The Translation of QI to Clinical Research and Precision Medicine - Goals and Challenges

RSNA Quantitative Imaging Biomarkers Alliance (QIBA)

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QIB Challenges

General QIB challenges:

- Little support (historically) from imaging equipment vendors
  - No documented competitive advantage of QIB (regulatory or payer)
  - Diagnostic imaging equipment generally engineered for best image quality in shortest time (*qualitative*), not for reproducible *quantitative* results.
- Lack of detailed assessment of sources of bias and variance
- Lack of standards (acquisition, analysis, and reporting)
- Highly variable quality control procedures
  - Typically not specific for *quantitative* imaging

All lead to varying measurement results across vendors, centers, and/or time

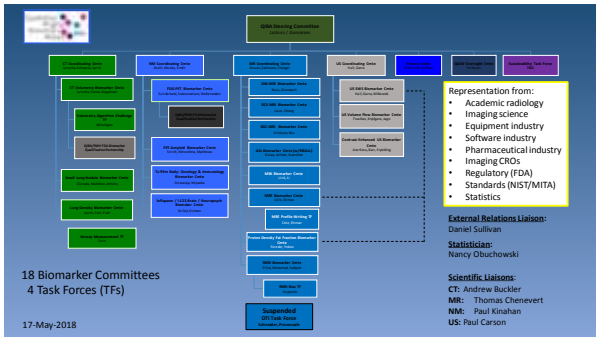
Quantitative Imaging Biomarkers Alliance

- 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, sites, patients, and time.
  - "Industrialize imaging biomarkers"

Imaging as an Assay

Assays are characterized by their:

- Technical Performance
- Clinical Performance
  - Clinical validation
  - Clinical utility



18 Biomarker Committees
4 Task Forces (TFs)

17-May-2018

Representation from:
- Academic radiology
- Imaging science
- Equipment industry
- Software industry
- Pharmaceutical industry
- Imaging CROs
- Regulatory (FDA)
- Standards (NIST/MITA)
- Statistics

External Relations Liaison:
Daniel Sullivan

Statistician:
Nancy Obuchowski

Scientific Liaisons:
CT: Andrew Buckler
MR: Thomas Chenevert
NM: Paul Kinahan
US: Paul Carson

Variability in imaging measurements is related to:

1. Image acquisition variability
2. Measurement method variability
3. Radiologist/Reader variability

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FDG-PET SUV Example

Overall Goal of QIBA

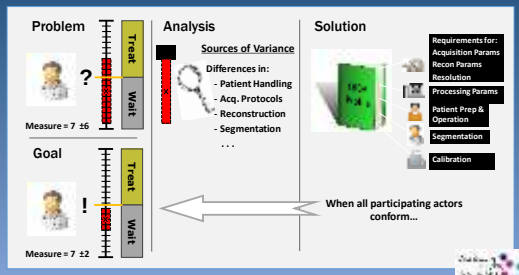

Image compliments of Kevin O'Donnell

QIBA Process

Write a Profile (systems-engineering, technical standards document)

- Claim
- Specifications

QIBA Metrology Project

GOAL: Improve study design and analysis of QIB studies by

1. Standardizing terminology
2. Identifying relevant performance metrics
3. Developing methods for algorithm comparison

Five-paper series on study design and statistical methods for QIBs in *Statistical Methods in Medical Research* (SMMR)

QIBA Metrology Working Group Publications

Available at www.rsna.org/qiba

QIBA Process

Write a **Profile** (systems-engineering, technical standards document)

- Claim
- Specifications

Key technical parameters to characterize for an imaging biomarker are:

- Bias
- Precision (Test-Retest Repeatability or Reproducibility)
- Linearity

Sources of data to determine variance

- Scientific literature
  - Analyze data in published studies
- Phantom studies
  - "Ground truth" is known with certainty
  - Synthetic scans (digital reference objects) and hybrid scans (lesions or noise inserted into clinical scans).
- Pilot or "groundwork" studies
  - QIBA has funded several of these
- Manufacturers' Specifications

QIBA Claim Templates

- Cross-sectional
- Claim 1: For a [measurement] of *X*, a 95% confidence interval for the true [measurand] is [*X* ± q%].
- Longitudinal (Change)
- Claim 2: A measured increase in [measurand] of y% or more indicates that a true increase has occurred with 95% confidence.
- Claim 3: For a measured change in [measurand] of *Y*, a 95% confidence interval for the true change is $(Y_2 - Y_1) \pm$ the precision value.

Examples of QIBA Claim Statements

CROSS-SECTIONAL CLAIM Template: *For a QIB measurement of X units, a 95% confidence interval for the true QIB value is X ± precision value.*

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- **However, Precision varies depending on many factors, such as (for CT) the size of the nodule, whether the same scanner, software and reader are used for both time points, and many additional factors.**

CT Variables That Affect Quantification

1. # Slice scanner
2. kVp
3. mas
4. Rotation time
5. Table speed
6. Table position
7. Slice thickness
8. Slice overlap
9. Reconstruction kernel
10. Field of view;
11. Matrix
12. Collimation
13. Etc. …

Examples of QIBA Claim Statements

LONGITUDINAL CLAIM Template:

For a measured change of Δ, a 95% confidence interval for the true change is Δ ± precision value.

For example,

"If Y_1 and Y_2 are the nodule volume measurements at the two time points, a 95% confidence interval for the true change is
$(Y_2 - Y_1) \pm 1.96 \times \sqrt{(Y_1 \times wCV)^2 + (Y_2 \times wCV)^2}$."

(wCV = within-tumor coefficient of variation).

Clinical Context Examples Illustrating How Precision is Dependent on Object Size

- Example 1: A true change in tumor volume has occurred with 95% confidence if the measured volume change is larger than 24% when the longest in-plane diameter at baseline is within 50-100mm.
- Example 2: A true change in tumor volume has occurred with 95% confidence if the measured volume change is larger than 29% when the longest in-plane diameter at baseline is within 35-49mm.
- Example 3: A true change in tumor volume has occurred with 95% confidence if the measured volume change is larger than 39% when the longest in-plane diameter at baseline is within 10-34mm.

Minimum Detectable Change in Tumor Volume, as a Function of Other Variables

Tumor Diameter	Different Scanner				Same Scanner			
	Different Radiologist		Same Radiologist		Different Radiologist		Same Radiologist	
	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	Same Analysis Tool	Different Analysis Tool	Same Analysis Tool
>50mm	43%	24%	43%	24%	37%	10%	37%	8%
35-49mm	67%	33%	65%	29%	62%	22%	60%	14%
10-34mm	139%	120%	80%	39%	136%	117%	75%	28%

Example Caveats (in QIBA CT Volumetry Profile)

- "Whether a biologic change in tumor volume constitutes *clinically meaningful* disease progression or response is a distinct decision that requires a clinician's judgment. There are currently no validated response criteria based on volume. The most commonly used response criteria in solid tumors, RECIST 1.1, uses unidimensional measurements. For comparison, RECIST 1.1 specifies that progression has occurred when there has been a 20% increase in tumor diameter from baseline, which corresponds to a 73% increase in volume for a spherical tumor, and favorable treatment response has occurred when there has been a 30% decrease in diameter, which corresponds to a 66% decrease in volume."

Current Profile Status (As of 3/17/2018)

- 20 Profiles (4 CT, 3 NM, 10 MR, 3 US)
- Technically Confirmed Stage:
  - NM: *FDG-PET/CT SUV as an Imaging Biomarker for Measuring Response to Cancer Therapy*
- Consensus Stage:
  - CT: *Tumor Volume Change* (v2.2) for tumor response (expected to be Technically Confirmed 2018)
  - CT: *Lung Nodule Volume Assessment & Monitoring in Low Dose CT Screening Quantification*
  - NM: *Quantifying Dopamine Transporters with ^{123}Iodine-labeled Ioflupane in Neurodegenerative Disease* (SPECT)
  - MR: *DCE-MRI Quantification* (v1.0) for tumor response
- In Public Comment Stage:
  - MR: DW-MRI for tumor response
  - MR: Elastography for liver fibrosis
  - MR: fMRI for pre-surgical planning
  - NM: F-18 PET amyloid for Alzheimer's Disease

Current Profile Status (As of 3/17/2018)

- In Final Stage of Development for Public Comment Release:
  - CT: Lung densitometry for COPD
  - US: Ultrasound shear wave speed for liver fibrosis
  - MR: Proton density fat fraction (PDFF) for liver disease
- In Earlier Stages of Development:
  - CT: Tumor volume change for liver lesions
  - MR: Dynamic susceptibility contrast (DSC)-MRI for perfusion assessment in brain
  - MR: Diffusion tensor imaging (DTI) for traumatic brain injury – on hold
  - MR: Revised DCE-MRI to address 3T and parallel imaging
  - MR: T_2 and $T_{1\rho}$ MSK MR for degenerative joint disease
  - US: Contrast-enhanced ultrasound (CEUS) for perfusion studies
  - US: Ultrasound volume flow for perfusion studies – *collaboration with AIUM*
  - MR: Arterial spin labeling (ASL) MR – *collaboration with ESR EIBALL*

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
  - 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
  - fMRI DROs (motor and language mapping)
  - PET SUV DRO
  - SPECT DRO (^{123}I dopamine transporter, DaTscan/Ioflupane; in develop
- Datasets & Data Analysis Applications on QIDW

Dissemination Activities

- QIBA has been referenced in multiple publications
- AAPM Task Group No. 174 Utilization of 18F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in Radiation Therapy
- AAPM Task Group No. 294 - MR Biomarkers in Radiation Oncology
- With IASLC, International pilot project on Conformance Certification to QIBA Profile on Small Lung Nodule Volume Assessment and Monitoring in Low Dose CT Screening
- Discussions with Alliance for Clinical Research Excellence and Safety (ACRES), to integrate QIBA Profiles into clinical trial site accreditation.

Key Points

- The variability inherent in subjective, qualitative radiologist interpretations is a huge problem.
- The sources of quantitative variation (uncertainty) in clinical images are complex, and mitigation requires adherence to rigorous standards.
- The mission of the Quantitative Imaging Biomarkers Alliance (QIBA) is to reduce variability across sites, devices, patients and time.

Thank you.