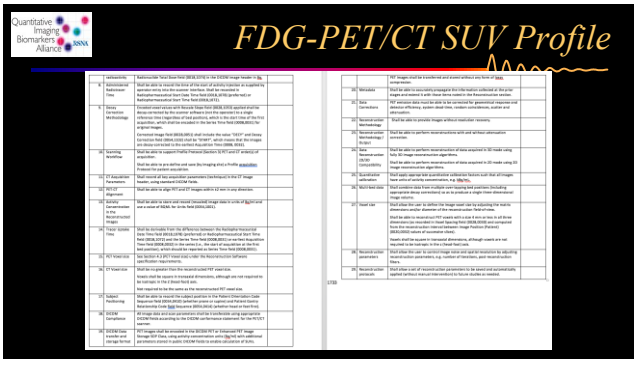
QIBA FDG PET/CT Imaging Site

The following checklist may be used to ascertain a PET imaging site's qualification for quantitative imaging according to the QIBA FDG PET/CT profile. Answers may be provided either as "current practice" or as "feasible", depending on the context, but it should be made clear both which was expected and how this was answered.

Site and Personnel Qualifications







Summary

- Translation of QIBs to clinical practice requires metrological approaches to characterizing the sources of bias and variance, mitigation of such sources to the degree possible, and harmonization of QIB measurements across vendor platforms and time.
- Standardization of QIBs (acquisition, data analysis, reporting) are critical for translation to clinical practice.
- Such standardization will also enable more robust radiomics / imaging genomics applications.

Acknowledgments

- RSNA and RSNA QIBA Staff
- RSNA QIBA Process Committee & Metrology Working Group, especially Daniel Sullivan, MD, Kevin O'Donnell, MS, and Nancy Obuchowski, PhD
- Michael Boss, PhD, Thomas Chenevert, PhD - NIST / U Mich: ADC Phantom & Software
- Ehsan Samei, PhD, Berkman Sahiner, PhD, Nick Petrick, PhD, Binshang Zhao, PhD - RSNA QIBA (CT DRO & Liver Phantom)
- Paul Kinahan, PhD - FDG-PET DRO
- RSNA and QIBA Biomarker Committee & Task Force Co-Chairs & Members
- NIBIB Contracts HHSN268201000050C, HHSN268201300071C, HHSN268201500021C

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