AAPM – July 13, 2015

Translating NIH / NIBIB Funding to Clinical Reality in Quantitative Diagnostic Imaging

Edward F. Jackson, PhD
Chair, RSNA QIBA
Departments of Medical Physics (Chair), Radiology, and Human Oncology
University of Wisconsin School of Medicine & Public Health – Madison

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.

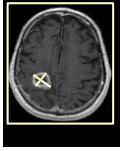
NIH Biomarkers Definitions Working Group, Clin Pharmacol Therap 69(3):89-95, 2001

2

MR QIB Applications

Potential MR QIBs:

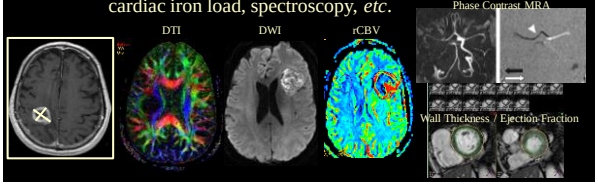
- From lesion dimension (single- or bi-dimensional)
  - RECIST: Response Evaluation Criteria in Solid Tumors
  - RANO: Revised Assessment in Neuro-Oncology



MR QIB Applications

Potential MR QIBs:

- From lesion dimension (single- or bi-dimensional)
  - RECIST: Response Evaluation Criteria in Solid Tumors
  - RANO: Revised Assessment in Neuro-Oncology
- To numerous functional assessments
  - Diffusion, perfusion, blood flow, myocardial wall thickness, ejection fraction, and perfusion, liver and cardiac iron load, spectroscopy, *etc*.



Modality-Independent Issues

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 System:
  - Typical target: best image quality in shortest time
  - No specific requirements for reproducible *quantitative* results (with few exceptions)

5

Modality-Independent Issues

General QIB challenges:

- Lack of detailed assessment of sources of bias and variance
- Lack of standards (data acquisition, data analysis, and reporting)
- Little support from imaging equipment vendors
  - No documented competitive advantage of QIBs (customer demand, regulatory or payer requirement)
- Highly variable quality control procedures
  - QC programs, if in place, typically do not address QIBs

Result:

- Varying measurement results across centers, vendors, and time

6

Modality-Independent Issues

General QIB challenges:

- Cost of QIB studies (comparative effectiveness)
- Reimbursement
- Resource availability
  - Technologists trained in advanced, quantitative, protocols
  - Imaging scientists, data processing capabilities, *etc*.
- Radiologist acceptance
  - QIBs are not part of radiologist education & training.
  - The software and workstations needed to calculate and interpret QIBs are often not integrated into the radiologists' workflow.
  - Clinical demand on radiologists is high --- "time is money".
  - There are few guidelines for QIB reporting.

7

Potential reasons for the slow integration of QI into routine clinical radiology practice

- Primary clinical question considered to be qualitative in nature
- Qualitative answer to the clinical question considered sufficient
- Concern that quantitative measurement may obscure important qualitative information
- Concern that quantitative metrics do not allow sufficient expression of uncertainty
- Concern that quantitative techniques are not adequately validated under real-life conditions
- Practical workflow limitations to quantitative imaging

Abramson, *et al. Magn Reson Imaging* 30(9):1357, 2012

8

Early QI Initiatives

NIST USMS Workshop 2006

Representative Agencies / Organizations

9

Selected QI Initiatives

- NCI: Reference Image Database for Evaluation of Response (RIDER) and Academic Center Contracts
  Imaging Response Assessment Teams (IRATs)
  Quantitative Imaging Network (QIN)
- ISMRM: *Ad Hoc* Committee on Standards for Quantitative MR
- AAPM: QI Initiatives, including those of the Technology Assessment Committee (TAC)
- Core Labs: ACRIN, IROCs, CROs, *etc*.
- RSNA: Quantitative Imaging Biomarker Alliance (QIBA)

10

RSNA Premise and Perspective

- Premise: Variation in clinical practice results in poorer outcomes and higher costs.
- Perspective: Extracting objective, quantitative results from imaging studies will improve the value of imaging in clinical practice.

11

Why Must Imaging Become More Quantitative?

- *Precision medicine* requires quantitative test results
- *Evidence-based medicine & QA programs* depend on objective data
- *Decision-support tools* need quantitative input
- *Early assessment of treatment efficacy* benefits from (or requires) quantitative measures
- *Multi-parametric / multi-modality* applications require quantitative data

12

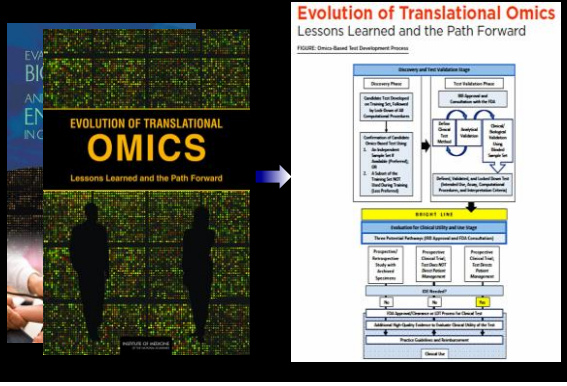
Biomarker Assays

Assays are characterized by their:

- Technical Performance → Quantitative Imaging Biomarkers Alliance
- Clinical Performance
  - Clinical validation
  - Clinical utility

13

IOM Reports: May 2010 & March 2012



RSNA QIBA

- Started in 2007 under the leadership of Daniel Sullivan
- Mission
  - Improve the value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time.
  - "Industrialize imaging biomarkers"
- Focused Specifically on Technical Performance

15

RSNA QIBA Approach

- Four Components to QIBA Approach:
  - Identify sources of bias and variance in quantitative results
  - Develop potential solutions
  - Test solutions
  - Promulgate solutions
- Accomplished by developing "QIBA Profiles" and "QIBA Protocols"

16

RSNA QIBA Approach

- Profile
  - A document that describes the specific performance claim(s) and how the claim(s) 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; and 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.

17

QIBA Claim Template

- List Biomarker Measurand(s)
- Specify: cross-sectional *vs*. longitudinal measurement
- List Indices:
  - Bias
  - Precision
    - Test-retest Repeatability (Repeatability coefficient)
    - Reproducibility (Reproducibility coefficient; Intraclass Correlation Coefficient; Concordant Correlation Coefficient)
      - Specify conditions, *e.g.*,
        - Measuring system variability (hardware & software)
        - Site variability
        - Operator variability (intra- or inter-reader)
- Clinical Context

18

QIBA Claim Example (DW-MRI)

Biomarker measurand: *in vivo* tissue water mobility, commonly referred to as the apparent diffusion coefficient (ADC)

- Cross-sectional measurement: Disease state determination via absolute ADC value (thresholds)
  - Bias:
    - When measuring an ice-water phantom at isocenter, the ADC measurement will exhibit no more than a 5% bias from the reference value of 1.1 x 10^{-9} m^2/s
  - Precision:
    - Repeatability: When acquiring ADC values in solid tumors greater than 1 cm in diameter, or twice the slice thickness (whichever is greater), one can characterize *in vivo* diffusion with at least a 15% test/retest coefficient of variation (intra-scanner and intra-reader)

QIBA Claim Example (DW-MRI)

Biomarker measurand: *in vivo* tissue water mobility, commonly referred to as the apparent diffusion coefficient (ADC)

- Longitudinal measurement: measurement of ADC as an indicator of treatment response
  - Bias …
  - Precision …

Profile Template

Table of Contents

Profile Template

Table of Contents

v2.2, April 2015

Quantitative Imaging Biomarkers Alliance

Profile Template

Table of Contents

Open Issues: 3
Closed Issues: 3
1. Executive Summary 4
2. Clinical Context and Claims 4
Utilities and Endpoints for Clinical Trials 4
Claim: [short description] 4
Claim: [repeat for as many distinct claims as being made] 4
3. Profile Activities 5
3.1. Subject Handling 7
3.1.1 Timing Relative to Index Intervention Activity 7
3.1.2 Timing Relative to Confounding Activities 8
3.1.3 Contrast Preparation and Administration 8
3.1.4 Subject Positioning 9
3.1.5 Instructions to Subject During Acquisition 9
3.1.6 Timing/Triggers 9
3.2. Image Data Acquisition 10
3.3. Image Data Reconstruction 10
3.4. Image Analysis 11
4. Conformance Procedures 11
4.x. Performance Assessment: <Parameter X> 12
4.y. Performance Assessment: <Parameter Y> 12
References 13
Appendices 14
Appendix A: Acknowledgements and Attributions 14
Appendix B: Background Information 14
Appendix C: Conventions and Definitions 14
Appendix D: Model-specific Instructions and Parameters 15

v2.2, April 2015

Quantitative Imaging Biomarkers Alliance

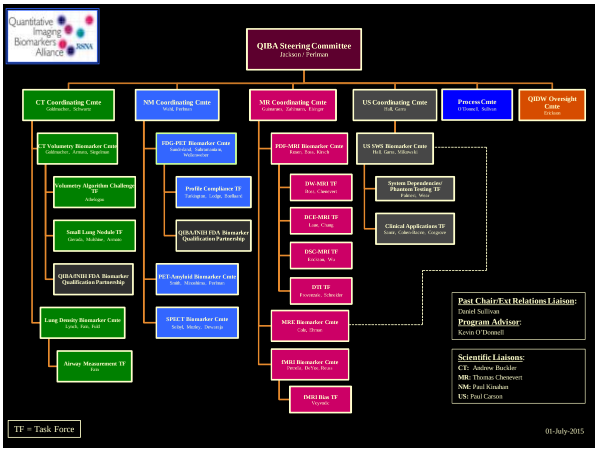
Profile Template

Table of Contents

Open Issues: 3
Closed Issues: 3
1. Executive Summary 4
2. Clinical Context and Claims 4
Utilities and Endpoints for Clinical Trials 4
Claim: [short description] 4
Claim: [repeat for as many distinct claims as being made] 4
3. Profile Activities 5
3.1. Subject Handling 7
3.1.1 Timing Relative to Index Intervention Activity 7
3.1.2 Timing Relative to Confounding Activities 8
3.1.3 Contrast Preparation and Administration 8
3.1.4 Subject Positioning 9
3.1.5 Instructions to Subject During Acquisition 9
3.1.6 Timing/Triggers 9
3.2. Image Data Acquisition 10
3.3. Image Data Reconstruction 10
3.4. Image Analysis 11
4. Conformance Procedures 11
4.x. Performance Assessment: <Parameter X> 12
4.y. Performance Assessment: <Parameter Y> 12
References 13
Appendices 14
Appendix A: Acknowledgements and Attributions 14
Appendix B: Background Information 14
Appendix C: Conventions and Definitions 14
Appendix D: Model-specific Instructions and Parameters 15

v2.2, April 2015

Quantitative Imaging Biomarkers Alliance


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
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
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
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
01-July-2015

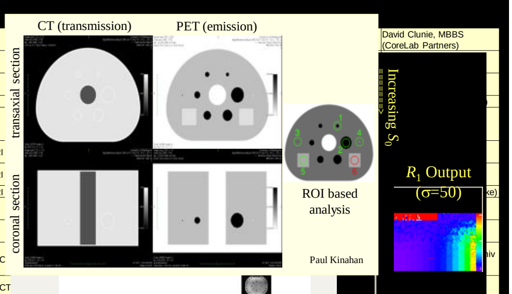
Groundwork Projects

- Funding for groundwork projects required for Profile development has been provided by two consecutive 2-year contracts from NIBIB to RSNA.
- Four rounds of groundwork project awards (total of ~50 projects) thus far, with a 5th round scheduled to start in September 2015*.

*Pending continued NIBIB support

26

RSNA QIBA Projects – Round 1



CT	VolCT		David Clunie, MBBS (CoreLab Partners)
CT	VolCT		
CT	VolCT		
CT	VolCT		
CT	VolCT		
MR	DCE-MRI		
MR	DCE-MRI		
MR	DCE-MRI		
MR	fMRI		
MR	fMRI		
NM	FDG-PET/C		
NM	FDG-PET/CT		
NM	FDG-PET/CT	Analysis of SARC 11 Trial PET Data by PERCIST with Linkage to Clinical Outcomes	Richard Wahl, MD (JHMC)
Cross	Cross Modality	Groundwork for QIBA Image Reference Database - QIBA Image Reference	Gudrun Zahlmann, PhD (Roche)
Cross	Cross Modality	Groundwork for QIBA Image Reference Database - QIBA Image Reference	Rick Avila, MS (Kitware)

RSNA QIBA Projects – Round 2

CT	VolCT	Extension of Assessing Measurement Data Sets: Variability Under Clinical W
CT	VolCT	Extension of Assessing Measurement Data Sets: Variability Under Clinical W
CT	VolCT	Comparative Study of Algorithms for th Lesions: Assessing the Effects of Softv Variability
CT	COPD	Impact of Dose Saving Protocols on Q Asthma
MR	DCE-MRI	Test-Retest Evaluation of Repeatability of
MR	fMRI	Validation of Breath Hold Task for Asse Responsiveness and Calibration of Lar Reproducibility
NM	FDG-PET/CT	Personnel Support for FDG-PET Profil
NM	FDG-PET/CT	Evaluation of the Variability in Determi Treatment Response Across Performa
NM	FDG-PET/CT	PERCIST Validation
NM	FDG-PET/CT	Evaluation of FDG-PET SUV Covariate

ACRIN AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

Quantitative Imaging Biomarkers Alliance

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK and QUANTITATIVE IMAGING BIOMARKERS ALLIANCE

ACRIN 6701

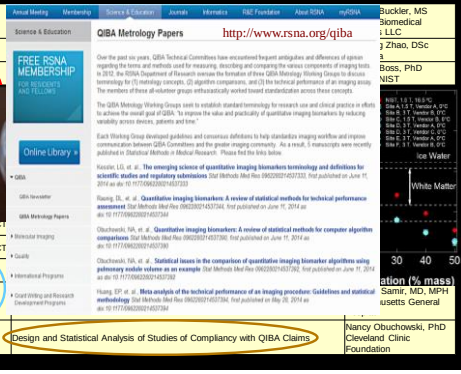
Repeatability Assessment of Quantitative DCE-MRI and DWI: A Multicenter Study of Functional Imaging Standardization in the Prostate

Primary goals and objectives – *in vivo* test/retest protocol

- 1) Determine the test-retest performance, as assessed by the coefficient of variation, of the median pixel values of K^{trans} and $IAUGC_{180}$, using the whole prostate as the target "tumor".
- 2) Determine the test-retest performance, as assessed by the coefficient of variation, of the median pixel value of AUC_{fast}, and ADC_{slow}, using the whole prostate as the target "tumor".

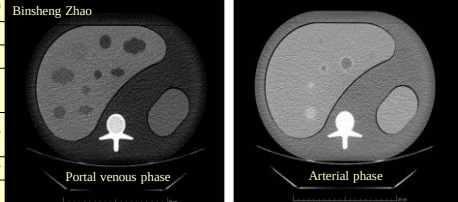
RSNA QIBA Projects – Round 3

CT	VolCT	Buckler, MS Biomedical LLC
CT	VolCT	Zhao, DSc
MR	PDF-MRI	Boss, PhD NIST
MR	PDF-MRI	
MR	PDF-MRI	
MR	PDF-MRI	
MR	fMRI	
NM	FDG-PET/CT	
NM	FDG-PET/CT	
US	US-SWS	Samir, MD, MPH
US	US-SWS	usetts General
Cross	Cross	Design and Statistical Analysis of Studies of Compliancy with QIBA Claims — Nancy Obuchowski, PhD, Cleveland Clinic Foundation



RSNA QIBA Projects – Round 4

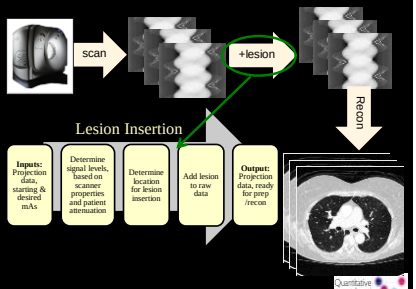
CT	VolCT	Methodology and Reference Image Set for Volumetric Characterization and Compliance	Ehsan Samei, PhD Duke University / Berkman Sahiner, PhD FDA
CT	VolCT	Phantoms for CT Volumetry of Hepatic and Nodal Metastasis – Year 2	Binsheng Zhao, DSc Columbia
CT	COPD / Lung Density		
MR	PDF-MRI		
MR	PDF-MRI		
MR	fMRI		
NM	FDG-PET/CT		
NM	FDG-PET/CT		
US	US-SWS	Development and Validation of Simulations and Phantoms Mimicking the Viscoelastic Properties of Human Liver	(Chen, Mayo; Jiang, Mich Tech Univ; McAleavey, Univ of Rochester)
US	US-SWS	Beyond Confounders: Addressing Sources of Measurement Variability and Error in Shear Wave Elastography	Anthony Samir, MD, MPH Massachusetts General Hospital
Cross	Cross	Design and Statistical Analysis of Studies of Compliancy with QIBA Claims	Nancy Obuchowski, PhD Cleveland Clinic Foundation



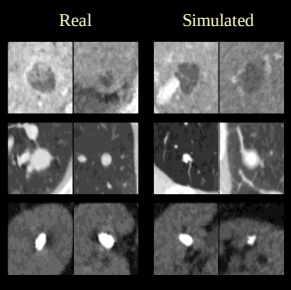
Virtual CT Lesions

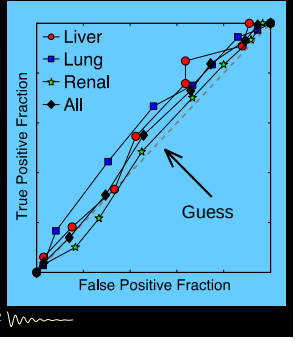
Techniques

1. Image space lesion addition
2. Projection space lesion addition



Virtual CT Lesions





Current QIBA Profiles

Profiles in development (in addition to revisions/extensions of current profiles):

- DWI-MRI (ADC)
- fMRI (pre-surgical motor mapping)
- US Shear Wave Speed (liver fibrosis)
- β-amyloid PET
- MR Elastography (MRE)
- DSC-MRI (rCBV)
- DTI-MRI (FA, RA)

Potential profiles in discussion:

- Proton Density Fat Fraction (PDFF) MR
- SPECT

Adoption of QIBA Products / Concepts

- Clinical trial applications: Early Profile concepts incorporated into clinical trial designs by at least two major pharmaceutical companies.
- Adoption and marketing of "QIBA compliance" by imaging core labs.
- Increasingly active imaging vendor representation on QIBA committees; senior NEMA/MITA, FDA, and NIST representation on QIBA Steering Committee.
- Internationalization of QIBA:
  - Active QIBA participants from South America, Europe, and Asia
  - EORTC / IMI – QIBA collaboration (MR DWI Profile and phantom)
  - European Imaging Biomarker Alliance (EIBALL)
  - São Paulo neuroradiology clinical trial adoption of MR DWI Profile & phantom
  - Japan Radiological Society & Korean Society of Radiology participation

34

Acknowledgments

- Daniel Sullivan, MD - Founding Chair, RSNA QIBA
- Linda Bresolin, PhD, MBA and all RSNA HQ staff members supporting QIBA
- RSNA Biomarker Committee & Task Force Co-Chairs & Members
- Daniel Barboriak, MD - Digital Reference Object (DCE)
- Mark Rosen, MD, PhD - ACRIN 6701 Protocol & PDF-MRI BC
- Paul Kinahan, PhD - RSNA QIBA (PET DRO)
- Michael Boss, PhD - RSNA QIBA (ADC Diffusion Phantom)
- Ehsan Samei, PhD, Berkman Sahiner, PhD, Nicholas Petrick, PhD, Binshang Zhao, DSc - RSNA QIBA (CT DRO & Liver Phantom)
- Laurence Clarke, PhD - NCI CIP
- NIBIB / RSNA Contract HHSN268201000050C

http://www.rsna.org/qiba http://qibawiki.rsna.org

35