The Quantitative Imaging Biomarkers Alliance (QIBA®)

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Quantitative Imaging 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)

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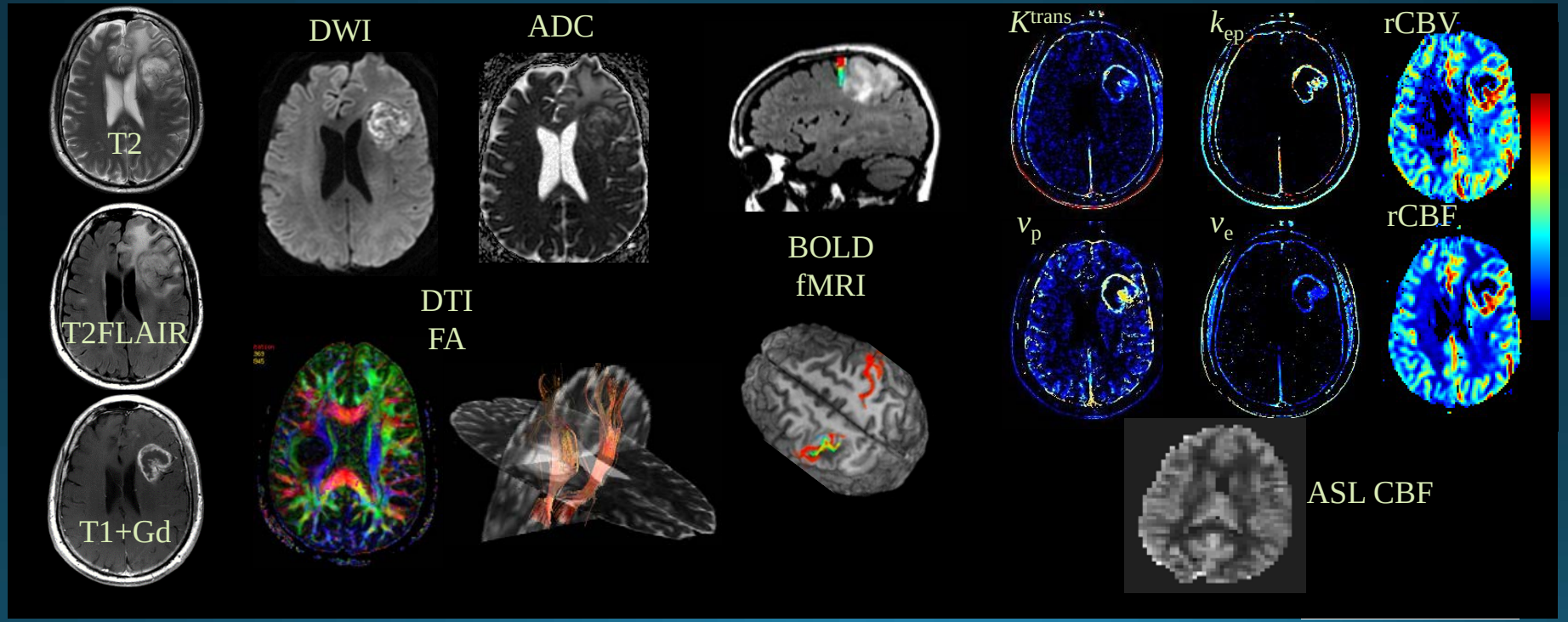
Example MR QIB Applications

Existing MR QIBs:

From simple morphological to numerous functional measures



Consumer Expectations for Quantification

- 94% of oncologists expect some or all tumors to be measured at the time of standard initial clinical imaging. (Jaffe T, *AJR* 2010)
- Neurologists and psychiatrists desire quantitative measures of brain disorders (IOM Workshop, August 2013).
- Pulmonologists desire CT-derived quantitative measures in COPD and asthma patients. (ATS/ERS Policy statement, *Am J Resp Crit Care Med* 2010)
- Hepatologists desire quantitative measures of liver fat infiltration (Fitzpatrick E, *World J Gastro* 2014)
- Rheumatologists desire quantitative measures of joint disease (Chu C, *JBJS:J Bone Joint Surg* 2014)
- U.S. regulatory agencies (*e.g.*, FDA) desire more objectivity in imaging scan interpretations.

Source: Daniel C. Sullivan, MD

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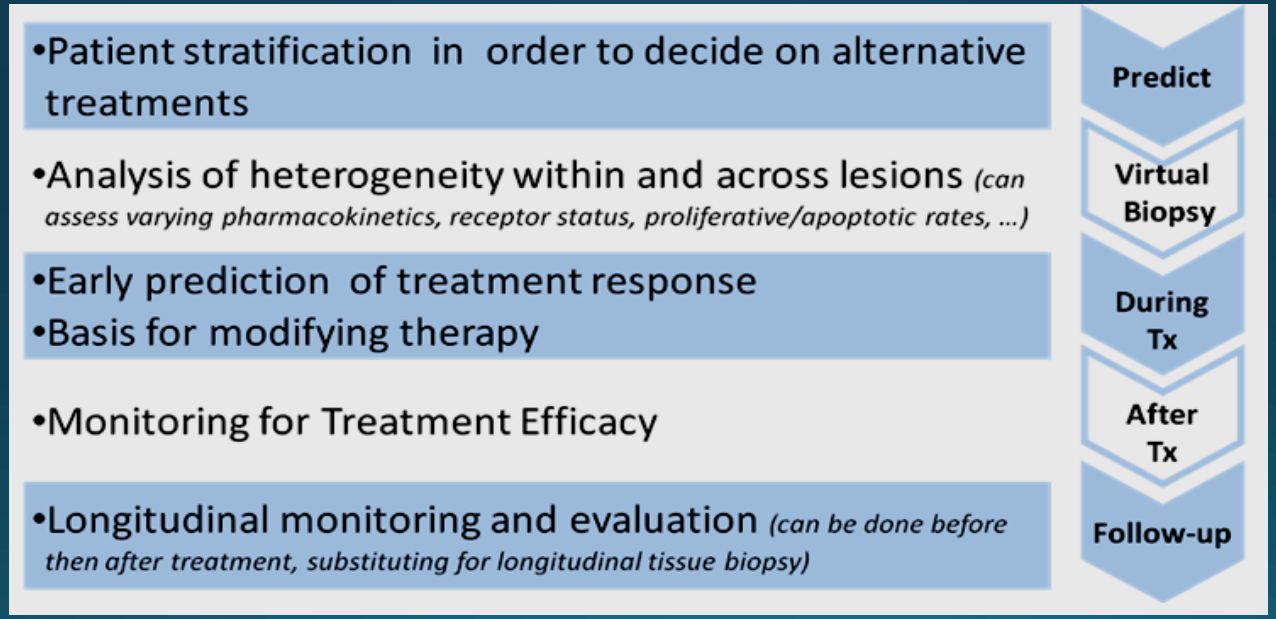
QIBs in Precision Medicine



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

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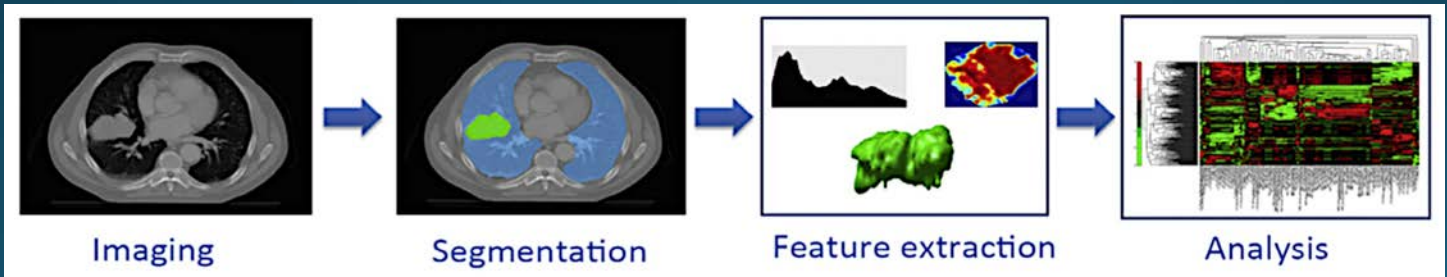
Quantitative Imaging

In addition:

- *Evidence-based medicine and QA programs* depend on objective data
- *Decision-support tools* need quantitative inputs
- *Radiomics and radiogenomics* studies require quantitative data



P. Lambin *et al.* *Eur J Cancer* 48:441-446 2012

QIB Challenges

Diagnostic Imaging Equipment ≠ 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)

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QIB Challenges

General QIB challenges:

- Lack of detailed assessment of sources of bias and variance
- Lack of standards (acquisition, analysis, and reporting)
- 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

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QIB Challenges

General QIB challenges:

- Cost of QIB studies (comparative effectiveness) / reimbursement
- Resource availability
  - Technologists are not trained in advanced, quantitative, protocols
  - Potential shortage of imaging scientists, data processing capabilities, *etc*.
- Radiologist acceptance
  - QIBs are not part of radiologist education & training
  - Lack of guidelines for QIB reporting
  - Software and workstations needed to calculate and interpret QIB measures are not integrated into the radiologist's workflow
  - Clinical demand on radiologists is high --- "time is money"

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QIB Challenges

QIB Implementation and Qualification

- Data acquisition => Need for physical phantoms
  - Application specific (potentially including human subjects)
- Data analysis => Need for synthetic phantoms
  - "Digital reference objects" or DROs
  - Application specific and, ideally, anthropomorphic
- Qualification => Need for clinical trials

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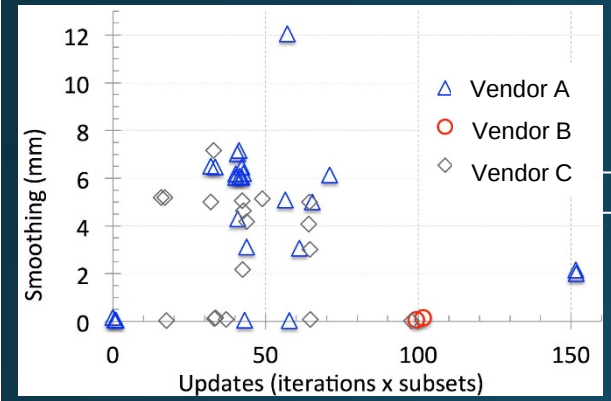
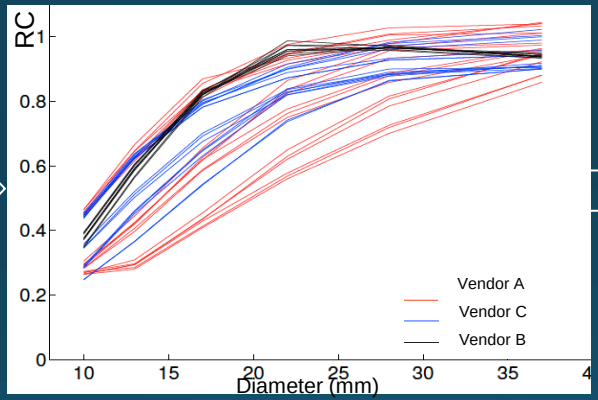
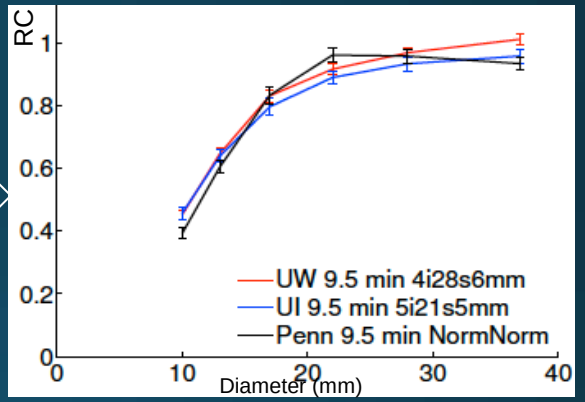
PET Reconstruction Harmonization



Sample of reconstruction settings from 68 academic centers



Range of biases as a function of object size (1.0 is no bias) for different reconstruction settings



Harmonized results

Source: Paul Kinahan, PhD
University of Washington

RC = Ratio of Observed Activity Concentration to Actual Activity Concentration

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Poor Reproducibility has Clinical Implications

- Willemink MJ, *et al.* Coronary artery calcification scoring with state-of-the-art CT scanners from different vendors has substantial effect on risk classification. *Radiology* 173:695-702, 2014

  "Among individuals at intermediate cardiovascular risk, state-of the-art CT scanners made by different vendors produced substantially different Agatston scores, which can result in reclassification of patients to the high- or low-risk categories in up to 6.5% of cases."

- Oberoi S, *et al.* Reproducibility of noncalcified coronary artery plaque burden quantification from coronary CT angiography across different image analysis platforms. *AJR Am J Roentgenol* 202:W43-9, 2014

  "Currently available noncalcified plaque quantification software provides …poor interplatform reproducibility. Serial or comparative assessments require evaluation using the same software. Industry standards should be developed to enable reproducible assessments across manufacturers."

Source: Daniel C. Sullivan, MD

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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
  - Need application-specific phantoms
- Precision* (variance):
  - Repeatability* – All conditions the same except short time separation ("test/retest")
    – Repeatability coefficient
  - Reproducibility* – Different operators, different days, *etc*.
    – Reproducibility coefficient

*Kessler, Barnhart, *et al.*, *Stat Meth Med Res* 24:9-26, 2015; Sullivan, Obuchowski, *et al. Radiology* 277:813-825, 2016

available at www.rsna.org/qiba

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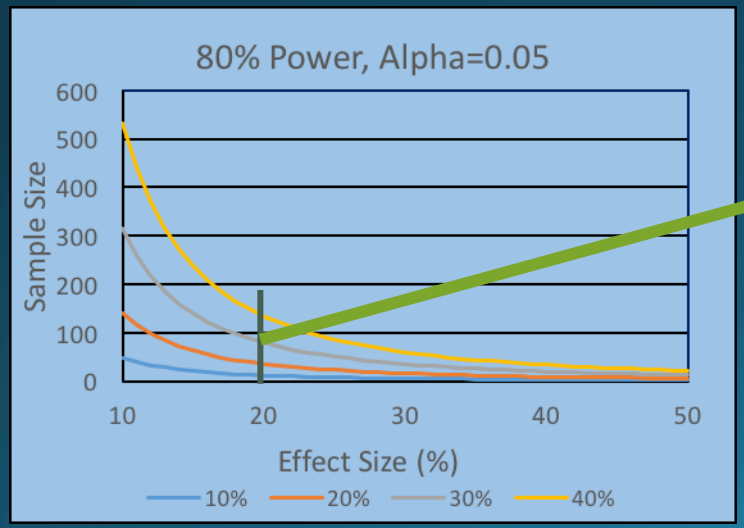
Adopting Metrology Principles in Imaging

- 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

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RSNA QIBA

- QIBA was initiated in 2007 under the leadership of Dan Sullivan
- 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, patients, and time.
  - "Industrialize imaging biomarkers"

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Qualitative Imaging => Biomarker Assays

Assays are characterized by their:

- Technical Performance

- Clinical Performance
  - Clinical validation
  - Clinical utility

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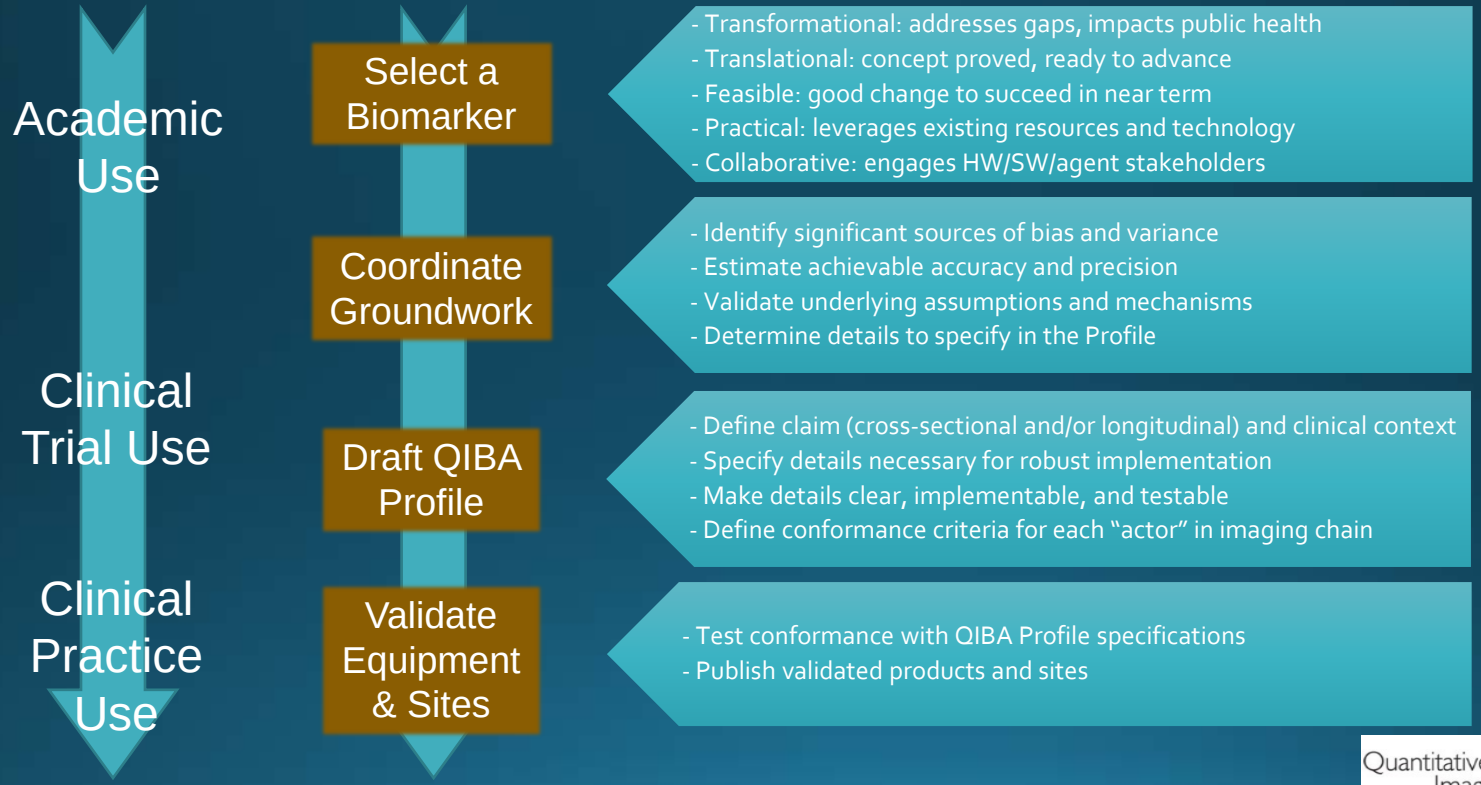
RSNA QIBA Approach



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RSNA QIBA Approach

- Profile
  - Describes a specific performance claim and how it can be achieved.
  - Claims: tell a user what can be accomplished by following the Profile.
  - Details: tell a vendor what must be implemented in their product; tell a user what procedures are necessary.
- Protocol
  - Describes how clinical trial subjects or patients should be imaged so as to achieve reproducible quantitative endpoints when those tests are performed utilizing systems that meet the specific performance claims stated in the QIBA Profiles.

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Profile Template

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v2.2, April 2015

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Example Claim Language

CROSS-SECTIONAL CLAIM Example: For a <*QIB*> measurement of *X* in solid tumors greater than *Y* cm in diameter or twice the section thickness (whichever is greater), a 95% confidence interval for the true <*QIB*> value is X ⌖ <*1.96*wSD*>.

LONGITUDINAL CLAIM Example: A measured change in <*QIB*> of *Z* or larger indicates a true change has occurred with 95% confidence. For a measured change of *Z*, a 95% confidence interval for the true change is *Z* ⌖ <*1.96 * √2 * wSD*>.

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Profile Template

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Profile Stages

- Stage 1: Public Comment
  - Biomarker Committee experts have drafted the profile and believe it is practical and expect it to achieve the claimed performance.
- Stage 2: Consensus
  - The wider community has read the profile and believe it to be practical and expect it to achieve the claimed performance.
- Stage 3: Technically Confirmed
  - Sites (at least 2 and with at least 2 vendor platforms) have implemented the profile and found it to be practical and expect it to achieve the claimed performance.
- Stage 4: Claim Confirmed
  - Sites (at least 2 and with at least 2 vendor platforms) have implemented the profile and found it achieved the claimed performance.
- Stage 5: Clinically Confirmed
  - Many sites have implemented the profile and demonstrated the claimed performance is widely achievable.

http://qibawiki.rsna.org/index.php/QIBA_Profile_Stages

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Who Forms QIBA?

- Over 850 individuals have joined the QIBA effort, representing all major stakeholders in the quantitative imaging initiative:
  - Radiologists
  - Imaging scientists
  - Pharmaceutical companies
  - Imaging device companies
  - Imaging informatics and other software companies
  - Government agencies
  - Professional societies
  - Clinical trialists and clinicians
  - Statisticians and metrologists
- 297 individuals from over 100 companies, 20 from the FDA, 46 from government (excluding FDA)
- Vast majority of stakeholder efforts are voluntary

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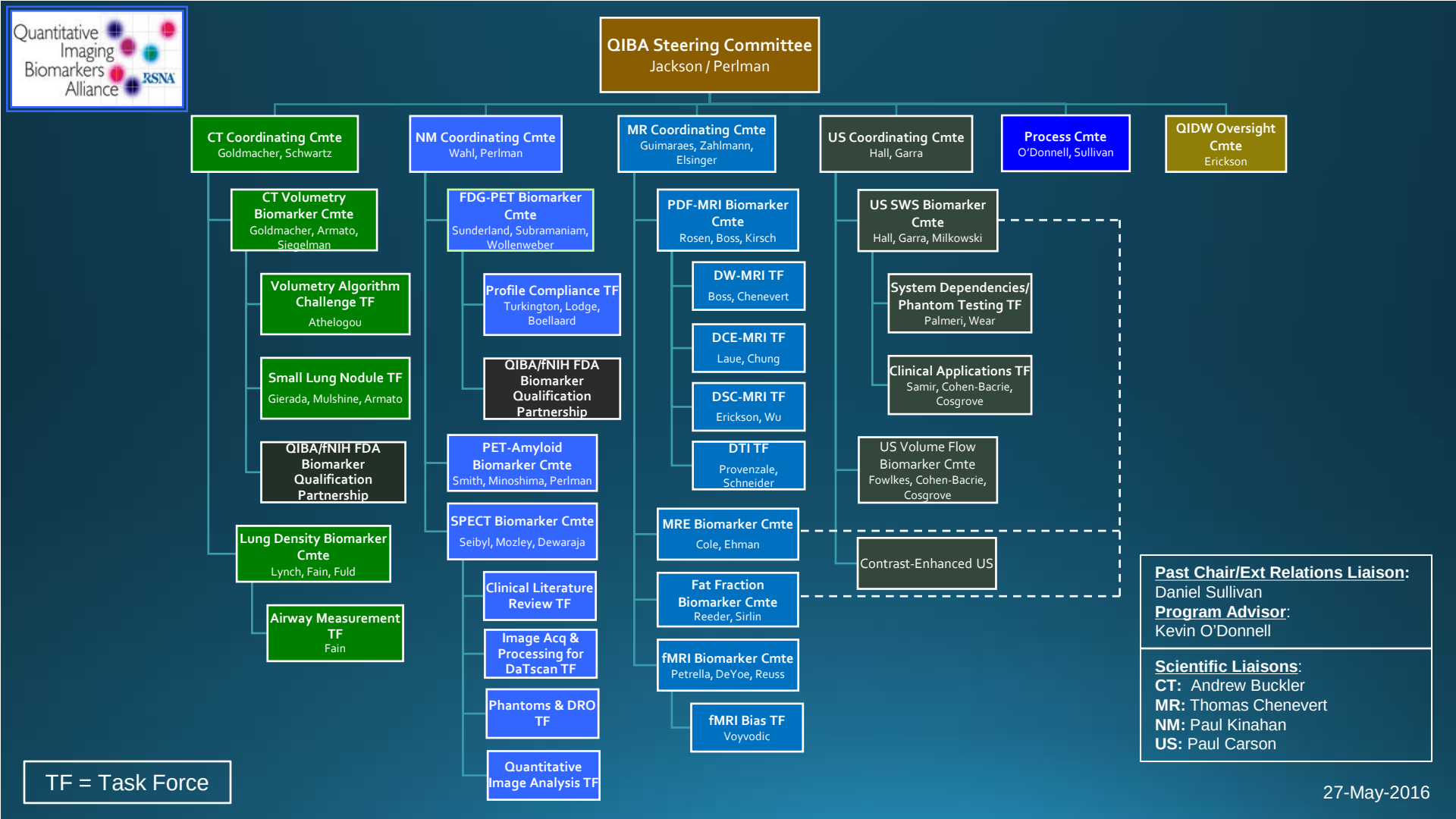
Quantitative Imaging Biomarkers Alliance
RSNA
QIBA Steering Committee
Jackson / Perlman
CT Coordinating Cmte
Goldmacher, Schwartz
NM Coordinating Cmte
Wahl, Perlman
MR Coordinating Cmte
Guimaraes, Zahlmann, Elsinger
US Coordinating Cmte
Hall, Garra
Process Cmte
O'Donnell, Sullivan
QIDW Oversight Cmte
Erickson
CT Volumetry Biomarker Cmte
Goldmacher, Armato, Siegelman
Volumetry Algorithm Challenge TF
Athelogou
Small Lung Nodule TF
Gierada, Mulshine, Armato
QIBA/fNIH FDA Biomarker Qualification Partnership
Lung Density Biomarker Cmte
Lynch, Fain, Fuld
Airway Measurement TF
Fain
FDG-PET Biomarker Cmte
Sunderland, Subramaniam, Wollenweber
Profile Compliance TF
Turkington, Lodge, Boellaard
QIBA/fNIH FDA Biomarker Qualification Partnership
PET-Amyloid Biomarker Cmte
Smith, Minoshima, Perlman
SPECT Biomarker Cmte
Seibyl, Mozley, Dewaraja
Clinical Literature Review TF
Image Acq & Processing for DaTscan TF
Phantoms & DRO TF
Quantitative Image Analysis TF
PDF-MRI Biomarker Cmte
Rosen, Boss, Kirsch
DW-MRI TF
Boss, Chenevert
DCE-MRI TF
Laue, Chung
DSC-MRI TF
Erickson, Wu
DTI TF
Provenzale, Schneider
MRE Biomarker Cmte
Cole, Ehman
Fat Fraction Biomarker Cmte
Reeder, Sirlin
fMRI Biomarker Cmte
Petrella, DeYoe, Reuss
fMRI Bias TF
Voyvodic
US SWS Biomarker Cmte
Hall, Garra, Milkowski
System Dependencies/ Phantom Testing TF
Palmeri, Wear
Clinical Applications TF
Samir, Cohen-Bacrie, Cosgrove
US Volume Flow Biomarker Cmte
Fowlkes, Cohen-Bacrie, Cosgrove
Contrast-Enhanced US
Past Chair/Ext Relations Liaison:
Daniel Sullivan
Program Advisor:
Kevin O'Donnell
Scientific Liaisons:
CT: Andrew Buckler
MR: Thomas Chenevert
NM: Paul Kinahan
US: Paul Carson
TF = Task Force
27-May-2016

NIBIB Groundwork Project Funding

Summary of NIBIB-funded groundwork projects (~$625K per round):

- Round 1 (2011-12): N=16 – complete
- Round 2 (2012-13): N=12 – complete

} HHSN268201000050C

- Round 3 (2013-14): N=13 – complete
- Round 4 (2014-15): N=13 – complete

} HHSN268201300071C

- Round 5 (2015-16): N=12 – in progress
- Round 6 (2016-17): TBD

} HHSN268201500021C

NIH National Institute of Biomedical Imaging and Bioengineering

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Current Profile Status

- Publicly Reviewed and Posted*:
  - *CT Tumor Volume Change* (v2.2) for tumor response
  - *FDG-PET/CT SUV as an Imaging Biomarker for Measuring Response to Cancer Therapy* (v1.05)
  - *DCE-MRI Quantification* (v1.0) for tumor response
  - *FDG-PET/CT Protocol* (with summary published in JNM in April 2015)
- In Final Stage of Development for Public Comment Phase:
  - CT Small Nodule Volumetry for lung cancer CT screening
  - CT Lung Densitometry for COPD
  - PET Amyloid for Alzheimer's Disease
  - DW-MRI for tumor response
  - fMRI for pre-surgical planning
  - Ultrasound Shear Wave Speed for liver fibrosis

*www.rsna.org/qiba

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Current Profile Status

- In Development:
  - Revised CT Tumor Volume Change for liver lesions
  - Revised DCE-MRI to address 3T and parallel imaging
  - MR Diffusion Tensor Imaging (DTI) for traumatic brain injury
  - MR Elastography for liver fibrosis
  - Dynamic Susceptibility Contrast (DSC)-MRI for perfusion assessment in stroke
  - MR Proton Density Fat Fraction (PDFF) for liver disease
  - Ultrasound Volume Flow for perfusion studies
  - Contrast-Enhanced Ultrasound (CEUS) for perfusion studies
  - SPECT for brain diseases

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Current Status

QIBA Metrology Working Group

- Five manuscripts published in *Statistical Methods for Medical Research* in 2014.
- One manuscript published in *Radiology* in 2015.

QIBA Deliverables Based on Groundwork Projects with NIBIB and RSNA Support

Profiles* + Protocols	Manuscripts	Presentations	Posters	Physical Phantoms	DROs	Software Apps	Datasets
3 + 1	31	35	25	3	5	4	5

As of May 20, 2016
*Publicly reviewed stage

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Adoption of QIBA Products / Concepts

- Increasingly active imaging vendor representation on QIBA committees; senior NEMA/MITA, FDA, and NIST representation on QIBA Steering Committee
- Marketing of PET/CT scanners now emphasizes quantitative ability, and marketing of such ability by other modalities is expected
- QIBA Profiles adopted in whole or in part in clinical trials (Roche, Merck, ECOG-ACRIN)
- QIBA approach has been endorsed at several conferences (*e.g.*, IOM DTI workshop; NIST Workshop on Standards for Quantitative MR)
- Requests for QIBA presentations at national / international meetings of scientific and professional organizations (*e.g.*, AAPM 2015 Presidential Symposium, 2016 SPIE Plenary Symposium, 2016 ISMRM Plenary Symposium, 2016 75th Annual Meeting of the Japan Radiological Society, *etc*.)

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Adoption of QIBA Products / Concepts

- Adoption and marketing of "QIBA compliance" by some imaging core labs
- Internationalization of QIBA:
  - Active participation from individuals in South America, Europe, and Asia
  - European Society of Radiology European Imaging Biomarker Alliance (EIBALL)
  - EORTC / IMI – QIBA collaboration (MR DWI)
  - Japan Radiological Society ("QIBA/Japan")
  - São Paulo neuroradiology clinical trial adoption of QIBA profiles
  - Korean Society of Radiology participation

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Current QIBA Challenges

Conformance certification

- Establish formal processes for conformance certification.

Field tests / Implementation of QIBA Profiles

- Field tests take time and money.
- QIBA cannot currently fund human subject field tests using NIBIB funds.
- Need to collaborate with other organizations to accomplish field testing, *e.g.*, ECOG/ACRIN and other clinical trial (cooperative) groups, IMI/EORTC, *etc*.

Image datasets

- Large sets of QIBA-conformant scans are needed to test algorithms, but there is still resistance to the concept of data sharing.

Sustainability

- Need to seek additional sources of funds.

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