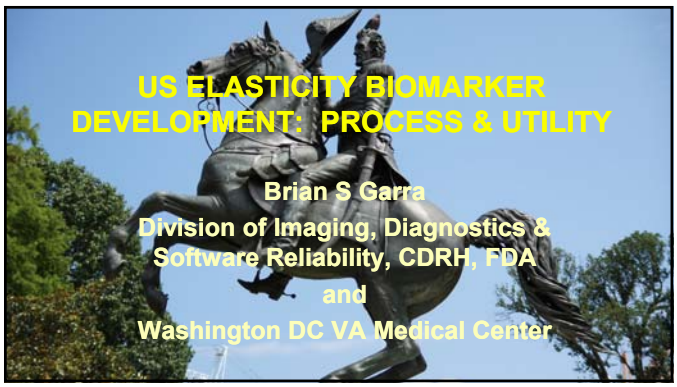


US ELASTICITY BIOMARKER DEVELOPMENT: PROCESS & UTILITY

Brian S Garra
Division of Imaging, Diagnostics & Software Reliability, CDRH, FDA
and
Washington DC VA Medical Center

GOALS

- Establish the Need for Quantitative Imaging
- Introduce the RSNA Quantitative Imaging Biomarker Alliance (QIBA)
- Review the Steps in the QIBA Process for Qualifying the US Elasticity Quantitative Biomarker
- Discuss the Challenge of Verification of Profile Compliance
- Profile Applications and Future Biomarkers

WHY QUANTITATIVE IMAGING?

- Objective Quantifiable Results Enhance the Value of Diagnostic Imaging
- Evidence Based Medicine Uses Objective vs. Subjective Data
- Computerized Decision Support Tools Use Quantitative Input
- Quantitative Measures More Easily Adapted to Personalized Molecular Diagnosis and Treatment

BASIC RSNA PREMISE

Extracting objective, quantitative results from imaging studies will improve the value of imaging in clinical practice.

Why Must Imaging Become More Quantitative?

- *Molecular medicine (personalized medicine)* requires quantitative test results.
- *Evidence-based medicine & QA Programs* depend on objective data.
- *Decision-support tools* (CADx, CDSS) need quantitative input.

Quantitative Imaging Biomarkers Alliance (QIBA)

Quantitative Imaging Biomarkers Alliance RSNA

- First meeting: May, 2008
- Mission: Improve value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time.
  - Convert "measuring devices" into "imaging devices".
  - Industrialize/Commercialize imaging biomarkers

CURRENT QIBA STRUCTURE

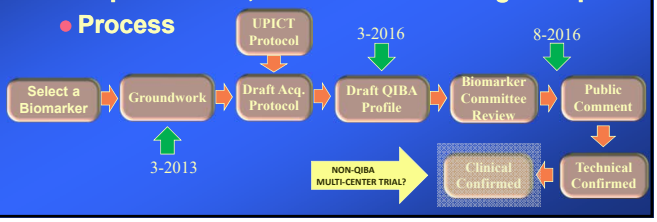
- Steering Committee
  - Four Modality Coordinating Committees
    - Computed Tomography
    - Magnetic Resonance Imaging
    - Nuclear Medicine
    - Ultrasound
  - Six Biomarker Committees – One for Each Specific Biomarker
    - WORKING GROUPS: FOR EACH MAJOR TASK i.e. Profile Writing; Phantom Development; Instrumentation/Software

IMAGING BIOMARKER EXAMPLES

Biomarker	Test	Metric
COPD: Air-tissue ratio	CT scan densitometry	MLD (mean lung density)
Cancer: Tumor burden	CT & MR scan volumetry	Volume
Cancer: Glucose avidity	FDG-PET scan	SUV (standardized uptake value)
Cancer: Vascular permeability	DCE-MRI scan	K_{trans}; IAUC
Brain surgery risk: Proximity to eloquent cortex	fMRI scan brain-mapping	Center and magnitude of cortical activation
Liver Mechanical Stiffness	US Elastography Using ARFI	US Shear Wave Speed
Organ Perfusion	US Color Doppler	Volume Blood Flow (mL/min.)
Liver Lesion Blood Flow Patterns	Contrast Enhanced Ultrasound	Wash-in and wash-out times; intensity change

US SWS BIOMARKER COMMITTEE

- Organized Into Phantom/System Dependencies, and Clinical Working Groups
- Process



QIBA PROFILE COMPONENTS I

- Listing of Open and Closed Issues
- Executive Summary
- Profile Context and Claims
  - Context: Description of Proposed Intended Uses

CLINICAL CONTEXT

"Elastography used as a biomarker for the identification of moderate fibrosis grade defined as ≥ F2 fibrosis in the METAVIR system of staging liver fibrosis. This might be used to monitor progression of fibrosis during anti-fibrosis therapy or to monitor regression of fibrosis."

QIBA PROFILE COMPONENTS II

- Profile Context & Claims
  - Claims:
    - Biomarker measurement and specific intended clinical application.

      Example: Shear Wave Speed in patients with suspected liver fibrosis / cirrhosis
    - A Claim for Bias and Precision of the Measurement

      Example: "SWS will be within ± 5% of the true SWS…and the 95% CI is Y ± (1.96 * Y * 0.05) where CV = 5%"
    - Statement of the Range of Values over which the Claim Holds
  - Optional Discussion of the Diagnostic Use of the Values

QIBA PROFILE COMPONENTS III

- Profile Activities Section
  - Each Process / Procedure ("Activity") is Listed with the Device or Person Responsible ("Actor") for that Step in the Biomarker Acquisition.
  - The Activities for Each "Actor" are Tabulated and Organized Into Groups of Parameters for Which Required Specifications are Given
  - Example:

ACTOR	ACTIVITY	PARAMETER	SPECIFICATION
Sonographer/Radiologist	Image Acquisition	Transducer Position	Perpendicular to Skin

QIBA PROFILE COMPONENTS IV

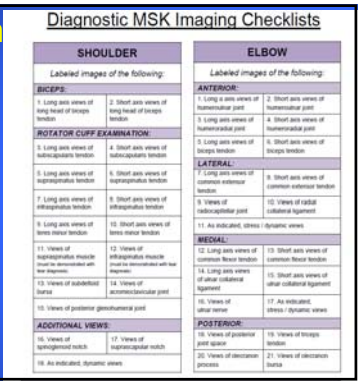
- Assessment Procedures (QA)To Check Conformance to Profile
- Procedures for Conformance Still Under Discussion
  - Self Attestation
  - Actor Testing
  - Review of on-site Equipment Tests
  - External Observers Watch Acquisition under Profile
  - Combination Approach
- Remediation for Non-Conformant Sites??

PROFILE CONFORMANCE FOR SWS

- SWS Draft Conformance Plan Uses External Audit
  - Checklists Used During Acquisition
  - Review of Biomarker Values
- Conformance Checklists Are Adapted Versions of the Profile Execution Checklists
  - Transparent: Auditors and Site Know Exactly What Will be Reviewed
- Scoring on Point System with ~ 80% Passing

AIUM Accreditation Checklist

- A Similar Checklist—Possibly One Per Actor?
- Modified Version With Weighted Scoring for Auditors
- Pass/Fail Score May Initially be Arbitrary But Later Use Score Metrics to Redefine


Diagnostic MSK Imaging Checklists

SHOULDER

Labeled images of the following:

BICEPS:

ROTATOR CUFF EXAMINATION:

ADDITIONAL VIEWS:

ELBOW

Labeled images of the following:

ANTERIOR:

LATERAL:

MEDIAL:

POSTERIOR:

QIBA PROFILE COMPONENTS V

- Appendices
  - Acknowledgements
  - Background Information
  - Specific Acquisition Protocols (for SWS machine specific)
    - UPICT Protocols are Typically Used as a Model
  - Specific Equipment Tests for Equipment Performance Monitoring
  - Checklists and Other Aids

On-SITE EQUIPMENT QA

- Phantom Tests – A Logical Choice
- Existing Phantoms Used to Develop Profile
  - Homogeneous Zerdine Elastic Phantoms
  - Homogeneous Zerdine Based Visco Elastic Phantoms
- New Types of Phantoms
  - New Non-Proprietary Materials
  - Heterogeneous to Better Mimic Tissue
  - Heterogeneous With Inclusions for Focal Lesions

FDA PHANTOM EFFORTS

NEW MATERIALS DEVELOPMENT

- Tunable Polyvinyl Chloride Plastisol
  - Adjustable Acoustic and Stiffness Properties
  - Ingredients:
    - Polyvinyl Chloride Resin
    - Plasticizers : Benzyl Butyl Phthalate (BBP); diethylhexyl adipate (DEHA)
    - Glass Beads for Backscattering

MATERIAL FOR A BREAST PHANTOM

Breast tissue type simulated	BBP(v/v)	DEHA (v/v)	PVC (m/m)	Beads(mg/mL)
FATTY	42%	58%	8.4%	10 (38-63μm)
GLANDULAR	87%	13%	8.6%	30 (63-75μm)
BREAST LESION	87%	13%	13%	10 (38-63μm)

Lesion has the same speed of sound as Glandular tissue, a backscatter coefficient as Fatty tissue, and higher attenuation (about 20% higher than glandular)

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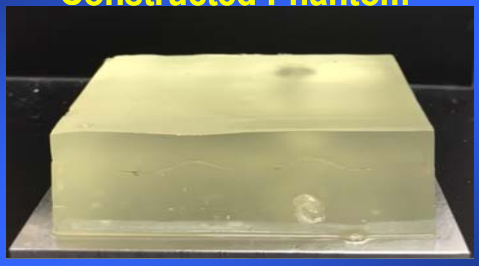
YOUNG'S MODULUS OF MATERIAL

Tissue type	Pf (kPa)	Pg (kPa)	Lesion (kPa)
Young's modulus	6.4	9.4	32.6

Young's modulus values were set to match published work by Krouskop et al, 1998

Constructed Phantom



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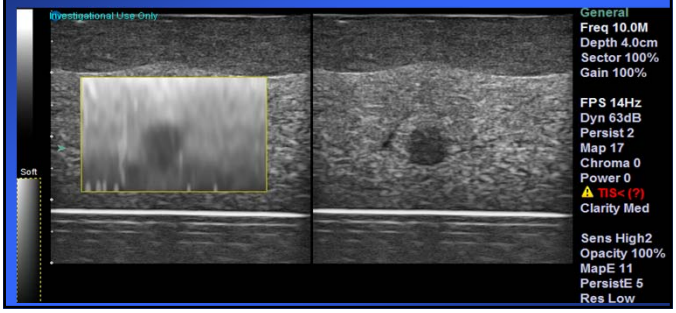
ELASTOGRAM + B-MODE IMAGES



PHANTOM POTENTIAL

- Material is Simple to Make
- Relatively Stable Acoustic and Mechanical Properties Over Many Months So Far
- Properties Verified by Acoustic & Mechanical Testing
- Tunability
- Potentially 3D Printable for Complex Phantom Production
- Visco-Elastic Properties Under Development

DIGITAL PHANTOMS & SIM DATA

- For Rapid Testing of Software Algorithms
- Allows for Rapid Prototyping of Software and Quick Iterative Software Modifications
- Stable and Reproducible
- Initial Versions for Homogeneous Phantoms Available From QIBA SWS
- Modeling of Complex Physical Phantom – testing of software AND hardware

AFTER THE DRAFT PROFILE

- Public Comment Period: 4-6 Weeks
- Further Revision Based on Comments
- Study to Achieve "Technically Confirmed" Status

TECHNICAL CONFIRMATION

- Verification that the Steps Outlined in Profile can Actually be Accomplished in a Clinic
- Verification that Claimed Performance Can be Achieved in Clinic Following the Profile
- No Profile Has Reached This Stage Yet

TECHNICAL CONFIRMATION STUDY

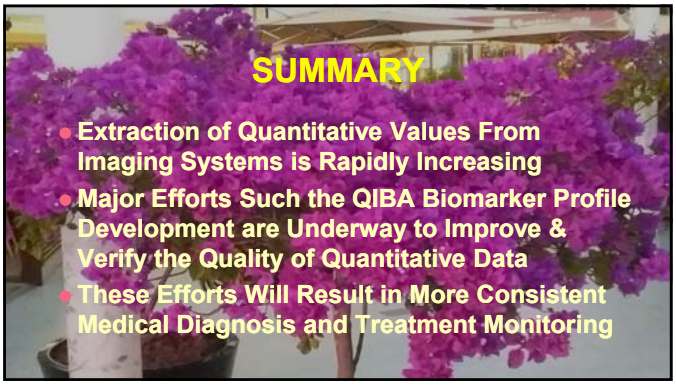
- One or Two Clinical Sites
- At Least Two Clinical Acquisition Systems
- Practice Runs Through Acquisition Procedure for Training and Optimization
- ? Other Details of Design?
- For SWS a Two Site Technical Confirmation Study is Planned
  - Additional Study of Effects of Profile Deviations

CLINICALLY CONFIRMED PROFILE

- Profile Meets Claims When Used Over A Broad Range of Clinical Environments and Patient Populations
- May Include Study to Verify Clinical Diagnostic Criteria Based on the Biomarker
- Envisioned to Require Some Sort of Multicenter Trial
- Not Within the Scope of QIBA

PROFILE EVOLUTION

- New Biomarkers
  - US Blood Volume Flow
  - CEUS Evaluation of Liver Lesions
- Extensions of Existing Biomarkers
  - Stiffness in Focal Lesions
  - Stiffness Heterogeneity
  - Stiffness Anisotropy
- Better Compliance Tests for Equipment & Personnel
- Adaptation to QA Programs, Accreditation Programs
- Internationalization of QIBA and Profiles



SUMMARY

- Extraction of Quantitative Values From Imaging Systems is Rapidly Increasing
- Major Efforts Such the QIBA Biomarker Profile Development are Underway to Improve & Verify the Quality of Quantitative Data
- These Efforts Will Result in More Consistent Medical Diagnosis and Treatment Monitoring

ACKNOWLEDGEMENT

FDA Office of Women Health, Critical Path Initiative provided research funding support for some of the work reported in this presentation

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