




Joint Imaging-Therapy Scientific Symposium – August 3, 2017
Advancements in MRI and MR-Guided Interventions
TH-EF-FS4-0

The Translation from Qualitative Assessments to Quantitative Measurements: Why and How

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



Declaration of Financial Interests or Relationships


Speaker Name: Edward F. Jackson, PhD

I have no financial interests or relationships to disclose with regard to the subject matter of this presentation.



Objectives

1. Understand the various approaches in development of 4D-MRI and their pros and cons.
2. Understand the principles and clinical applications of ultra-resolution diffusion MRI.
3. Understand the important and current developments in quantitative MR 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

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



From Qualitative Findings to QIB Assay

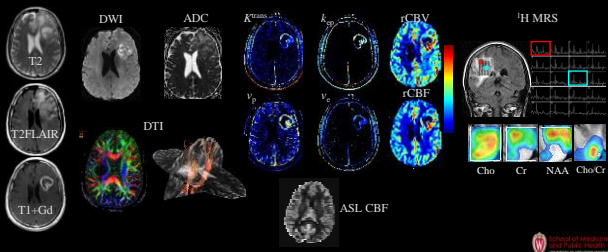
- **Validation:** “assessing the assay and its measurement performance characteristics, and determining the range of conditions under which the assay will give reproducible and accurate data”
- **Qualification:** “‘fit-for-purpose’ evidentiary process linking a biomarker with biology and clinical endpoints”
- **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

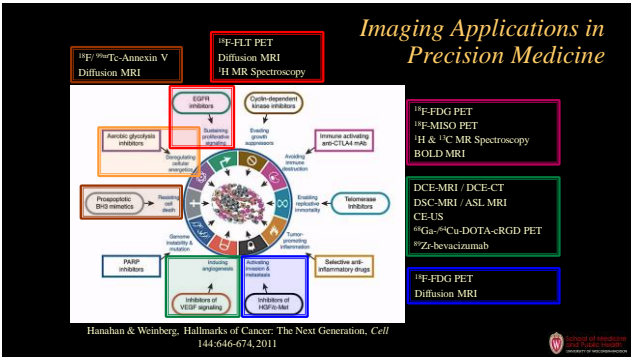
Existing MR QIBs in Glioma: Morphological to Functional



MR QIBs in Glioma

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, ↓AR2 ²
Angiogenesis / Permeability	DCE-MRI, DSC-MRI	↑K ^{trans} & v _e , ↑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



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.

Precision Medicine Requires a Transformation of Medical Imaging

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

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

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.”



2017 Fleischner Society Guidelines for Management of CT Pulmonary Nodules

Nodule Type	Size			Comments
	<6 mm (<100 mm ³)	6-8 mm (100-250 mm ³)	>8 mm (>250 mm ³)	
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 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



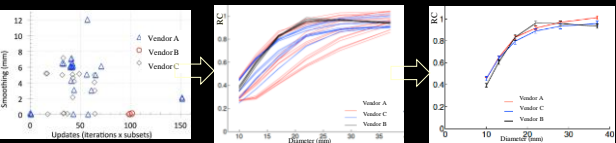
QIB Challenges

Other QIB challenges:

- Cost of QIB studies (comparative effectiveness) / reimbursement
- Radiologist acceptance
 - Limited number of use cases for QIBs vs. conventional practice
 - QIBs are not part of radiologist education & training
 - 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"



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



General Challenges in MR Quantification

Arbitrary (and spatially- / temporally-dependent) signal intensity units

- Magnitude and homogeneity of B_0
- Magnetic field gradient nonlinearities, eddy currents, concomitant fields, *etc.*
- RF coil dependency: RF coil type, B_1 sensitivity profiles, subject positioning within the coil
- Slice profile variations (with RF pulse shape, flip angle, *etc.*)
- Off resonance effects
- Parallel imaging, compressed sensing, and other acceleration techniques
- System stability issues (B_0 , RF & gradient subsystems, RF coils, *etc.*)



Adopting Metrology Principles in Imaging

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

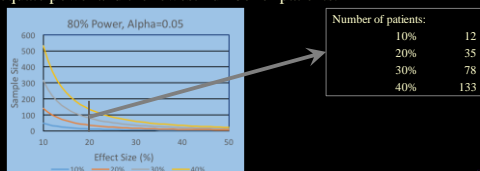
- Bias* (accuracy):
 - Often difficult to assess due to absence of reference standard (“ground truth”) measures
 - Potential role for application-specific phantoms
- Precision* (variance):
 - Repeatability* – All conditions the same except short time separation (“test/retest”)
 - Repeatability coefficient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

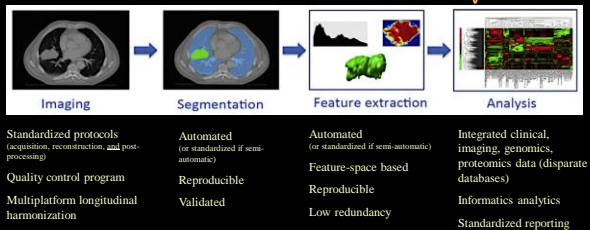


Need for Data Sharing

- 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



Radiomics / Imaging Genomics



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



Selected QIB Initiatives

NCI: Quantitative Imaging Network (QIN)



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



ISMRM: *Ad Hoc* Committee on Standards for Quantitative MR



NIST: Quantitative Imaging Physical Phantoms / Metrology

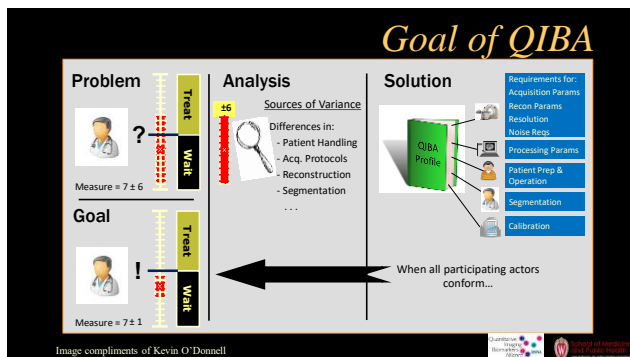
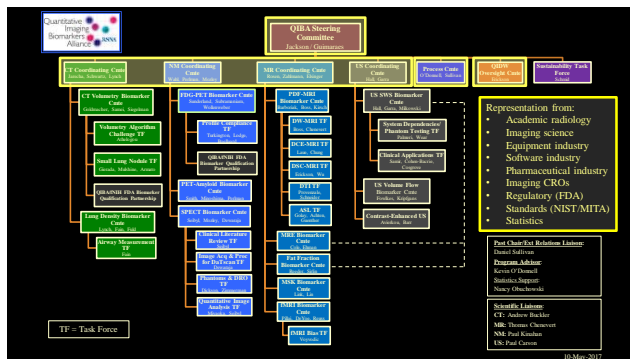


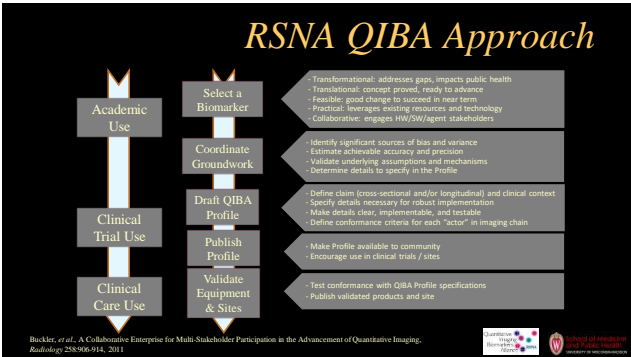
FDA: Quantitative Imaging Physical Phantoms & Regs

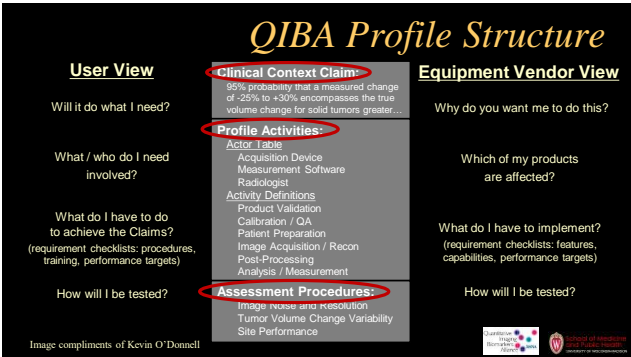


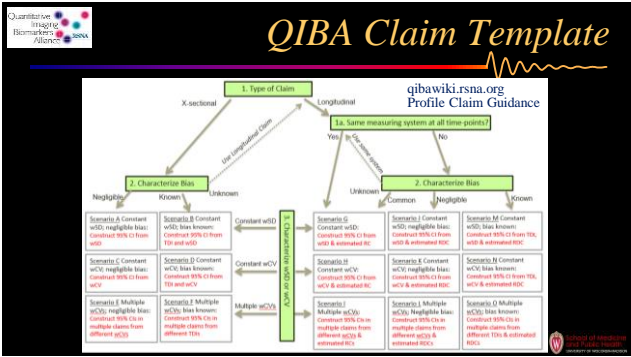
Quantitative Imaging Biomarkers Alliance

- 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”









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

FDG-PET/CT SUV Profile

Table of Contents	
Executive Summary	3
Summary for Clinical Trial Use	4
1 Clinical Context and Claims	5
1.1 Application and Indications for Clinical Trial	5
1.2 Claims: Measure Change in SUV	6
2 Data Elements	8
2.1 Subject Pooling	8
2.2 Image Data Acquisition	15
2.3 Imaging Data Reconstruction and Post-Processing	17
2.4 Image Analysis (SUV) Section 16	24
2.5 Image Interpretation and Reporting (SUV) Section 16	24
2.6 Quality Control	25
3 Data Elements	35
3.1 Image Acquisition Site	35
3.2 PET/CT Acquisition Device	36
3.3 Reconstruction Software	40
3.4 Image Analysis Workstation	44
3.5 Software Version Tracking	46
4 Metadata	47
Appendix A: Acknowledgments and Attributions	51
Appendix B: Background Information for Claims	54
Appendix C: Data Elements and Definitions	57
Appendix D: Clinical Trial Design and Population	62
Appendix E: Data Fields to be Reported in the Common Data Format Mechanism	65
Appendix F: Testing PET/CT Studies and Analysis Systems with the SUV PET/CT PRO	67
Appendix G: Vendor-neutral Parallel Codes for SUV Calculation	71
Appendix H: Common Data Format for Clinical Trial Data: Data Model Representation for SUV	74
Appendix I: Data CDE: PET/CT Imaging Site Data Model Representation	76

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 (SUV_{max}) is measurable from FDG-PET/CT with a within-subject coefficient of variation of 10-12%.

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

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

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 (PDF) 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- and T1- MSK MR for degenerative joint disease
 - Ultrasound volume flow for perfusion studies – collaboration with AIUM
 - Contrast-enhanced ultrasound (CEUS) for perfusion studies

QIBA Groundwork Projects

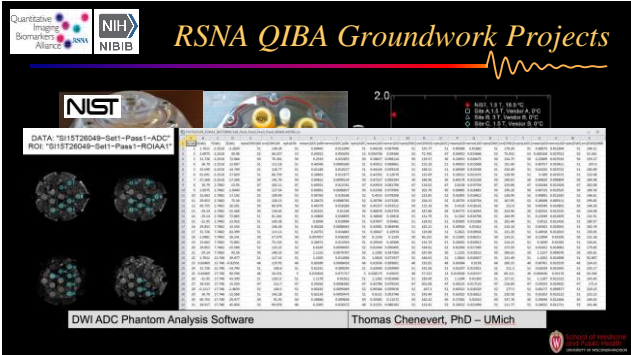
QIB Implementation and Qualification

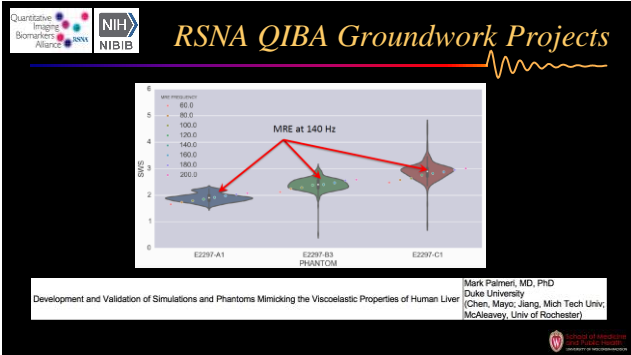
- Data acquisition => Physical phantoms & datasets
 - Application specific phantoms
 - Clinical trial datasets
- Data analysis => Synthetic phantoms & datasets
 - Application specific "digital reference objects" or DROs
 - Clinical trial datasets
- Qualification => "Fit for purpose" <=> clinical trials

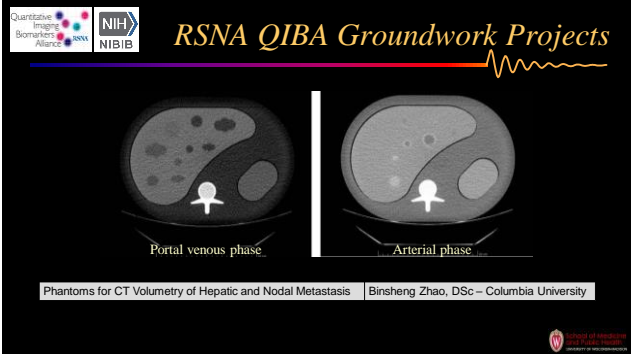
QIBA groundwork projects funded by 3 contracts from National Institute of Biomedical Imaging and Bioengineering

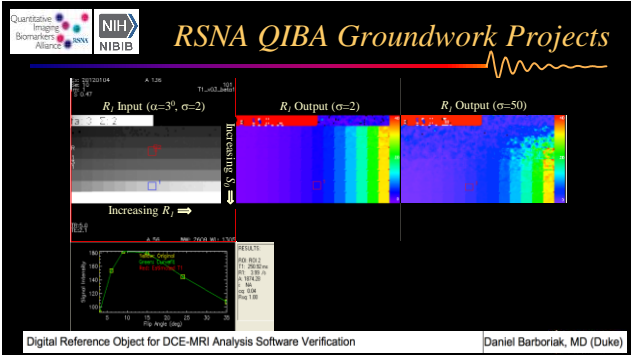
RSNA QIBA Groundwork Projects

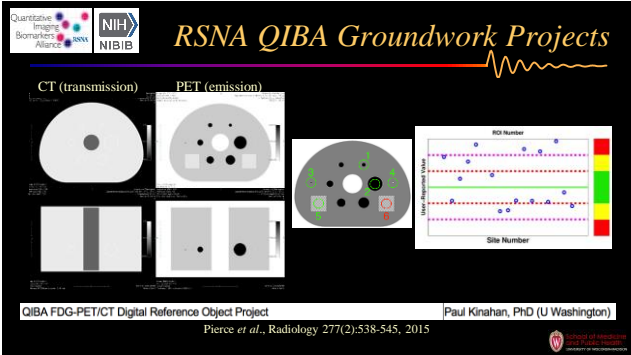
DCE-MRI Phantom Fabrication, Data Acquisition and Analysis, and Data Distribution | Edward Jackson, PhD (UW-Madison)

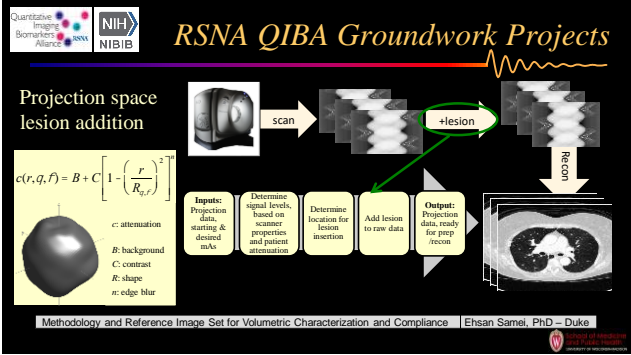












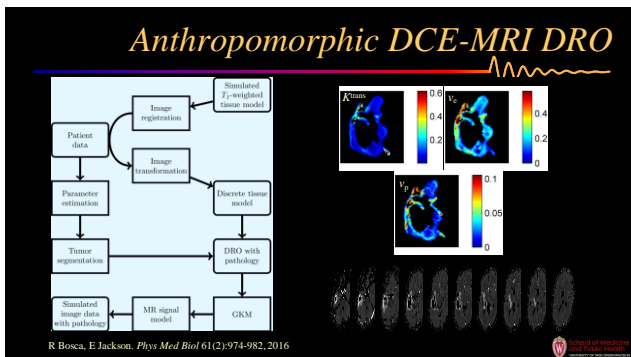
Quantitative Imaging Biomarkers Alliance | NIH | NIBIB

RSNA QIBA Groundwork Projects

Which lesions are real?

Real	Simulated	
		Liver
		Lung
		Renal

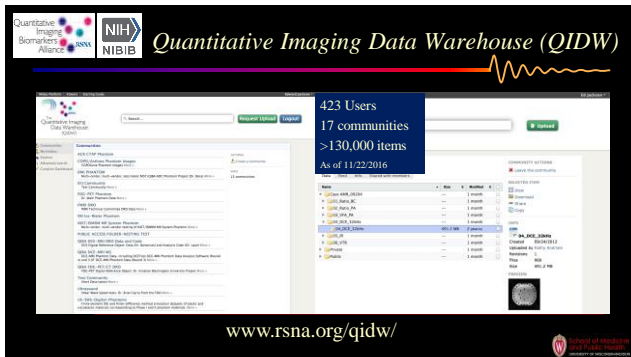
Methodology and Reference Image Set for Volumetric Characterization and Compliance | Ehsan Samei, PhD – Duke

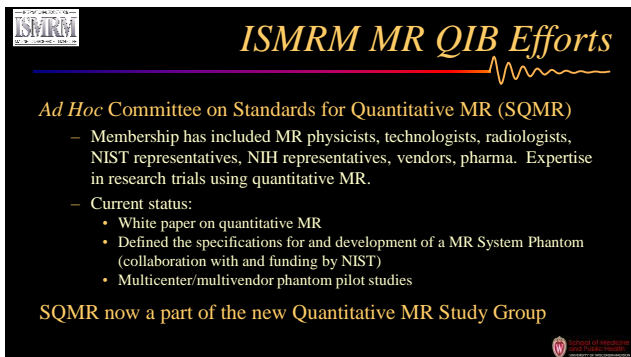


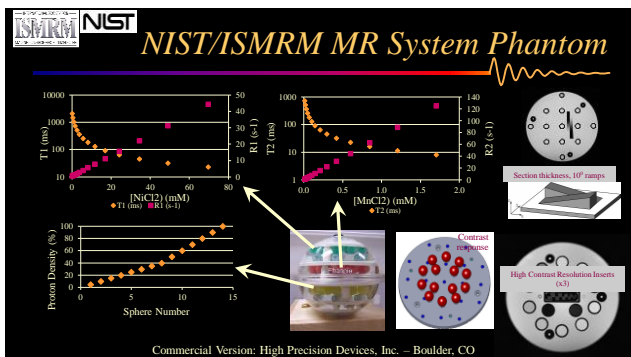
Quantitative Imaging Biomarkers Alliance | NIH | NIBIB

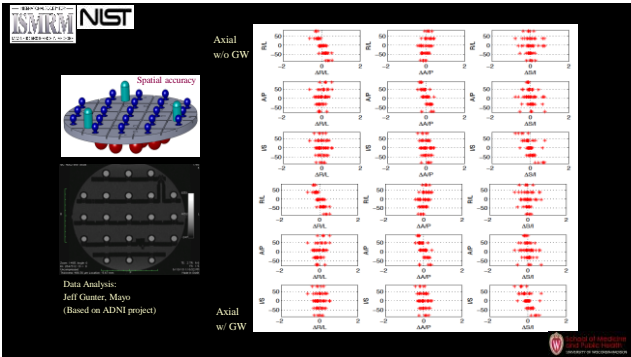
QIBA Phantoms & Datasets

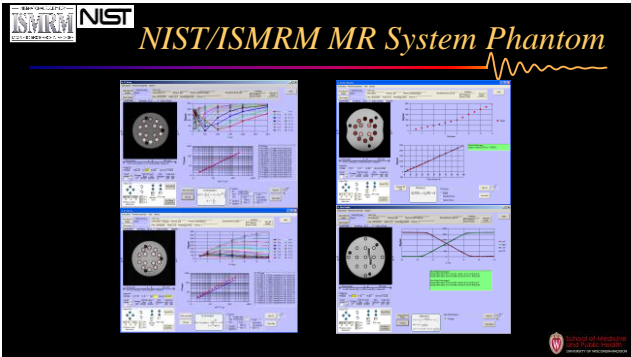
- Physical Phantoms**
 - Volumetric CT Liver Phantom (arterial/portal venous phase)
 - DCE-MRI Phantom and analysis software
 - DWI ADC Phantom and analysis software
 - DSC-MRI Phantom (in development; target release Q2/2017)
 - Shear Wave Speed Phantoms (varying viscoelastic properties) – for both US SWS and MRE
- Digital Reference Objects (Synthetic Phantoms) – 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)

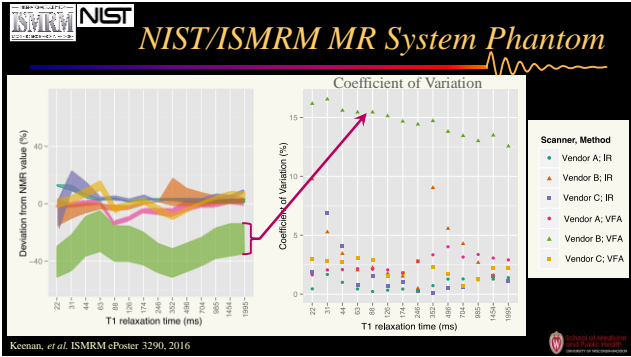













Quantitative Imaging Network (QIN)

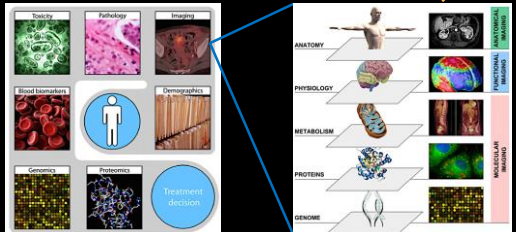
- NCI-funded (CIP)
 - PAR-17-128 & PAR-17-129
Quantitative Imaging Tools & Methods for Evaluation for Cancer Response Assessment
- Goal: Translate quantitative imaging methods and algorithms as clinical decision support tools into clinical utility
- 21 current teams with additional associates
(Per Robert Nordstrom, 7/17/2017)
- Working groups:
 - Image Analysis & Performance Metrics
 - Data Acquisition
 - Bioinformatics/IT and Data Sharing
 - Clinical Trial Design and Development
- Involved in development of a wide range of image analysis tools (N=46*) and a variety of algorithm comparison "challenges"



* As of 7/17/2017, per Robert Nordstrom
<https://imaging.cancer.gov/informatics/qin.htm>
 Accessed 7/17/2017

University of Maryland
 Center for Imaging Research
 Division of Biomedical Research

Precision Medicine Requires a Transformation of Medical Imaging



Non-invasive QIBs should be critical enablers of the practice of precision medicine

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

University of Maryland
 Center for Imaging Research
 Division of Biomedical Research


Summary


- Non-invasive QIBs should be critical enablers of the practice of precision medicine.
- 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.


University of Maryland
 Center for Imaging Research
 Division of Biomedical Research

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
- Daniel Barboriak, MD & Ryan Bosca, PhD - Digital Reference Objects (DCE)
- Stephen Russek, PhD, Kathryn Keenan, PhD, Michael Boss, PhD, Karl Stupic, PhD - NIST: MR System Phantom & ADC Phantom
- Ehsan Samei, PhD, Berkman Sahiner, PhD, Nick Petrick, PhD, Binshang Zhao, PhD - RSNA QIBA (CT DRO & Liver Phantom)
- Paul Kinahan, PhD - FDG-PET DRO
- Tim Hall, PhD, Brian Garra, MD, Mark Palmeri, PhD, Richard Ehman, MD - RSNA QIBA (Ultrasound and MRE Data)
- RSNA and QIBA Biomarker Committee & Task Force Co-Chairs & Members
- NIBIB Contracts HHSN268201000050C, HHSN268201300071C, HHSN268201500021C

National Institute of Biomedical Imaging and Bioengineering

Quantitative Imaging Biomarkers Alliance

University of Wisconsin-Madison

www.rsna.org/qibaqibawiki.rsna.org
