Quantitative Imaging

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Early QI Initiative

NIST USMS Workshop 2006

Representative Agencies / Organizations

Biomarkers

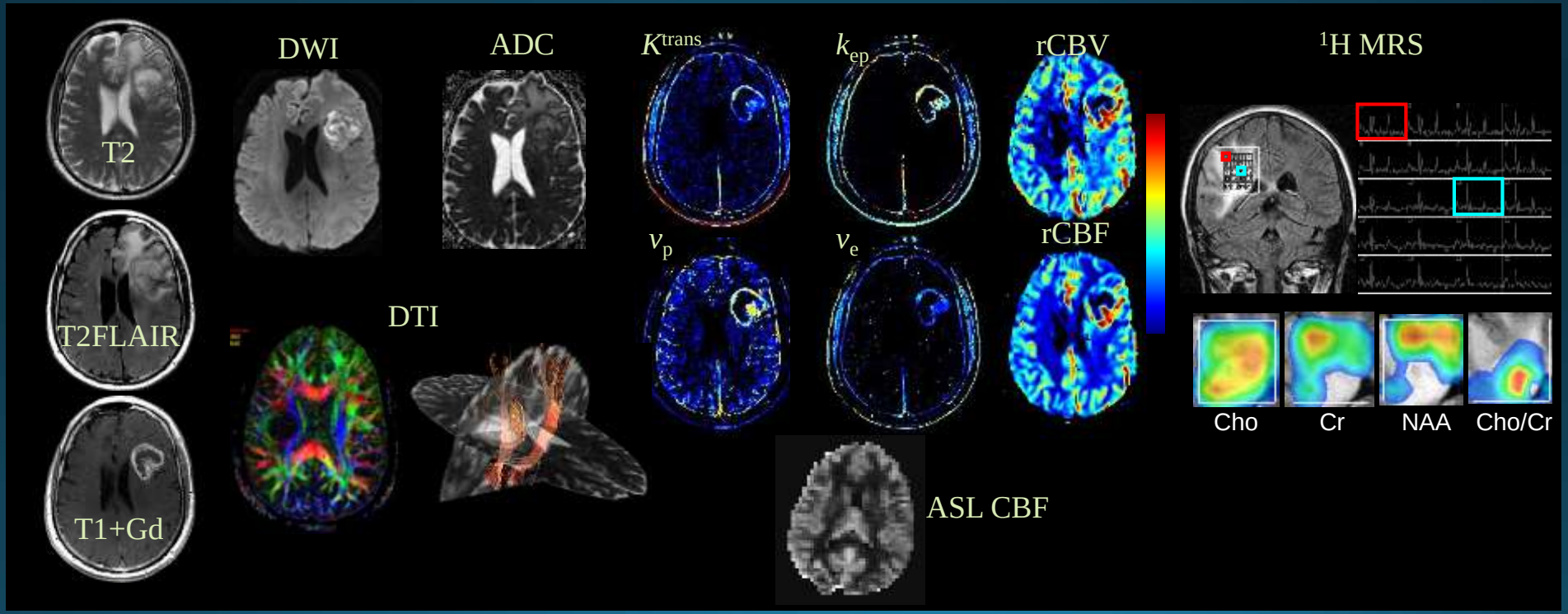
Biomarkers are characteristics that are *objectively measured* and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[1]

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)

Current MR QIB Applications

Existing MR QIBs in Glioma: Morphological to Functional



MR QIBs in Glioma

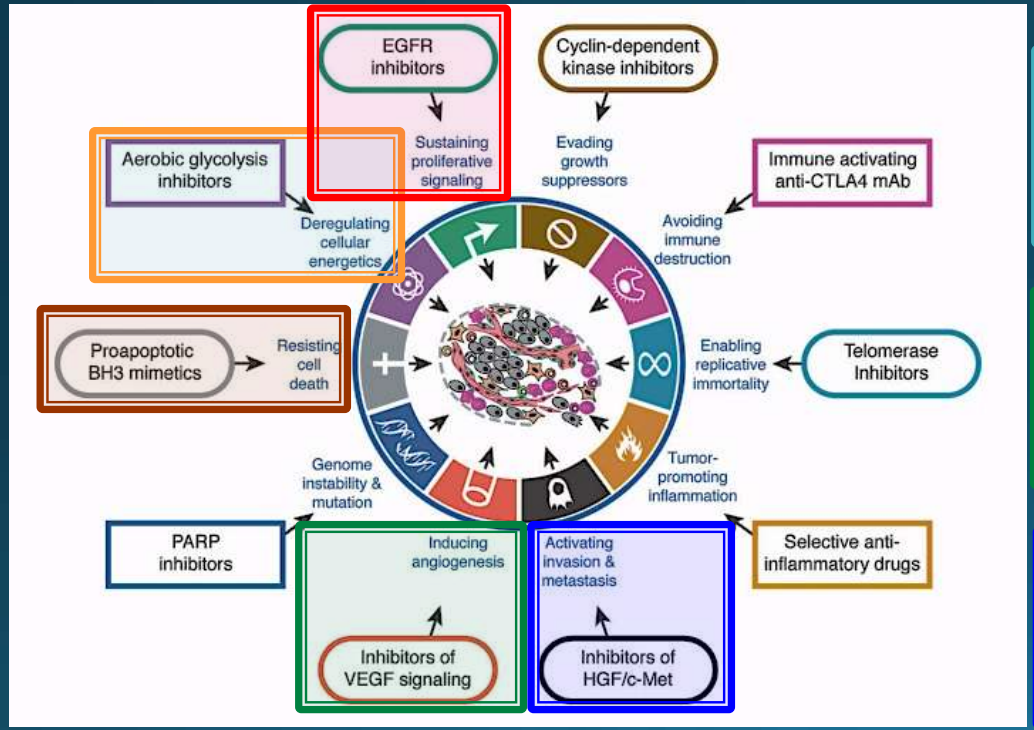
Biological Process	MR Technique	MR QIB Measurand
Tumor Cellularity / Proliferation	^{1}H MRS, DTI/DWI	↑Cho, ↑Cho/NAA, ↓ADC
Necrosis	^{1}H MRS, Gd-enhanced, T2W	↑lipids, No Gd uptake, ↑T2W signal
Edema	T2FLAIR, DTI/DWI	↑FLAIR signal, ↑ADC, ↓FA
Gliosis	^{1}H MRS (short TE)	↑myo-inositol
Hypoxia	^{1}H MRS, BOLD	↑lactate, ↓ΔR2*
Angiogenesis / Permeability	DCE-MRI, DSC-MRI	↑K^{trans} & v_P, ↑rCBV & rCBF
Invasion	DTI, ^{1}H MRS	↓FA, ↑ADC, ↓NAA
Radiation Effects	SWI, DTI	Micro-hemorrhages (late), ↓FA

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

Imaging Applications in Precision Medicine

^{99m}Tc-Annexin V
Diffusion MRI

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



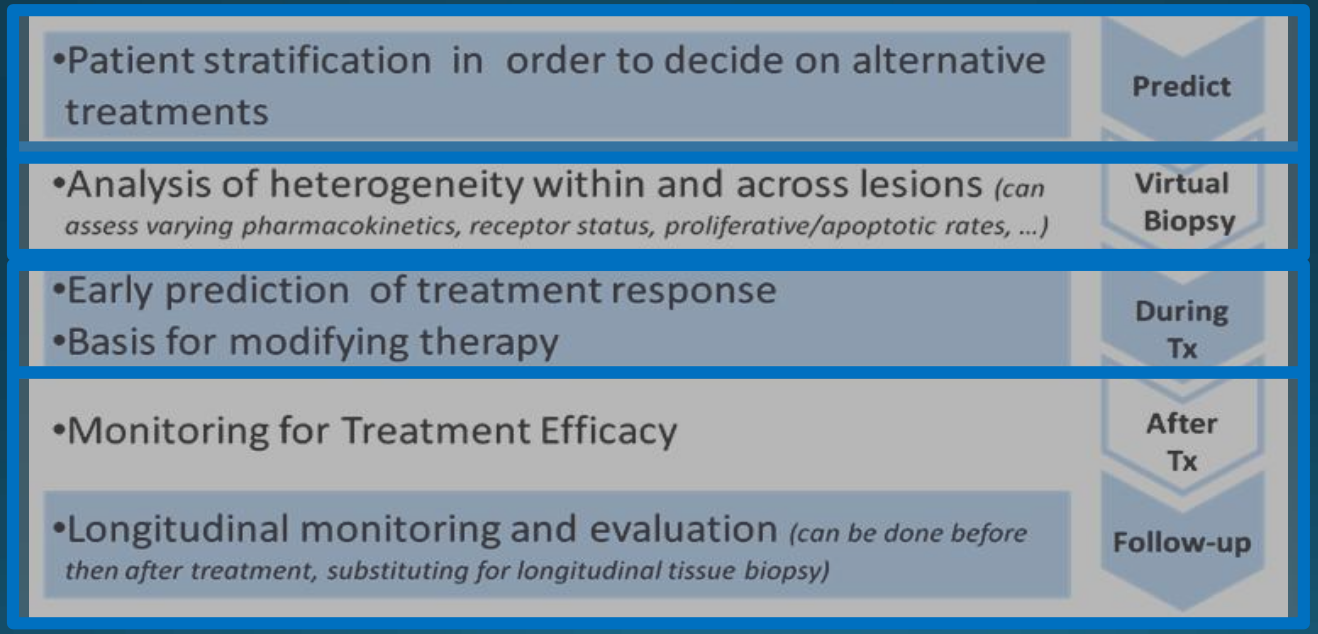
Hanahan & Weinberg, Hallmarks of Cancer: The Next Generation, *Cell* 144:646-674, 2011

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

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

Diffusion MRI
Whole-body DWI
^{18}F-FDG PET
Lymphography

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

Quantitative Imaging

In addition to *Precision Medicine*:

- *Evidence-based medicine and QA programs* depend on objective data
- *Decision-support tools* need quantitative input

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)
- 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)
- Neurologists and psychiatrists desire quantitative measures of brain disorders (IOM Workshop, August 2013).
- Regulatory agencies desire more objectivity in interpretations.

Modality-Independent Issues

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)

QIB Challenges

General QIB 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

QIB Challenges

Other QIB challenges:

- Cost of QIB studies (comparative effectiveness) / reimbursement
- Radiologist acceptance
  - QIBs are not part of radiologist education & training
  - Few compelling use cases for QIBs *vs.* conventional practice
  - The software and workstations needed to calculate and interpret QIBs are often not integrated into the radiologist's workflow
  - Clinical demand on radiologists is high --- "time is money"

Problem: QIB Uncertainties

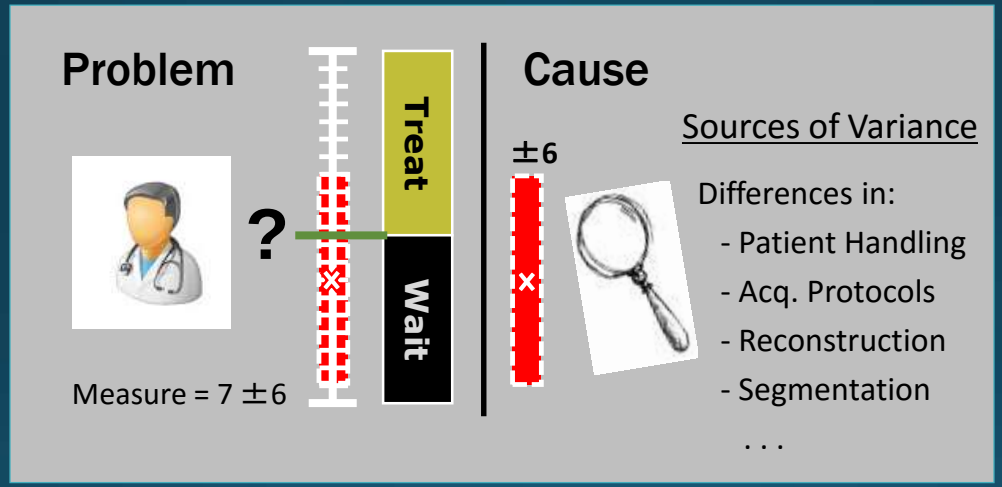


Image compliments of Kevin O'Donnell

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."

Adopting Metrology Principles in Imaging

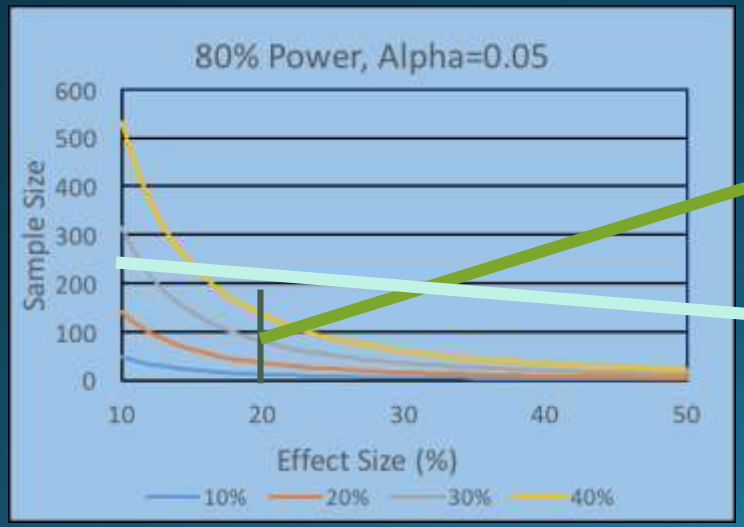
Sources of bias and variance in QIB measurands are identified and mitigated to the degree possible.

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



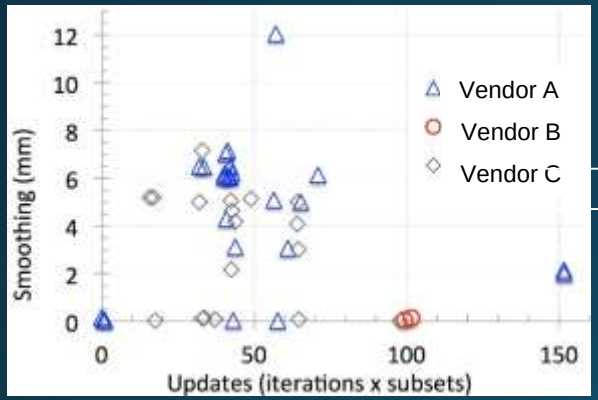
Number of patients:	
10%	12
20%	35
30%	78
40%	133

Number of patients:	
10%	47
20%	141
30%	314
40%	533

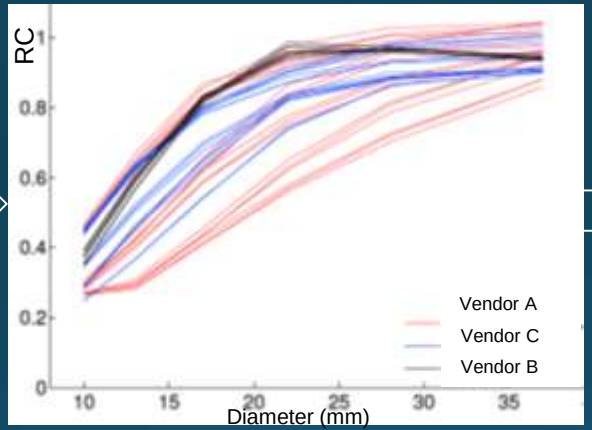
Data Sharing and Integration

- Clinical trials involving QIBs are expensive
  - Individual trials typically have small numbers of patients (Phase I / II)
- Shared data with vetted metadata
  - Meta analysis studies
  - Algorithm development, validation, and comparison
  - Evidence-based medicine / comparative effectiveness studies
  - Radiomics / radiogenomics studies
- Integration of disparate databases
  - Radiomics / radiogenomics studies
  - Precision medicine

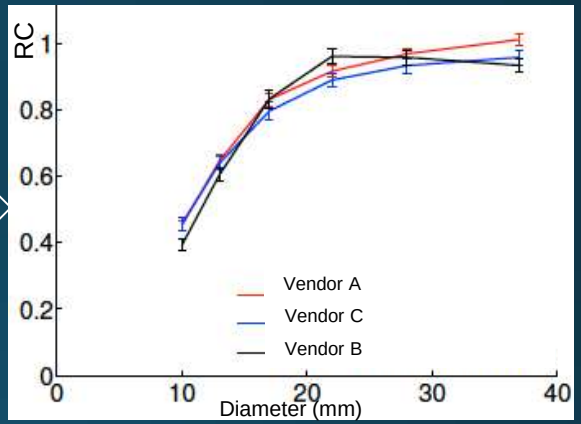
PET Reconstruction Harmonization



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)



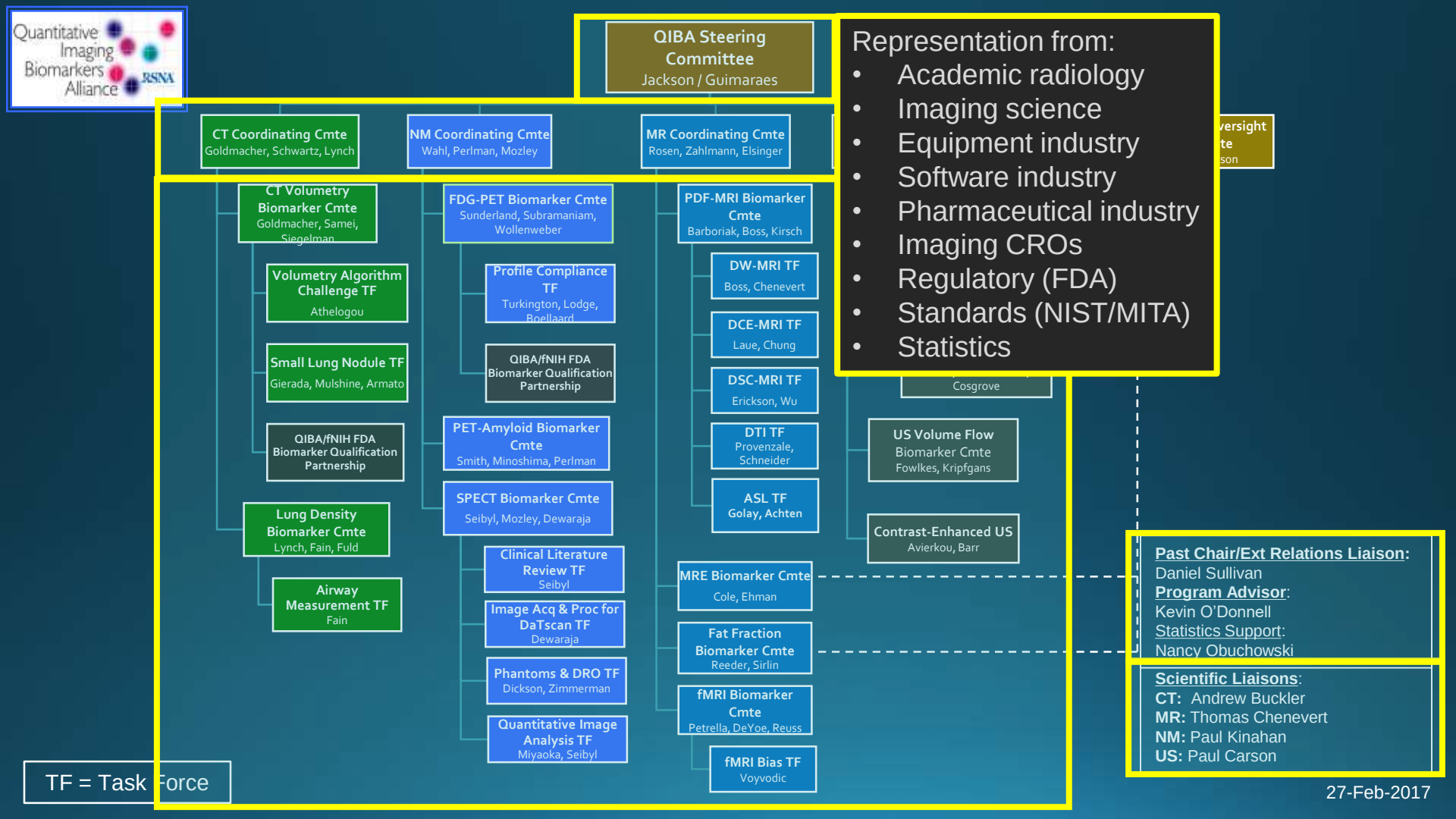
Harmonized results

RC = Ratio of Observed Activity Concentration to Actual Activity Concentration

Source: Paul Kinahan, PhD

RSNA QIBA

- 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"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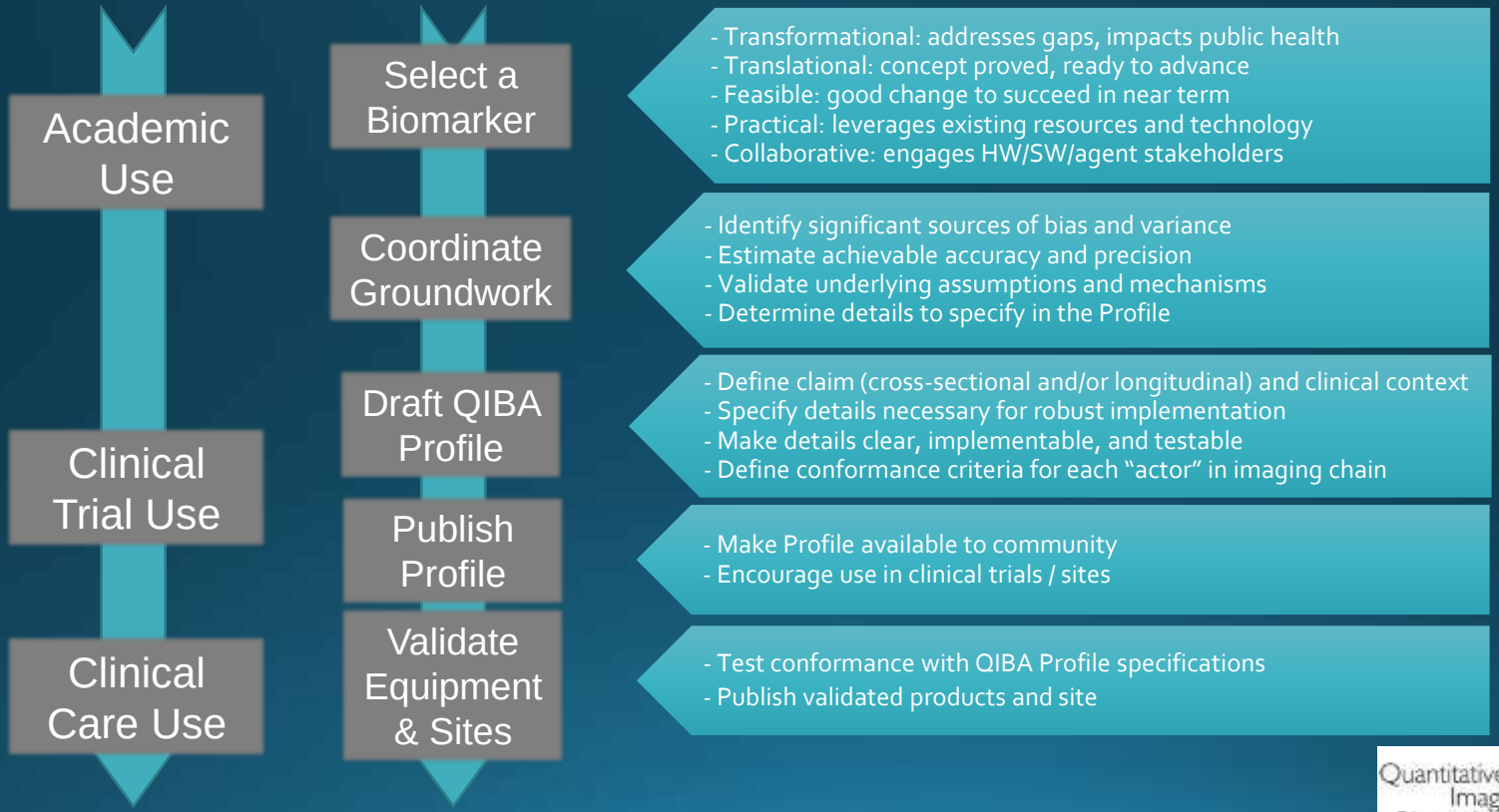
QIBA Steering Committee
Jackson / Guimaraes
Representation from:
• Academic radiology
• Imaging science
• Equipment industry
• Software industry
• Pharmaceutical industry
• Imaging CROs
• Regulatory (FDA)
• Standards (NIST/MITA)
• Statistics
CT Coordinating Cmte
Goldmacher, Schwartz, Lynch
NM Coordinating Cmte
Wahl, Perlman, Mozley
MR Coordinating Cmte
Rosen, Zahlmann, Elsinger
CT Volumetry Biomarker Cmte
Goldmacher, Samei, 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
Seibyl
Image Acq & Proc for DaTscan TF
Dewaraja
Phantoms & DRO TF
Dickson, Zimmerman
Quantitative Image Analysis TF
Miyaoka, Seibyl
PDF-MRI Biomarker Cmte
Barboriak, Boss, Kirsch
DW-MRI TF
Boss, Chenevert
DCE-MRI TF
Laue, Chung
DSC-MRI TF
Erickson, Wu
DTI TF
Provenzale, Schneider
ASL TF
Golay, Achten
MRE Biomarker Cmte
Cole, Ehman
Fat Fraction Biomarker Cmte
Reeder, Sirlin
fMRI Biomarker Cmte
Petrella, DeYoe, Reuss
fMRI Bias TF
Voyvodic
Cosgrove
US Volume Flow Biomarker Cmte
Fowlkes, Kripfgans
Contrast-Enhanced US
Avierkou, Barr
Past Chair/Ext Relations Liaison:
Daniel Sullivan
Program Advisor:
Kevin O'Donnell
Statistics Support:
Nancy Obuchowski
Scientific Liaisons:
CT: Andrew Buckler
MR: Thomas Chenevert
NM: Paul Kinahan
US: Paul Carson
TF = Task Force
27-Feb-2017

RSNA QIBA Approach



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Goal of QIBA

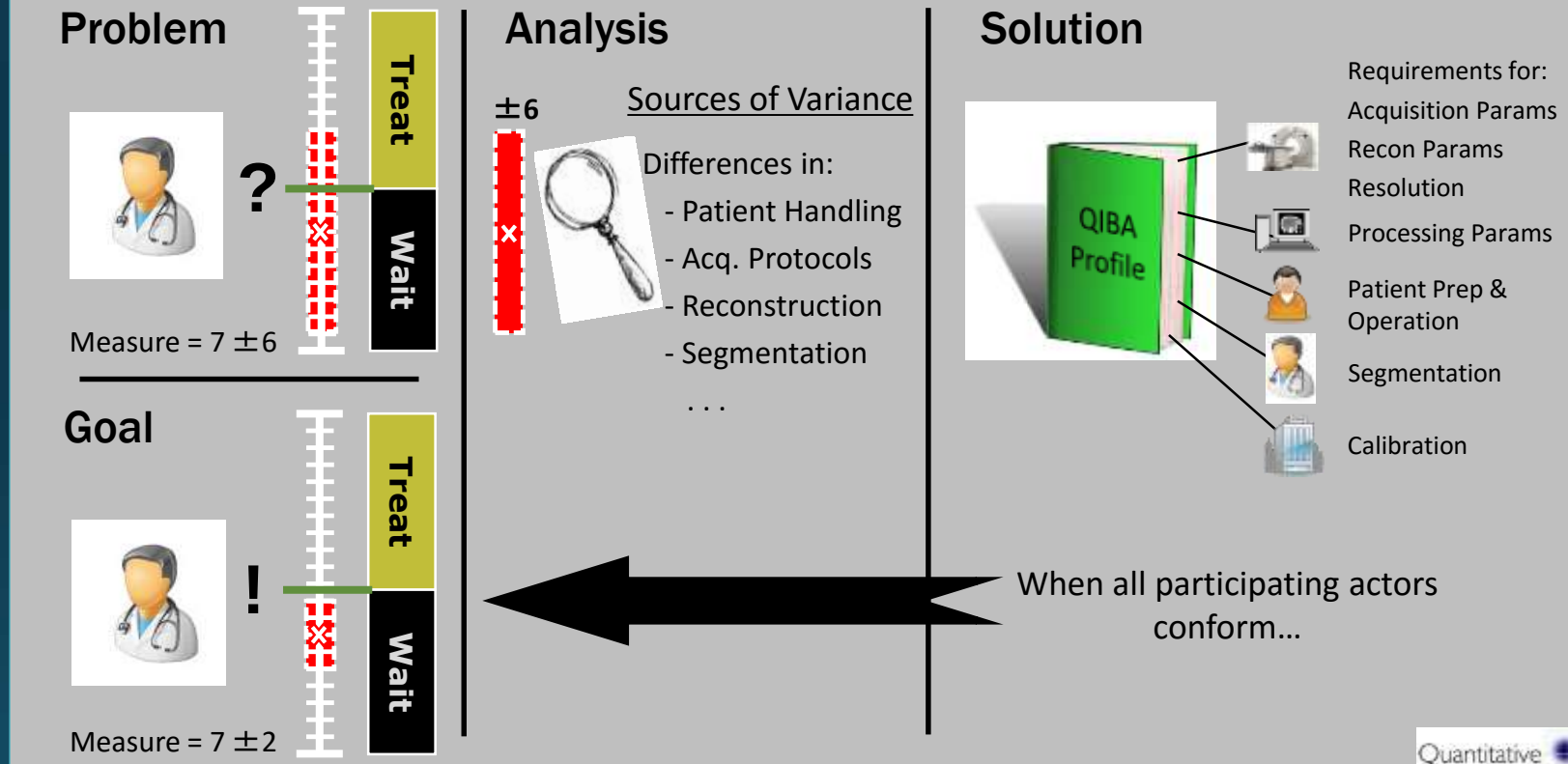

Image compliments of Kevin O'Donnell

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?

Claims:
"95% probability that measured change -25% to +30% encompasses the true tumor volume change…"

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

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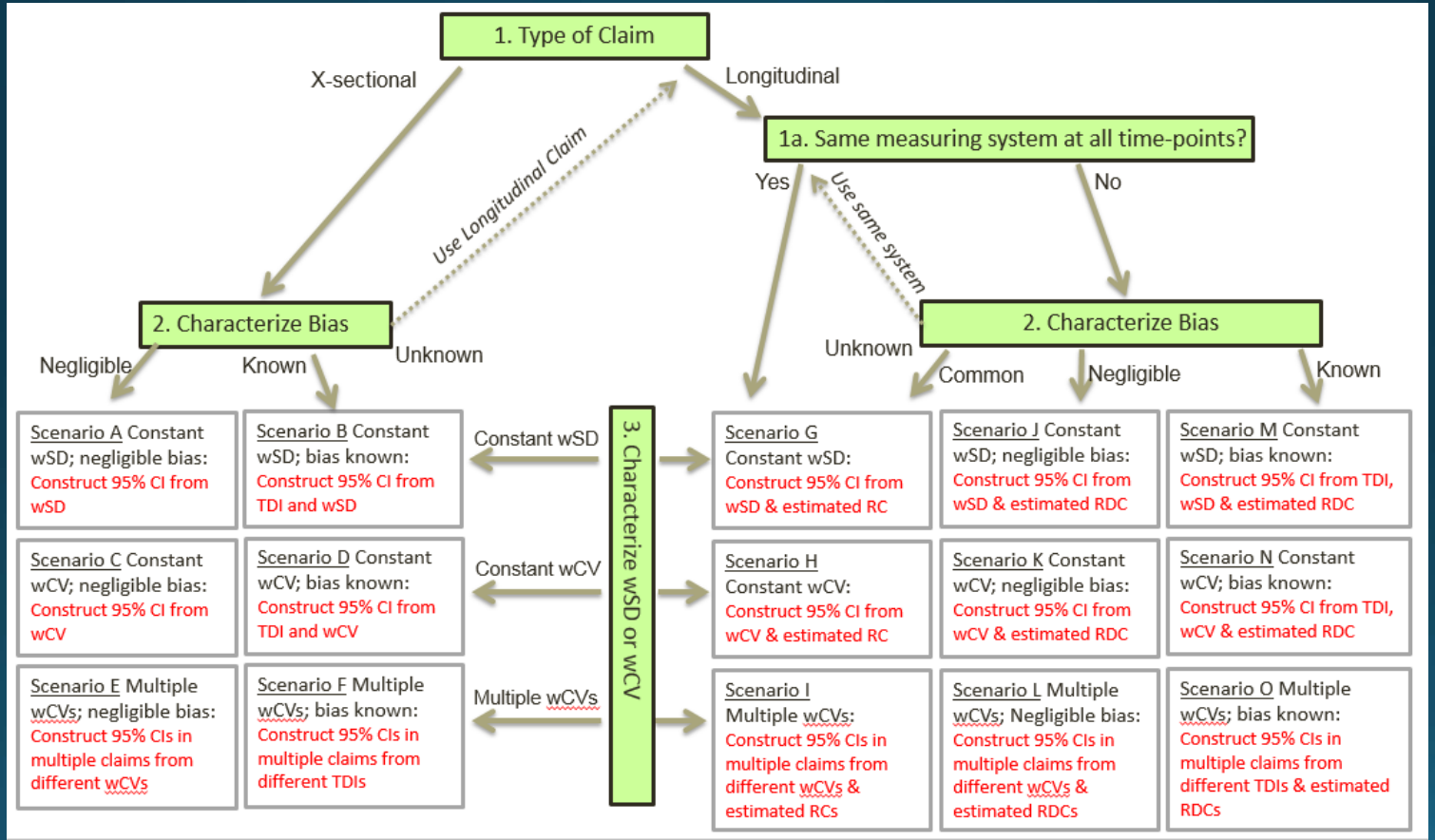
QIBA Claim Template



QIBA Claim Examples

- List Biomarker Measurand(s)
- Specify: cross-sectional and/or longitudinal claim(s)
  - 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 $X \pm$ <*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 $Z \pm$ <*1.96 * √2 * wSD*>.
- Specify clinical context

qibawiki.rsna.org

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Profile Stages

Stage Name	Stage Meaning	Stage Criteria
Stage 1 Draft for Public Comment	Key factors affecting the claim(s) are described and procedures address each/most of the factors.	• Open issues clearly listed • Some groundwork may be ongoing • Actor requirements clear & justified
Stage 2 Consensus	Consensus has been reached and Profile is ready for feasibility testing.	• Text reasonably stable • Public comments addressed • Open issues mostly resolved
Stage 3 Technically Confirmed	The Profile is practical to understand and implement, and is ready for claim testing.	• Text stable • Open issues resolved • Procedures implemented at test sites & multiple vendor platforms (≥2 each)
Stage 4 Claim Confirmed	Claimed performance can be achieved. The Profile is ready for clinical testing.	• Performance measured at test site • Profile Claims achieved at limited number of sites / vendors (≥2 each)
Stage 5 Clinically Confirmed	Claimed performance will typically be achieved.	• Profile Claims achieved in clinical use at multiple sites

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

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Current Profile Status (As of 2/27/2017)

- 19 Profiles (4 CT, 3 NM, 9 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 Q1/2017)
  - *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*

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Current Profile Status (As of 2/27/2017)

- In Final Stage of Development for Public Comment Stage:
  - 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
- 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
  - Ultrasound volume flow for perfusion studies – collaboration with AIUM
  - Contrast-enhanced ultrasound (CEUS) for perfusion studies

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QIBA Metrology Working Group

Working Group Publications

Sullivan DC, Obuchowski NA, Kessler LG, et al. **Metrology Standards for Quantitative Imaging Biomarkers**. *Radiology*. 2015 Aug 12. Epub ahead of print. doi: 10.1148/radiol.2015142202.

Kessler, LG, et. al., **The Emerging Science of Quantitative Imaging Biomarkers Terminology and Definitions for Scientific Studies and Regulatory Submissions,** *Stat Methods Med Res 0962280214537333, first published on June 11, 2014 as doi:10.1177/0962280214537333*

Raunig, DL, et. al., **Quantitative Imaging Biomarkers: A Review of Statistical Methods for Technical Performance Assessment,** *Stat Methods Med Res 0962280214537344, first published on June 11, 2014 as doi:10.1177/0962280214537344*

Obuchowski, NA, et. al., **Quantitative Imaging Biomarkers: A Review of Statistical Methods for Computer Algorithm Comparisons,** *Stat Methods Med Res 0962280214537390, first published on June 11, 2014 as doi:10.1177/0962280214537390*

Obuchowski, NA, et. al., **Statistical Issues in the Comparison of Quantitative Imaging Biomarker Algorithms Using Pulmonary Nodule Volume as an Example,** *Stat Methods Med Res 0962280214537392, first published on June 11, 2014 as doi:10.1177/0962280214537392*

Huang, EP, et. al., **Meta-analysis of the Technical Performance of an Imaging Procedure: Guidelines and Statistical Methodology,** *Stat Methods Med Res 0962280214537394, first published on May 28, 2014 as doi:10.1177/0962280214537394*

Available at www.rsna.org/qiba

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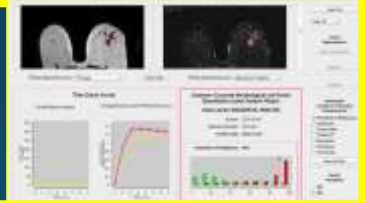
QIBA Groundwork Projects

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

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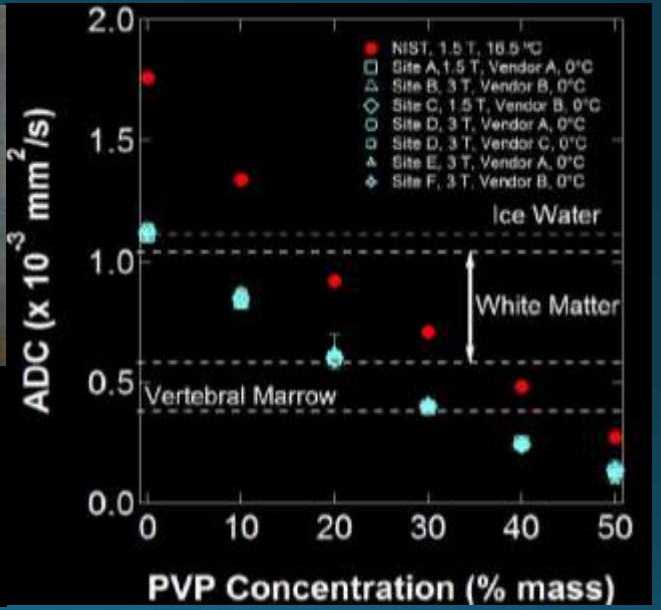
RSNA QIBA Groundwork Projects

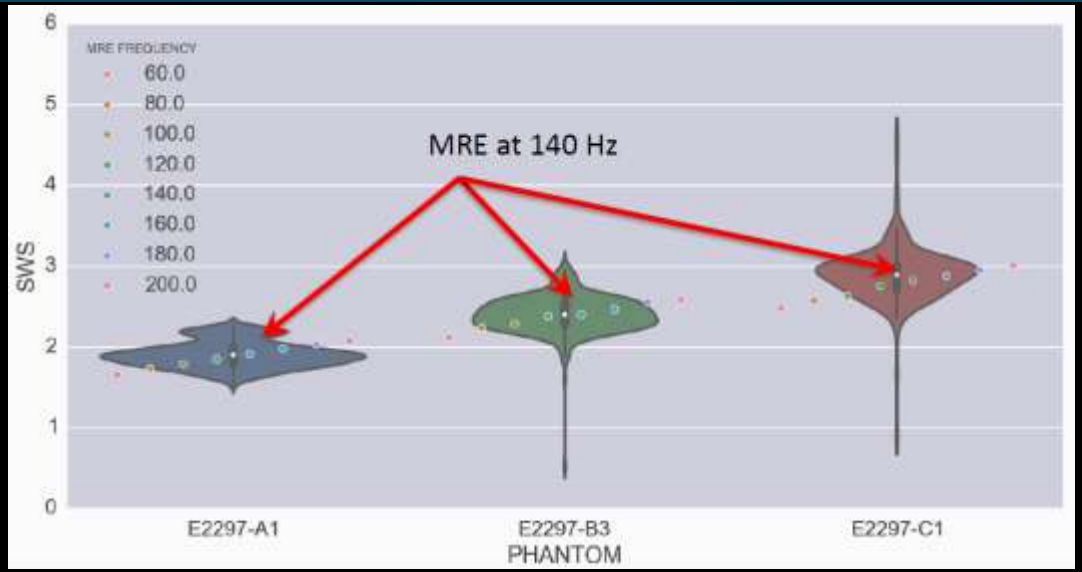
ADC Phantom analysis software publicly available.

DWI MR DRO publicly available.



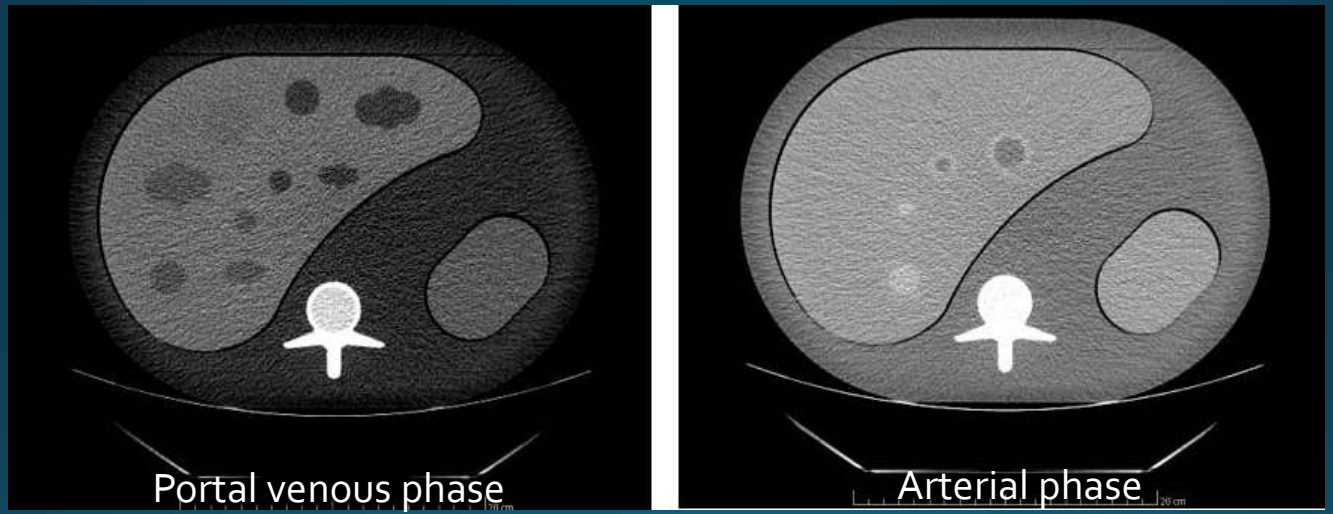
DWI ADC Phantom	Michael Boss, PhD – NIST-Boulder

RSNA QIBA Groundwork Projects



Development and Validation of Simulations and Phantoms Mimicking the Viscoelastic Properties of Human Liver	Mark Palmeri, MD, PhD Duke University (Chen, Mayo; Jiang, Mich Tech Univ; McAleavey, Univ of Rochester)

RSNA QIBA Groundwork Projects



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

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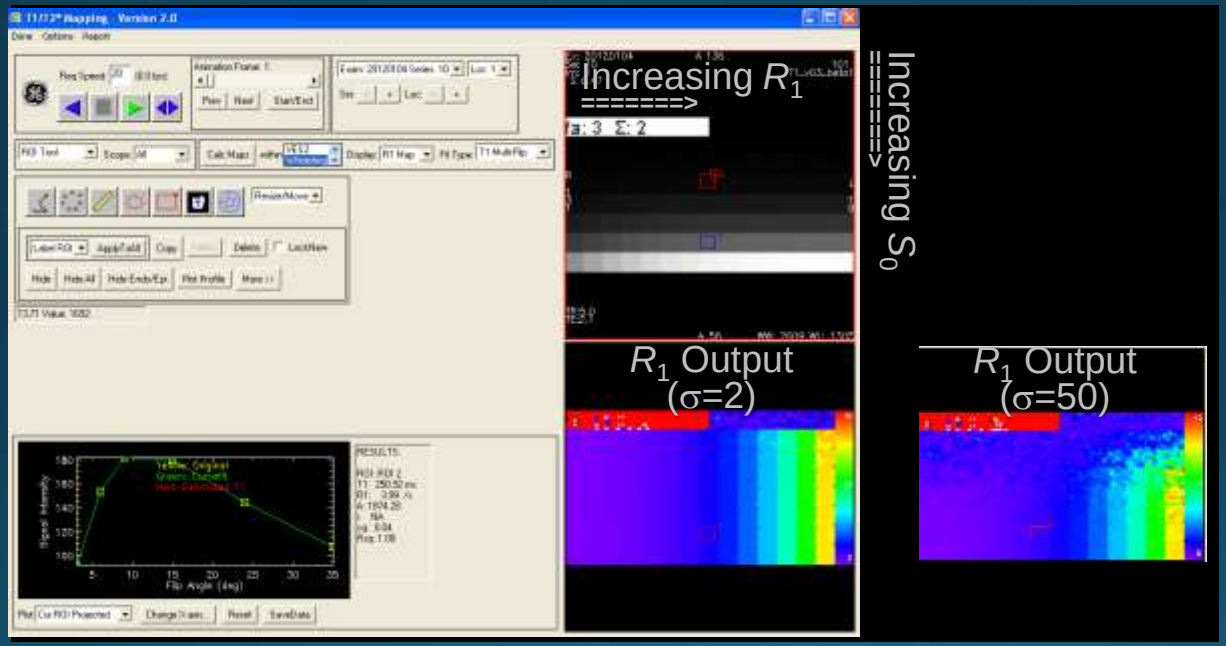

Digital Reference Object for DCE-MRI Analysis Software Verification	Daniel Barboriak, MD (Duke)

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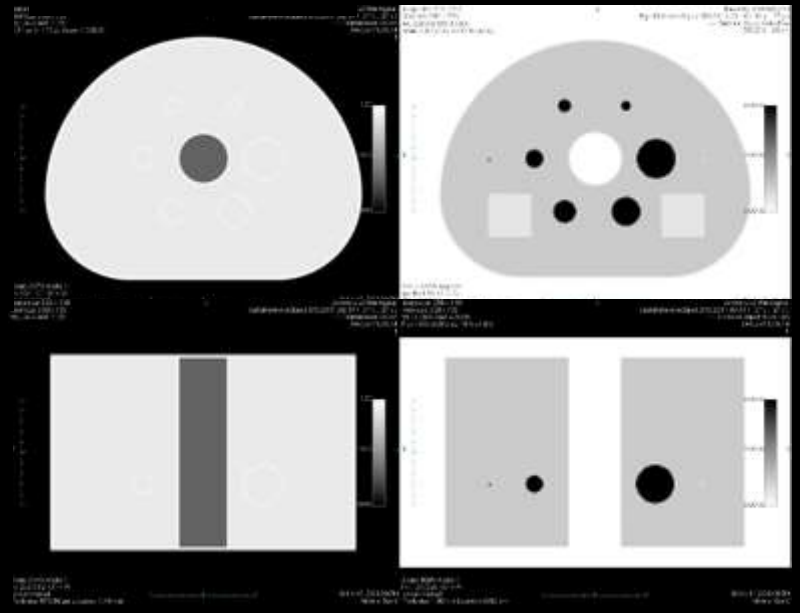
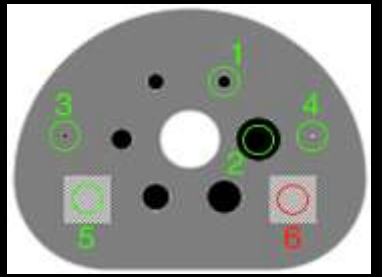
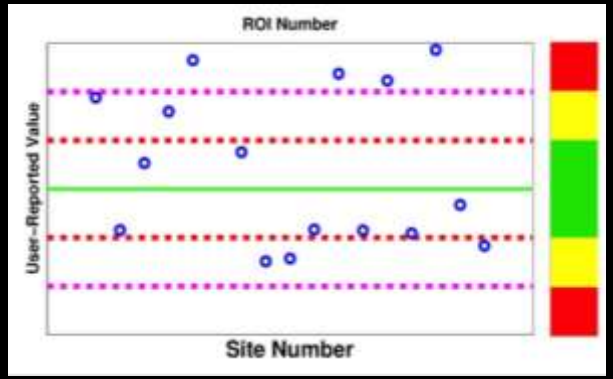






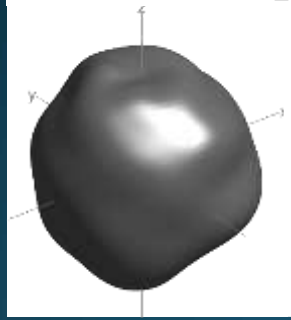
QIBA FDG-PET/CT Digital Reference Object Project	Paul Kinahan, PhD (U Washington)

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

RSNA QIBA Groundwork Projects

Projection space lesion addition

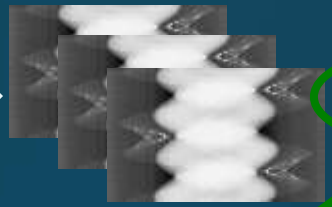
$$c(r,q,f) = B + C\left[1 - \left(\frac{r}{R_{q,f}}\right)^2\right]^n$$



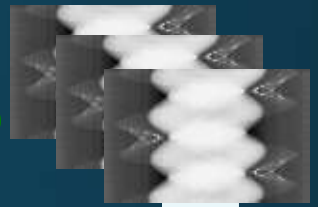
c: attenuation

B: background
C: contrast
R: shape
n: edge blur

scan



+lesion



Recon

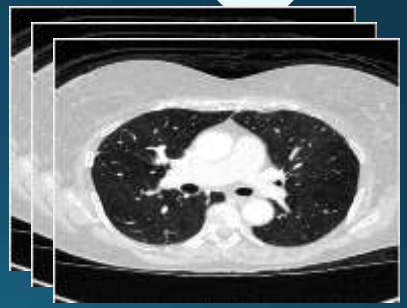
Inputs: Projection data, starting & desired mAs

Determine signal levels, based on scanner properties and patient attenuation

Determine location for lesion insertion

Add lesion to raw data

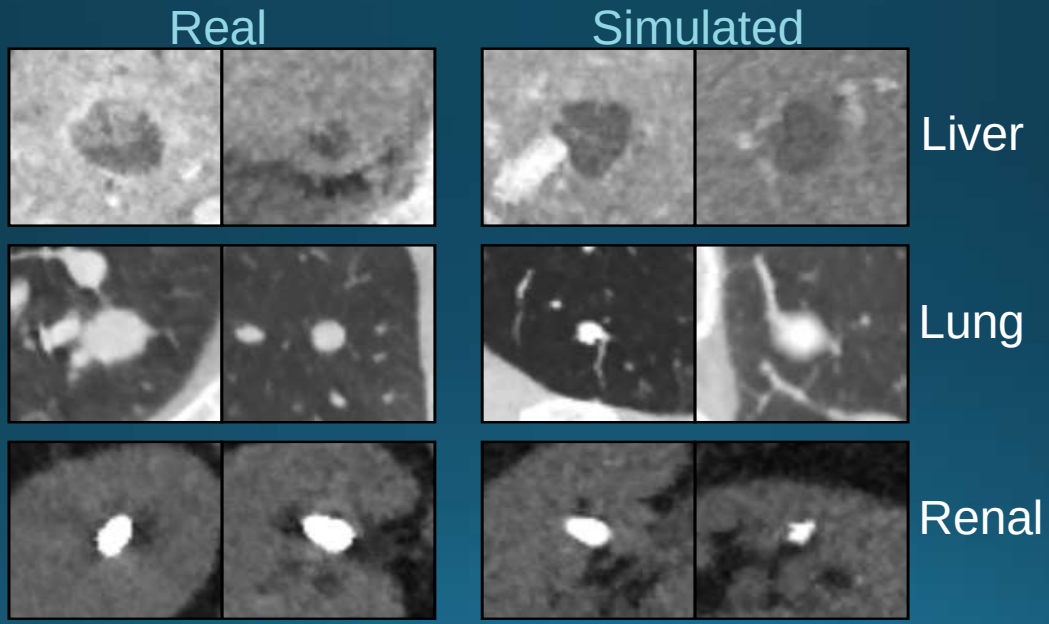
Output: Projection data, ready for prep /recon



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

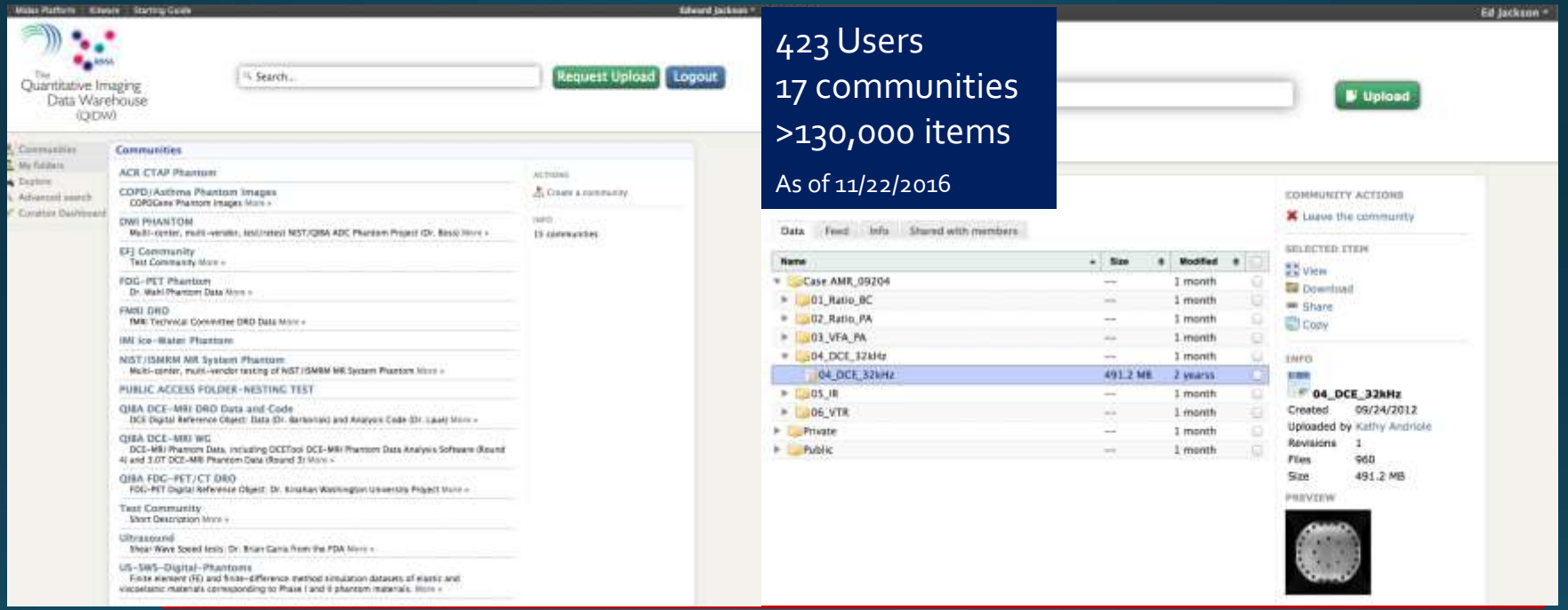
QIBA Phantoms & Datasets

- 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 Q2/2017)
  - Shear Wave Speed Phantoms (varying viscoelastic properties) – for both US SWS and MRE
- Digital Reference Objects (Synthetic Phantoms)
  - 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/Ioflupane; in development; Q3/2017)
- Datasets on QIDW

NIH NIBIB

Quantitative Imaging Biomarkers Alliance RSNA

Quantitative Imaging Data Warehouse (QIDW)



423 Users
17 communities
>130,000 items

As of 11/22/2016

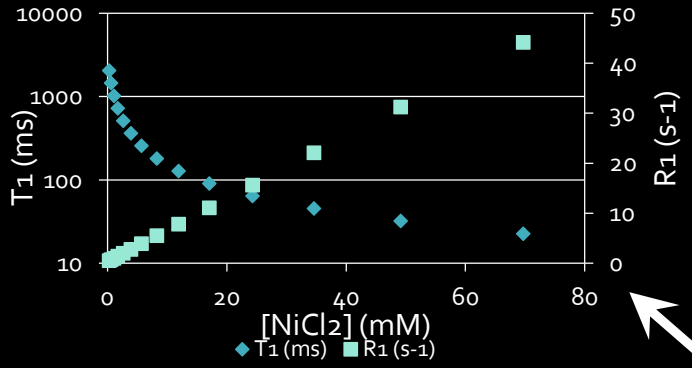
www.rsna.org/qidw/

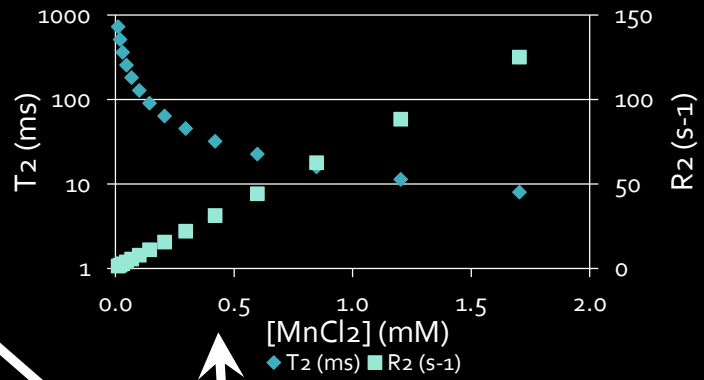
ISMRM MR QIB Efforts

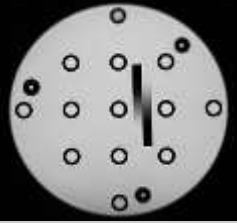
Ad Hoc Committee on Standards for Quantitative MR

- Membership has included MR physicists, technologists, radiologists, NIST representatives, NIH representatives, vendors, pharma. Expertise in research trials using quantitative MR.
- Current status:
  - White paper on quantitative MR (submitted to *J Res NIST*)
  - Defined the specifications for and development of a MR System Phantom (collaboration with and funding by NIST)
  - Multicenter/multivendor phantom pilot studies

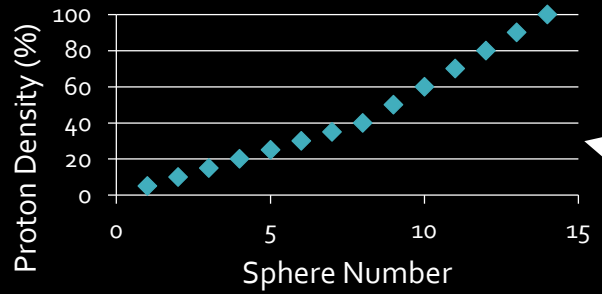
NIST/ISMRM MR System Phantom

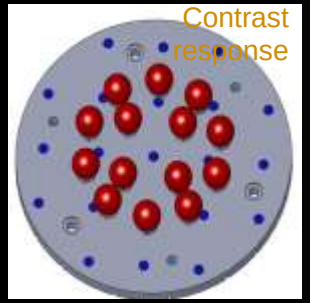




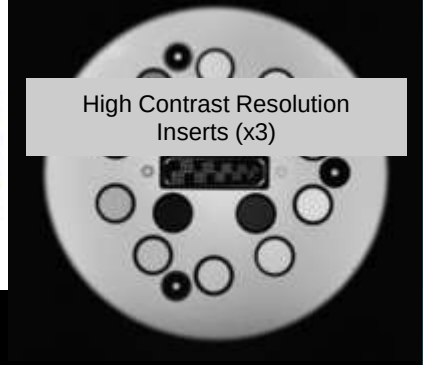


Section thickness, 10^0 ramps

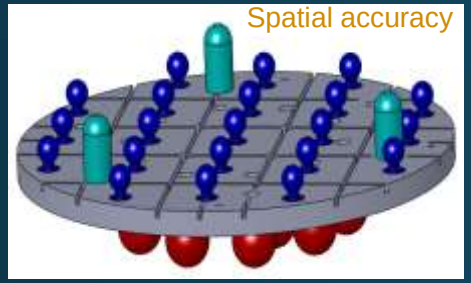


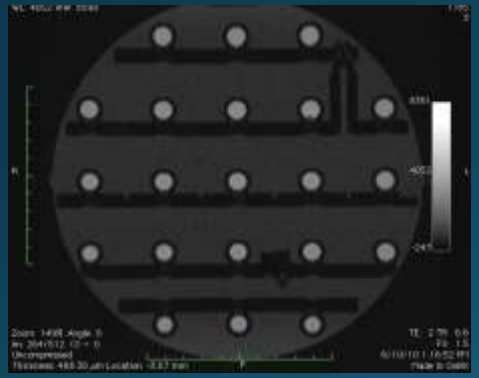


High Contrast Resolution Inserts (x3)



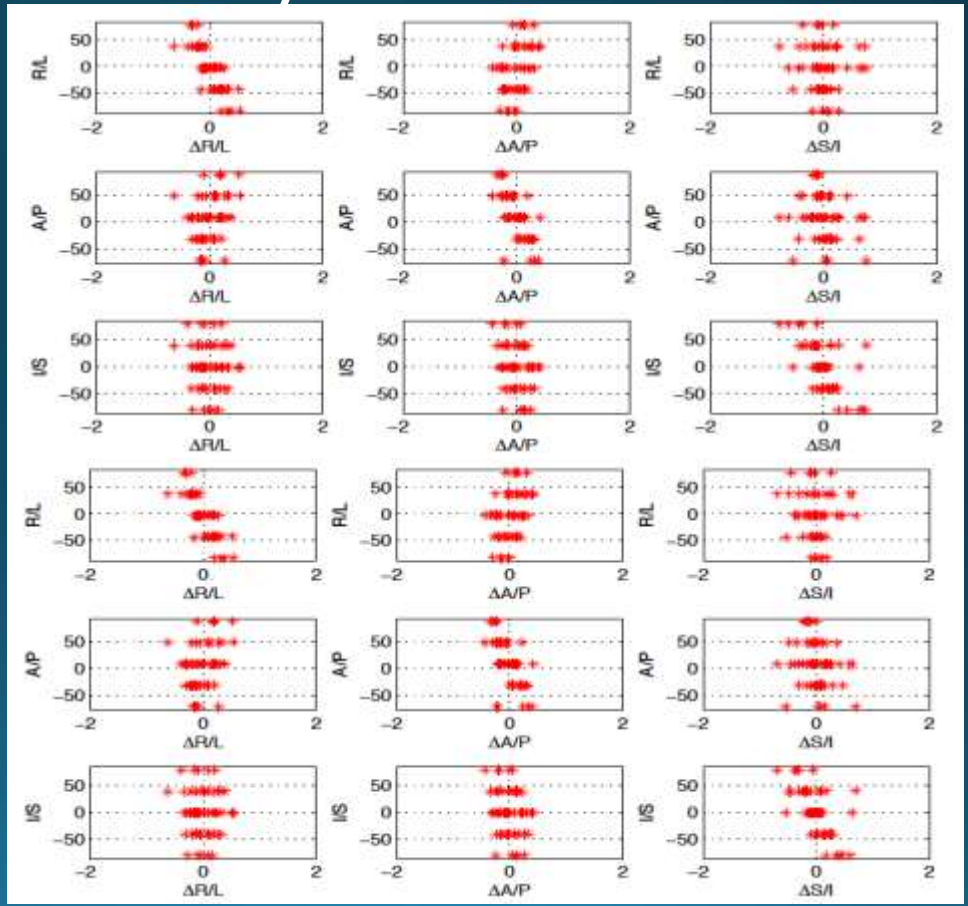
NIST/ISMRM MR System Phantom





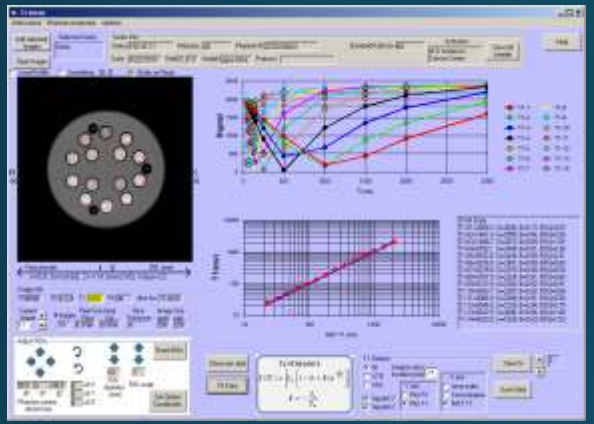
Data Analysis:
Jeff Gunter, Mayo
(Based on ADNI project)

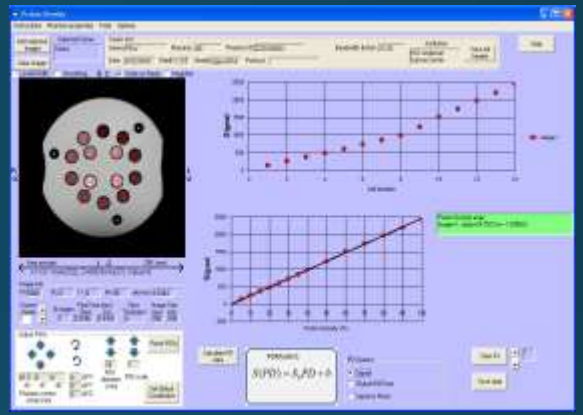
Axial
w/o GW

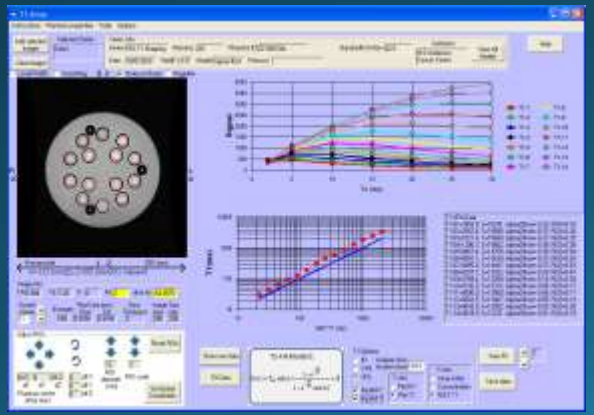


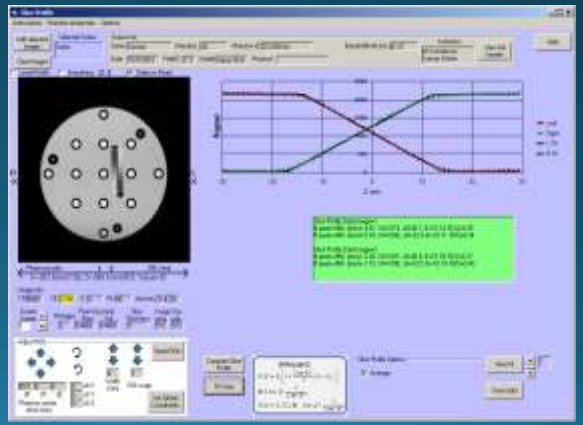
Axial
w/ GW

NIST/ISMRM MR System Phantom

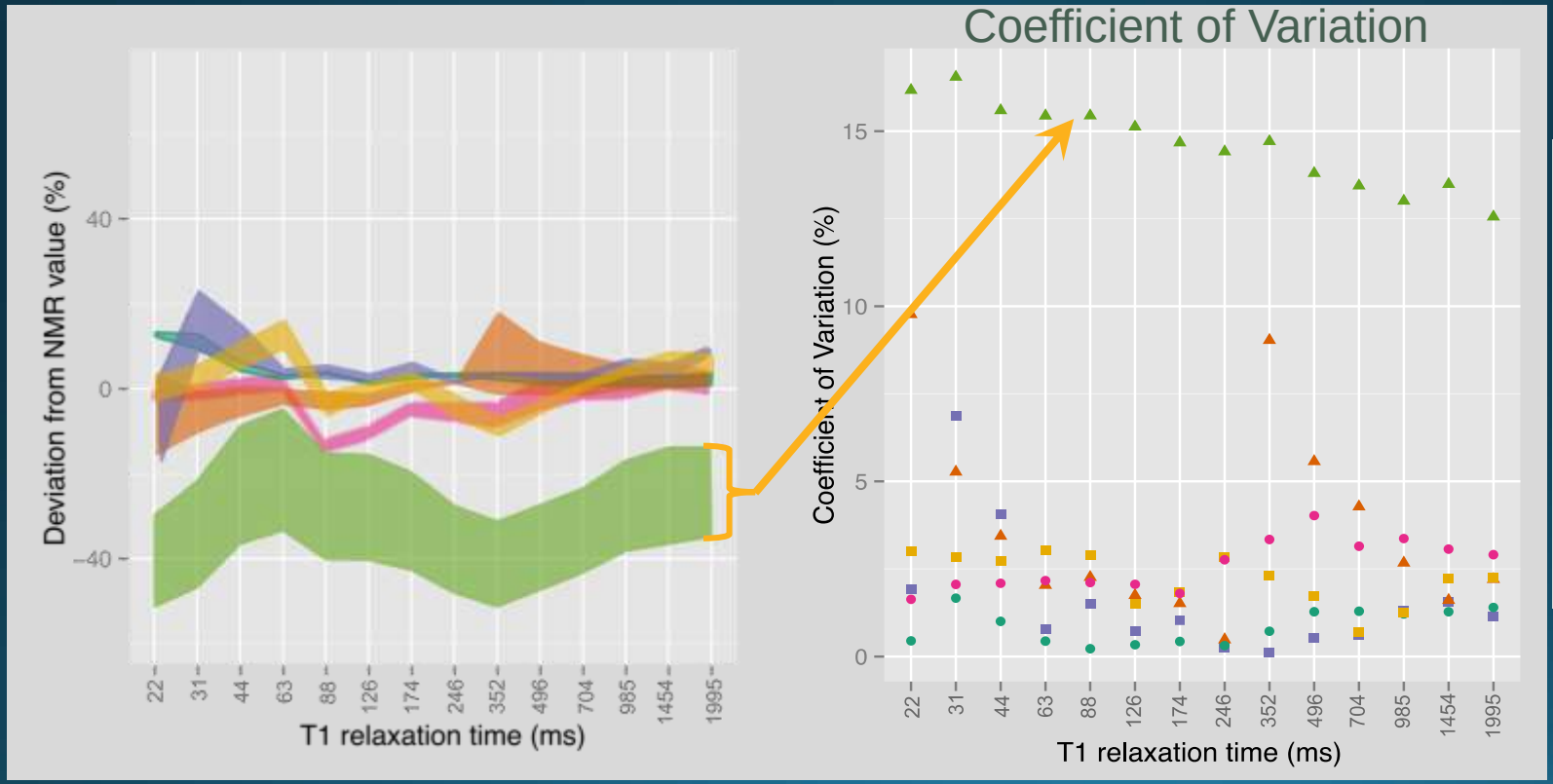








NIST/ISMRM MR System Phantom



Keenan, *et al.* ISMRM ePoster 3290, 2016

Quantitative Imaging Network (QIN)

- NCI-funded (CIP) – U01 mechanism
  - PAR-14-116 Quantitative Imaging for Evaluation of Response to Cancer Therapies
- QIN consists of groups at 28 centers
- Five working groups:
  - Data Collection Working Group
  - Image Analysis and Performance Metrics
  - Bioinformatics/IT and Data Sharing
  - Clinical Trial Design and Development
  - Outreach: External/Industrial Relations

- Involved in a variety of algorithm comparison "challenges" in addition to individual investigator research projects

http://imaging.cancer.gov/programsandresources/specializedinitiatives/qin
Accessed 2/25/2016

Summary

- Non-invasive QIBs should be a critical enabler for the practice of precision medicine.
- QIBs have been implemented effectively at "centers of excellence".
- 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.
- QIBA Profiles and associated deliverables, and efforts of other QI groups, are critical for translation of QIBs to clinical practice.

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
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- Binshang Zhao, PhD and Nick Petrick, PhD - CT Liver Phantom
- Michael Boss, PhD, Katy Keenan, PhD and Stephen Russek, PhD (NIST-Boulder) - DWI & MR System Phantoms
- Paul Kinahan, PhD - FDG-PET DRO
- Mark Palmeri, PhD, Tim Hall, PhD, Brian Garra, PhD - US SWS / MRE Phantom
- RSNA and QIBA Biomarker Committee & Task Force Co-Chairs & Members
- NIBIB Contracts HHSN268201000050C, HHSN268201300071C, HHSN268201500021C

NIH National Institute of Biomedical Imaging and Bioengineering