Quantitative Imaging

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Early QI Initiative

NIST USMS Workshop 2006

Representative Agencies / Organizations
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

Current MR QIB Applications

Existing MR QIBs in Glioma: Morphological to Functional
### MR QIBs in Glioma

<table>
<thead>
<tr>
<th>Biological Process</th>
<th>MR Technique</th>
<th>MR QIB Measurand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Cellularity / Proliferation</td>
<td>$^1$H MRS, DTI/DWI</td>
<td>$\uparrow$ Cho, $\uparrow$ Cho/NAA, $\downarrow$ ADC</td>
</tr>
<tr>
<td>Necrosis</td>
<td>$^1$H MRS, Gd-enhanced, T2W</td>
<td>$\uparrow$ lipids, No Gd uptake, $\uparrow$ T2W signal</td>
</tr>
<tr>
<td>Edema</td>
<td>T2FLAIR, DTI/DWI</td>
<td>$\uparrow$ FLAIR signal, $\uparrow$ ADC, $\downarrow$ FA</td>
</tr>
<tr>
<td>Gliosis</td>
<td>$^1$H MRS (short TE)</td>
<td>$\uparrow$ myo-inositol</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>$^1$H MRS, BOLD</td>
<td>$\uparrow$ lactate, $\downarrow$ $\Delta R_2^*$</td>
</tr>
<tr>
<td>Angiogenesis / Permeability</td>
<td>DCE-MRI, DSC-MRI</td>
<td>$\uparrow K^{\text{trans}}$ &amp; $v_p$, $\uparrow$ rCBV &amp; rCBF</td>
</tr>
<tr>
<td>Invasion</td>
<td>DTI, $^1$H MRS</td>
<td>$\downarrow$ FA, $\uparrow$ ADC, $\downarrow$ NAA</td>
</tr>
<tr>
<td>Radiation Effects</td>
<td>SWI, DTI</td>
<td>Micro-hemorrhages (late), $\downarrow$ FA</td>
</tr>
</tbody>
</table>

Modified version of Table 1 of Nelson, *NMR Biomed* 24:734-739, 2011
### QIBs in Precision Medicine

<table>
<thead>
<tr>
<th>Predict</th>
<th>Virtual Biopsy</th>
<th>During Tx</th>
<th>After Tx</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Patient stratification in order to decide on alternative treatments</td>
<td>• Analysis of heterogeneity within and across lesions <em>(can assess varying pharmacokinetics, receptor status, proliferative/apoptotic rates, ...)</em></td>
<td>• Early prediction of treatment response</td>
<td>• Basis for modifying therapy</td>
<td>• Monitoring for Treatment Efficacy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Longitudinal monitoring and evaluation <em>(can be done before then after treatment, substituting for longitudinal tissue biopsy)</em></td>
</tr>
</tbody>
</table>

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.
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

Problem: QIB Uncertainties

Sources of Variance

- Patient Handling
- Acq. Protocols
- Reconstruction
- Segmentation

Image compliments of Kevin O'Donnell
Poor Reproducibility has Clinical Implications

  “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.”

  “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

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.

<table>
<thead>
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<th>Number of patients:</th>
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<tbody>
<tr>
<td>10%</td>
</tr>
<tr>
<td>20%</td>
</tr>
<tr>
<td>30%</td>
</tr>
<tr>
<td>40%</td>
</tr>
</tbody>
</table>

- 10%  | 12 |
- 20%  | 35 |
- 30%  | 78 |
- 40%  | 133|

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<tr>
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</tr>
</tbody>
</table>

- 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
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”
RSNA QIBA Approach

- Transformational: addresses gaps, impacts public health
- Translational: concept proved, ready to advance
- Feasible: good change to succeed in near term
- Practical: leverages existing resources and technology
- Collaborative: engages HW/SW/agent stakeholders

- Identify significant sources of bias and variance
- Estimate achievable accuracy and precision
- Validate underlying assumptions and mechanisms
- Determine details to specify in the Profile

- Define claim (cross-sectional and/or longitudinal) and clinical context
- Specify details necessary for robust implementation
- Make details clear, implementable, and testable
- Define conformance criteria for each “actor” in imaging chain

- Make Profile available to community
- Encourage use in clinical trials / sites

- Test conformance with QIBA Profile specifications
- Publish validated products and site

Goal of QIBA

Problem: Measure = 7 ± 6

Analysis: Sources of Variance
Differences in:
- Patient Handling
- Acq. Protocols
- Reconstruction
- Segmentation

Goal: Measure = 7 ± 2

Solution: When all participating actors conform...

Requirements for:
- Acquisition Params
- Recon Params
- Resolution
- Processing Params
- Patient Prep & Operation
- Segmentation
- Calibration
**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

**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?

**Assessment Procedures:**

- Image Noise and Resolution
- Tumor Volume Change Variability
- Site Performance
QIBA Claim Template

1. Type of Claim
   - X-sectional
   - Longitudinal

   1a. Same measuring system at all time-points?
      - Yes
      - No

2. Characterize Bias
   - Negligible
   - Known
   - Unknown

   2. Characterize Bias
      - Common
      - Negligible
      - Known

3. Characterize wSD or wCV
   - Constant wSD
   - Constant wCV
   - Multiple wCVs

   3. Characterize wSD or wCV
      - Constant wSD
      - Constant wCV
      - Multiple wCVs

Scenarios:
- Scenario A: Constant wSD; negligible bias: Construct 95% CI from wSD
- Scenario B: Constant wSD; bias known: Construct 95% CI from TDI and wSD
- Scenario C: Constant wCV; negligible bias: Construct 95% CI from wCV
- Scenario D: Constant wCV; bias known: Construct 95% CI from TDI and wCV
- Scenario E: Multiple wCVs; negligible bias: Construct 95% CI in multiple claims from different wCVs
- Scenario F: Multiple wCVs; bias known: Construct 95% CI in multiple claims from different TDI and wCV
- Scenario G: Constant wSD; negligible bias: Construct 95% CI from wSD & estimated RC
- Scenario H: Constant wCV: Construct 95% CI from wCV & estimated RC
- Scenario I: Multiple wCVs: Construct 95% CIs in multiple claims from different wCVs & estimated RCs
- Scenario J: Multiple wCVs: Negligible bias: Construct 95% CIs in multiple claims from different TDI & estimated RDCs
- Scenario K: Multiple wCVs: Known bias: Construct 95% CIs in multiple claims from different TDI & estimated RDCs
- Scenario L: Multiple wCVs: Negligible bias: Construct 95% CIs in multiple claims from different TDI & estimated RDCs
- Scenario M: Multiple wCVs: Known bias: Construct 95% CIs in multiple claims from different TDI & estimated RDCs
- Scenario N: Multiple wCVs: Negligible bias: Construct 95% CIs in multiple claims from different TDI & estimated RDCs
- Scenario O: Multiple wCVs: Known bias: Construct 95% CIs in multiple claims from different TDI & estimated RDCs
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 $X \pm 1.96 \times wSD$.
  • 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 $Z \pm 1.96 \times \sqrt{2} \times wSD$.

• Specify clinical context

qibawiki.rsna.org
## Profile Stages

<table>
<thead>
<tr>
<th>Stage Name</th>
<th>Stage Meaning</th>
<th>Stage Criteria</th>
</tr>
</thead>
</table>
| **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
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 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
ADC Phantom analysis software publicly available.

DWI MR DRO publicly available.

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)
Portal venous phase

Arterial phase

Phantoms for CT Volumetry of Hepatic and Nodal Metastasis

Binsheng Zhao, DSc – Columbia University
RSNA QIBA Groundwork Projects

Digital Reference Object for DCE-MRI Analysis Software Verification

Daniel Barboriak, MD (Duke)
RSNA QIBA Groundwork Projects

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

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

- **c**: attenuation
- **B**: background
- **C**: contrast
- **R**: shape
- **n**: edge blur

**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

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**Methodology and Reference Image Set for Volumetric Characterization and Compliance**

Ehsan Samei, PhD – Duke
Which lesions are real?

Real

Simulated

Liver

Lung

Renal

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 $K^{\text{trans}}, v_e$) 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
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

- **Proton Density (%)** vs. **Sphere Number**
- **T1 (ms)** vs. **[NiCl2] (mM)**
- **T2 (ms)** vs. **[MnCl2] (mM)**
- **R1 (s⁻¹)** vs. **T1 (ms)**
- **R2 (s⁻¹)** vs. **T2 (ms)**

Contrast response in the NIST/ISMRM MR System Phantom.
NIST/ISMRM MR System Phantom

Data Analysis:
Jeff Gunter, Mayo
(Based on ADNI project)
NIST/ISMRM MR System Phantom
NIST/ISMRM MR System Phantom

Coefficient of Variation

Scanner, Method
- Vendor A; IR
- Vendor B; IR
- Vendor C; IR
- Vendor A; VFA
- Vendor B; VFA
- Vendor C; VFA

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
- Ehsan Samei, PhD and Berkman Sahiner, PhD - CT DRO
- 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
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