Quantitative Imaging:

Tools and Approaches for Assessing Safety and Effectiveness

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Mission

The mission of the Center for Devices and Radiological Health (CDRH) is to protect and promote the public health.

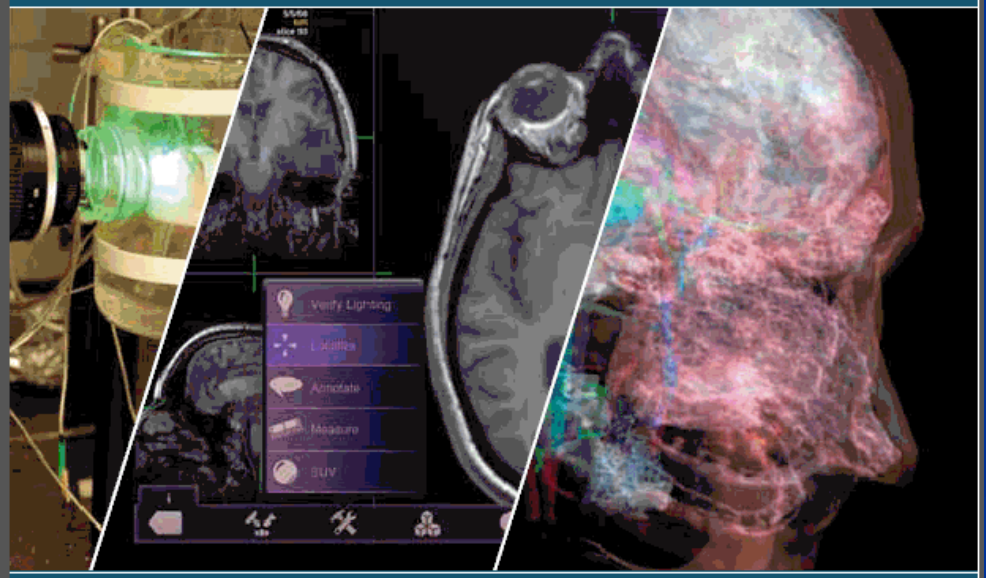
We assure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. We provide consumers, patients, their caregivers, and providers with understandable and accessible science-based information about the products we oversee.

We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.

FDA

Regulatory Science in FDA's Center for Devices and Radiological Health:

A VITAL FRAMEWORK FOR PROTECTING AND PROMOTING PUBLIC HEALTH



Regulatory science provides the tools, standards, and approaches needed to evaluate the safety, effectiveness, quality and performance of the products we regulate.

A. Advancing Medical Device Innovation and Evaluating New and Emerging Technologies

B. Improving Device Quality and Manufacturing

C. Analyzing Medical Device Performance

D. Improving Medical Device Safety

E. Developing Novel Ways to Use Clinical Data in Evaluating Medical Devices

F. Protecting Against Emerging Infectious Diseases and Terrorism

G. Improving Health of Pediatric and Other Special Populations.

http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/ucm274162.pdf

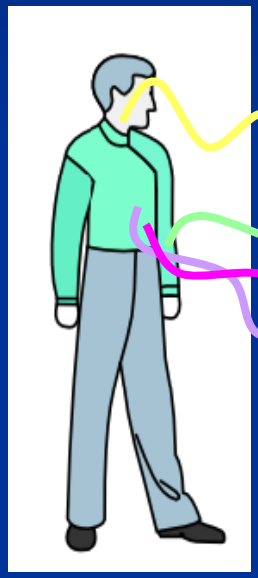
FDA's imaging research goal: Facilitate innovation and availability of new technologies through lab science

- Unique focus on assessment methodologies
  - Facilitate device evaluation, review, and improvement
- New statistical methods, phantom designs, simulation tools, and imaging clinical trial designs that reduce the need and expense of clinical trials and unnecessary patient radiation dose
- Independent data and analyses

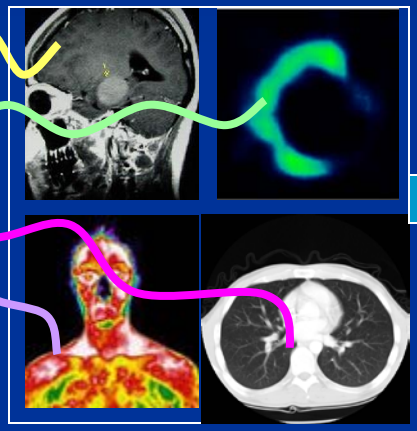
Image Science: Theory with Predictive Value

- Reasonably mature framework for evaluation and optimization of imaging systems for classification tasks
  - Decisions assigning images or patients to one or another health state or category
    - E.g., Presence or absence of a tumor; malignant vs. benign mass
- Next horizon: mensuration tasks
  - Estimation or Quantification of degree or extent of some quantity
    - E.g., Tumor size; cardiac ejection fraction; tissue stiffness
  - Output = estimate of quantity + uncertainty

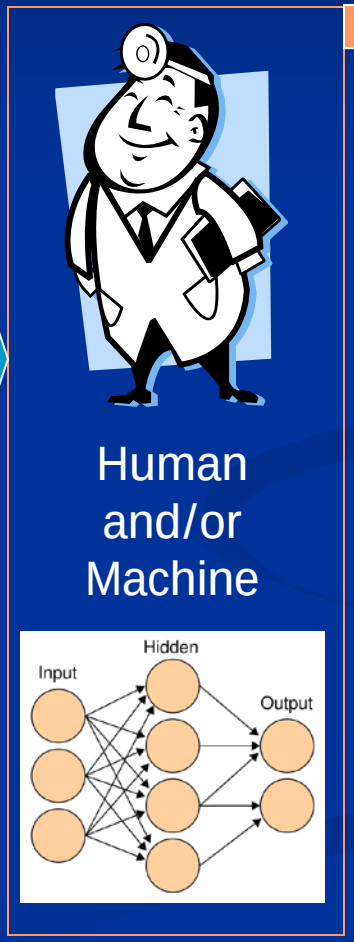
From Data to Decisions to Classification (ROC) Performance Measures

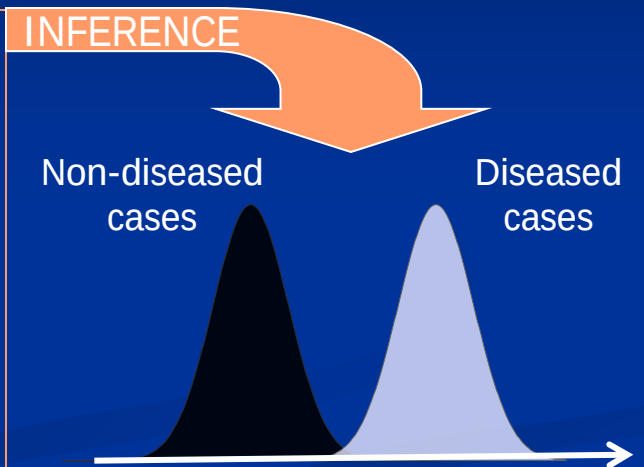


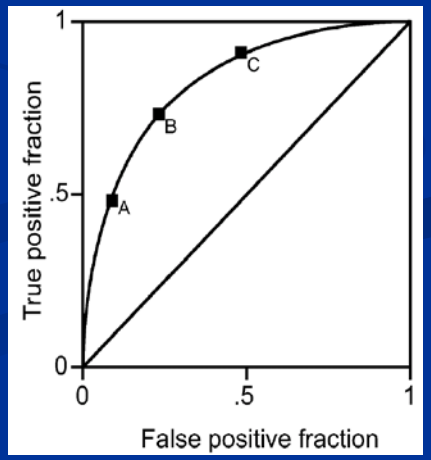
PATIENT
(object **f**)



DATA
(image **g**)

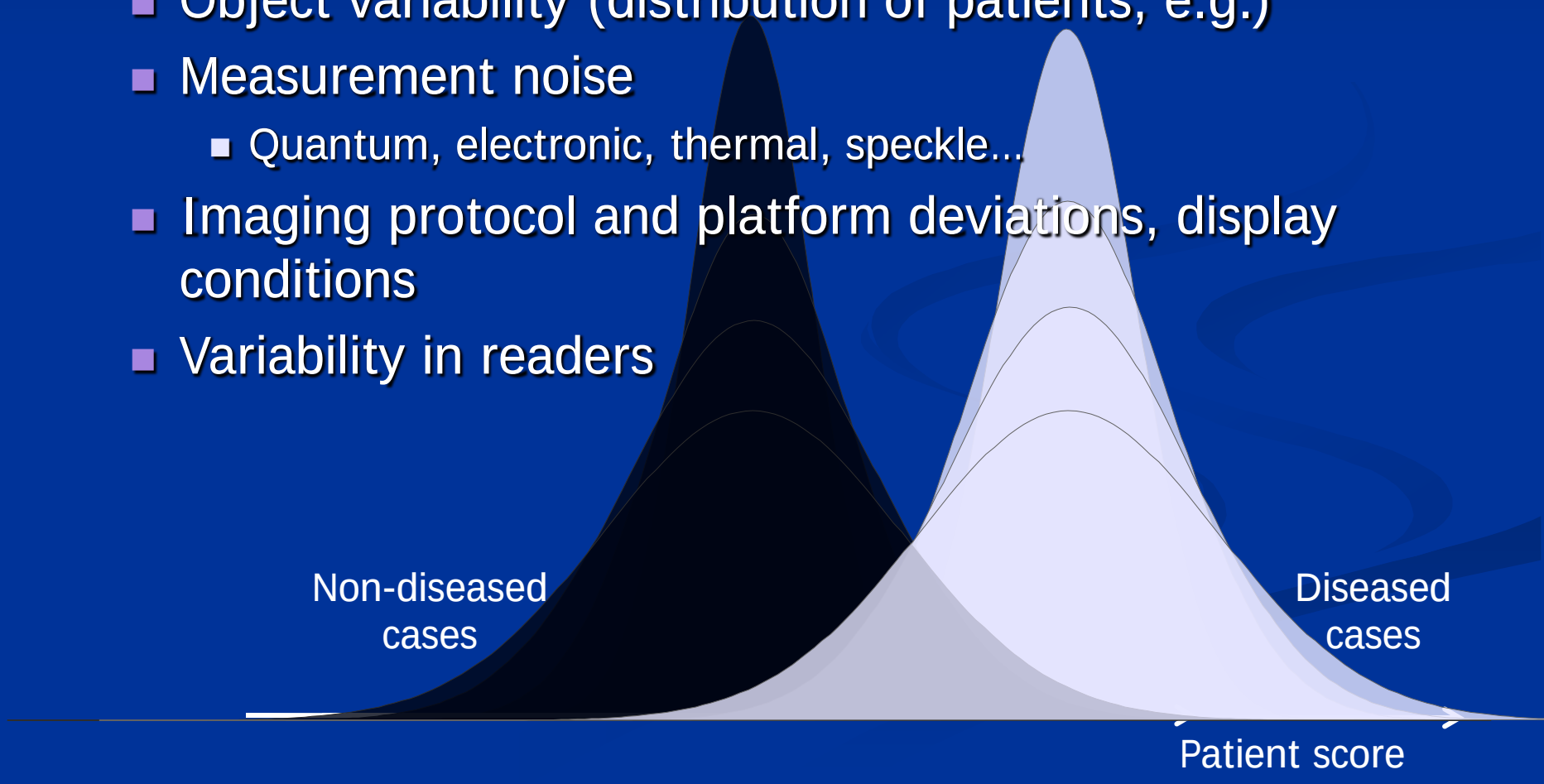






Assessment of Diagnostic Accuracy: Estimation of mean performance AND accounting for all sources of variability

- Spread in scores (image interpretations) due to
  - Object variability (distribution of patients, e.g.)
  - Measurement noise
    - Quantum, electronic, thermal, speckle…
  - Imaging protocol and platform deviations, display conditions
  - Variability in readers



To evaluate competing technologies in the midst of this variability:

- Requires random-effects or multivariate ROC
  - "MRMC" = Multi-Reader Multi-Case analysis
- Gives total uncertainty in ROC estimates from variability in images, observers (both skill and threshold) and their interactions
- Essential for testing significance of difference in competing modalities with multiple observers or classifiers.

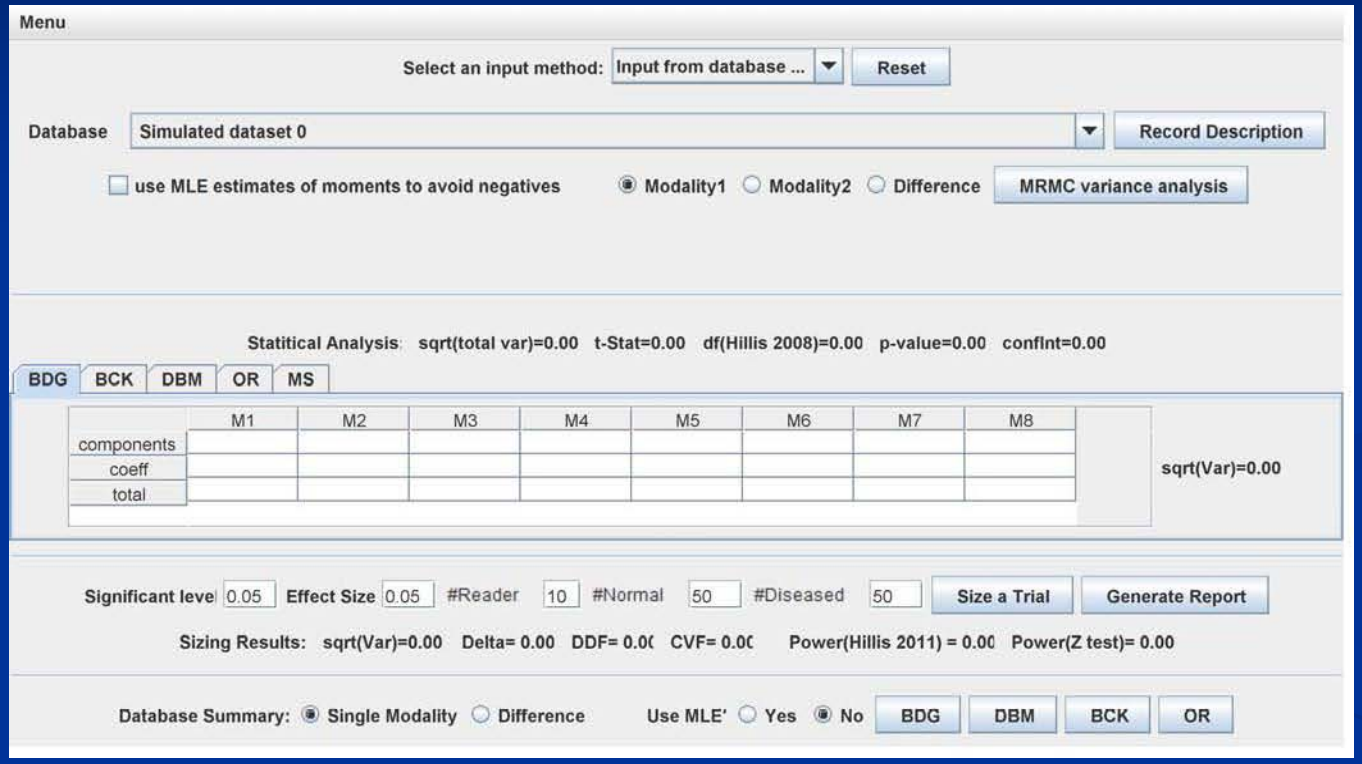
Special Review

Evaluating Imaging and Computer-aided Detection and Diagnosis Devices at the FDA

Brandon D. Gallas, PhD, Heang-Ping Chan, PhD, Carl J. D'Orsi, MD, Lori E. Dodd, PhD, Maryellen L. Giger, PhD, David Gur, ScD, Elizabeth A. Krupinski, PhD, Charles E. Metz, PhD, Kyle J. Myers, PhD, Nancy A. Obuchowski, PhD, Berkman Sahiner, PhD, Alicia Y. Toledano, ScD, Margarita L. Zuley, MD

Acad Radiol 2012; 19:463–477

iMRMC: Webpage and Software for Sizing an MRMC Clinical Trial



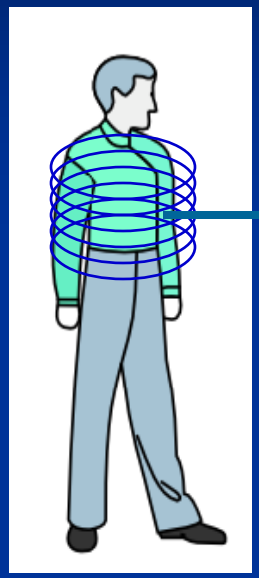
http://js.cx/~xin/index.html

- A resource for investigators designing a trial to compare two imaging modalities.
- Uses datasets from previous imaging trials to estimate power of new trial designs.
- Over time, database growth will benefit wide community of clinical trialists.

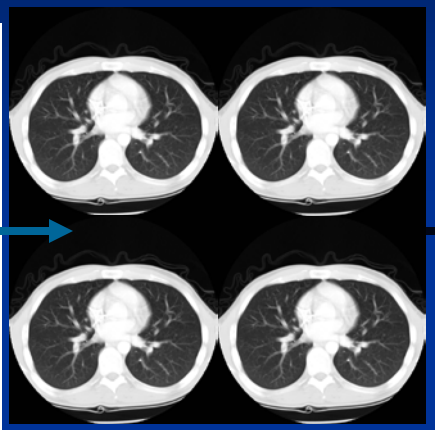
Image Science: Theory with Predictive Value

- Mature framework for evaluation and optimization of imaging systems for classification tasks
  - Decisions assigning images or patients to one or another health state or category
    - E.g., Presence or absence of a tumor; malignant vs. benign mass
- Next horizon: mensuration tasks
  - Estimation or Quantification of degree or extent of some quantity
    - E.g., Tumor size; cardiac ejection fraction; tissue stiffness
  - Output = estimate of quantity + uncertainty

Quantitation / Estimation: Output is continuous value

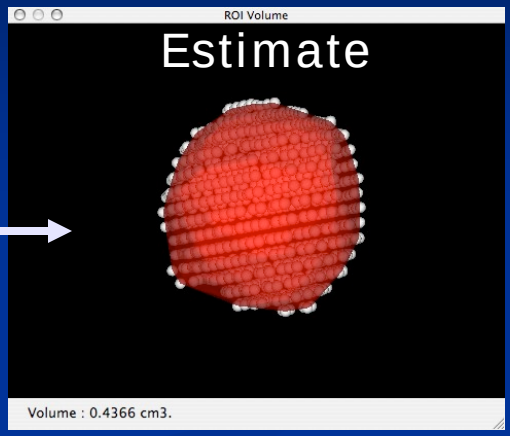


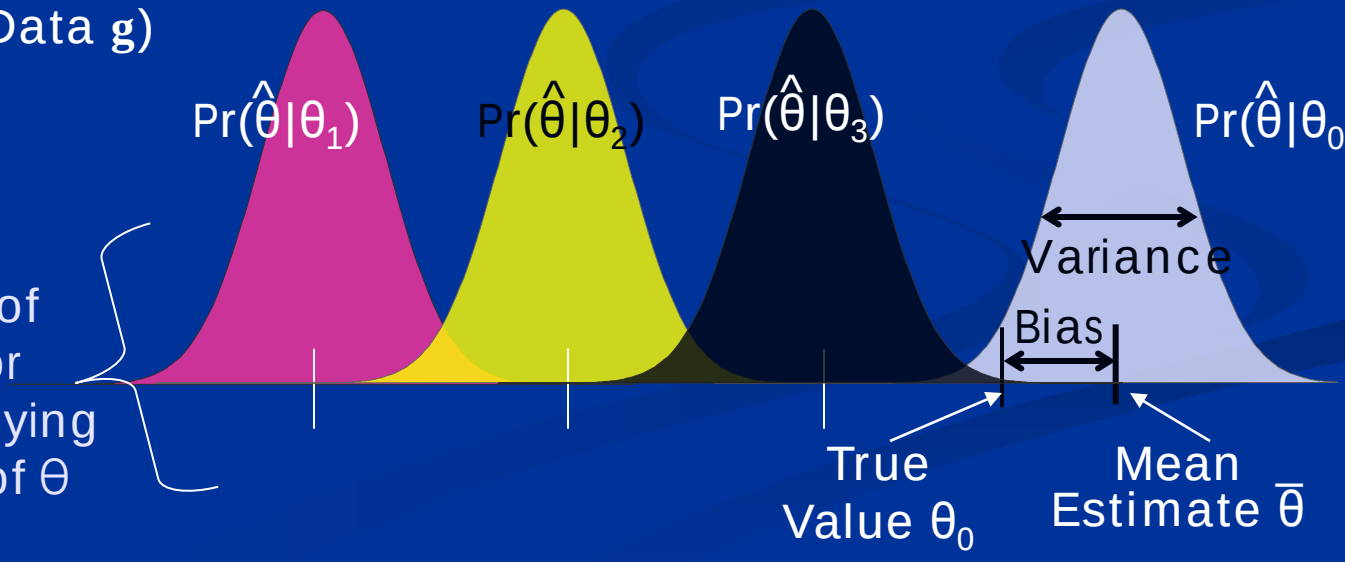
Patient
(Object **f**)



Images
(Data **g**)

Observer:
Human or Computer
Algorithm or Combination

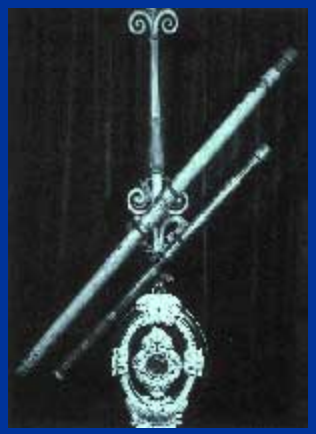


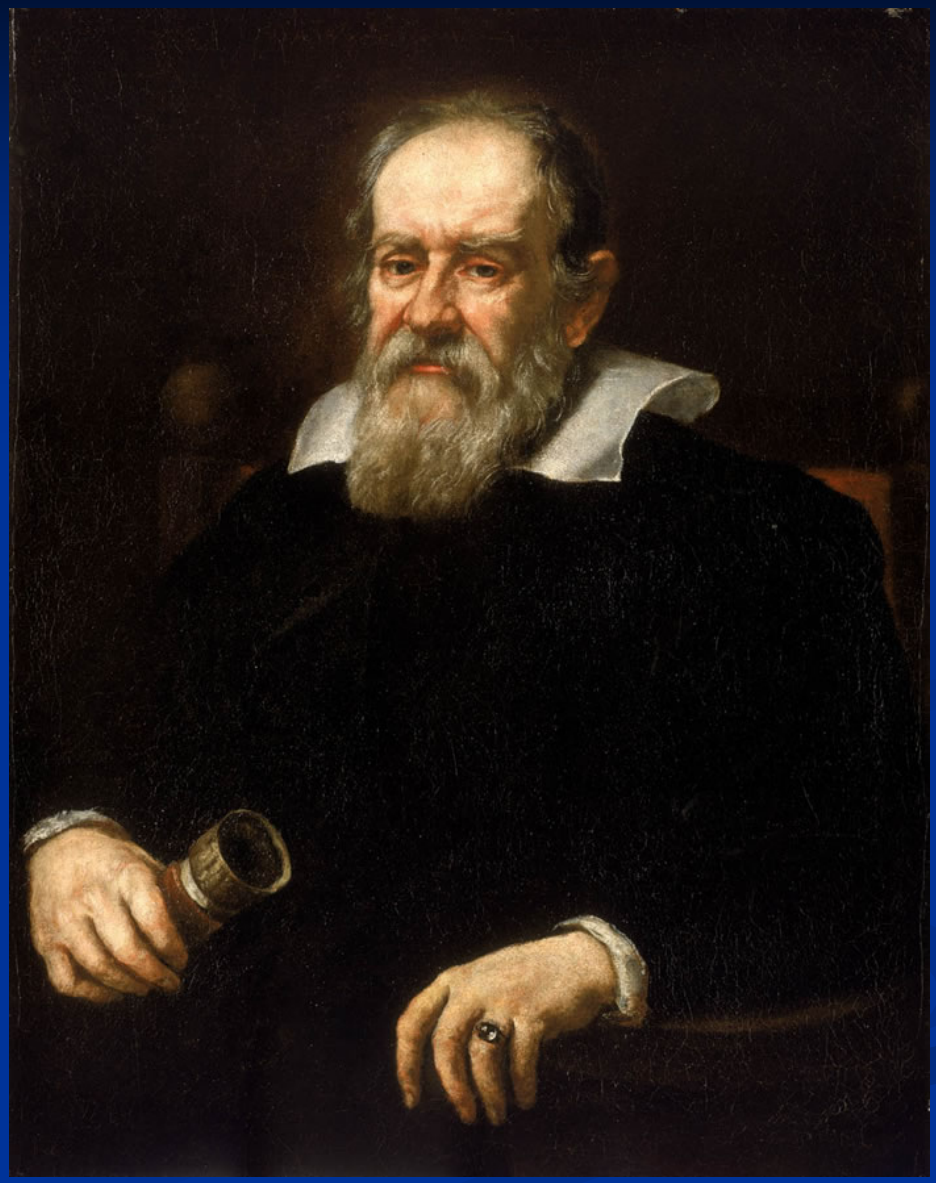


Distributions of
estimates for
different underlying
(true) values of θ

“Measure what is measurable,
and make measurable what is not so.”

-- Galileo Galilei
1564-1642





Imaging Tissue Properties

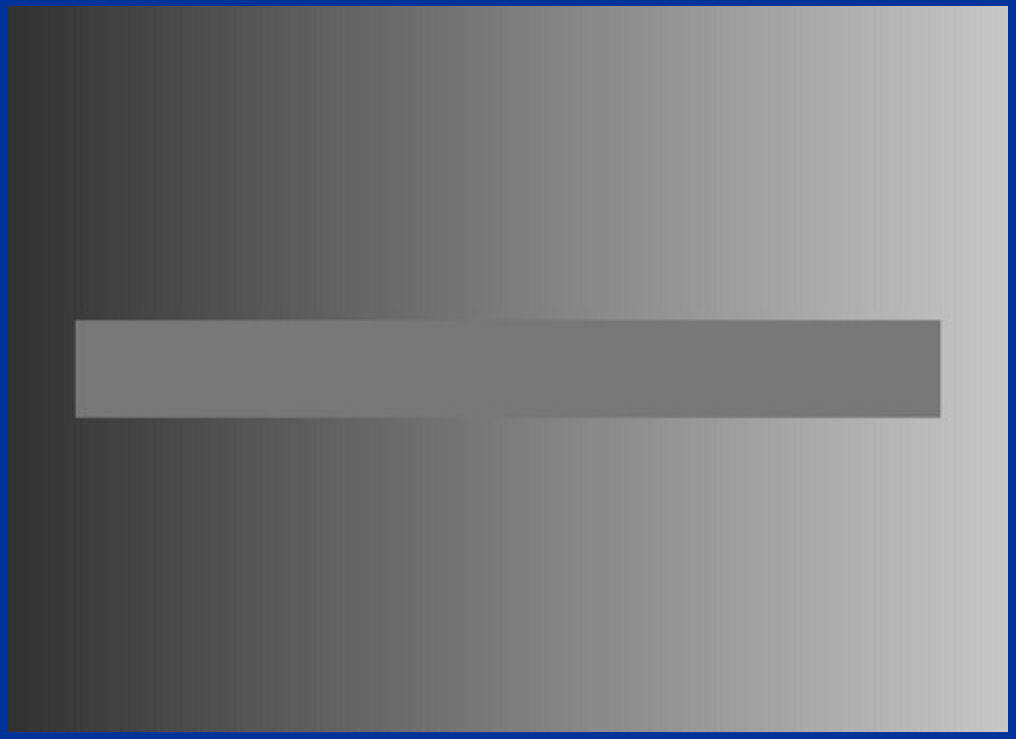
- Attenuation
  - Transmission x-ray
- Uptake & Concentration
  - Nuclear medicine
  - MRI (spin density)
  - MRS
  - IHC & FISH
- Electric, magnetic properties
  - Impedance tomography
  - MRI (magnetization
  - MRI (spin relaxation)
- Acoustic reflectance
  - Medical ultrasound
- Scattering properties
  - Medical ultrasound
  - Small-angle x-ray
- Index of refraction
  - Phase-contrast microscopy
- Elastic Properties
  - Ultrasound
  - MRI
- Field strength
  - Biomagnetic imaging
- Source strength
  - Fluorescence microscopy
- Gene expression
  - DNA chips, microarrays

Estimation of absolute levels is not perception's forte.

Relative comparisons are.

Advances in Digital Imaging and Computational Power ➔ enabling technologies for QI

Elicit more information from humans through tasks involving multiple comparisons.



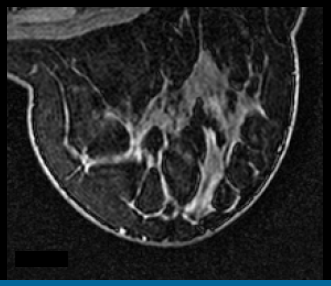
Sources of Images for Analysis

- Clinical images
  - Uncertainty analysis calls for repeat scans
    - Limitations include safety issues, unknown truth state
- Lab studies with phantoms
  - Allows investigation of range of system, pathology, and patient variables w/out concern for patient exposure
  - Realism continues to advance – enormous potential here!
- Simulation studies
  - Generation of images with realistic properties
  - Potential for hybrid studies in some circumstances
    - Simulated pathology in normal backgrounds, for example

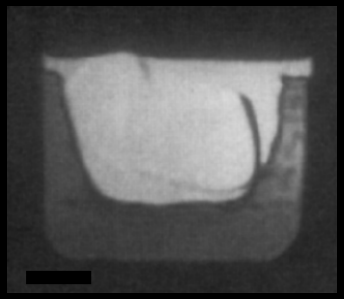
FDA/CDRH tissue-mimicking phantom for the quantitative evaluation of MRI and x-ray breast imaging: Reducing the need for trials involving patients and standardizing imaging protocols

CDRH phantom

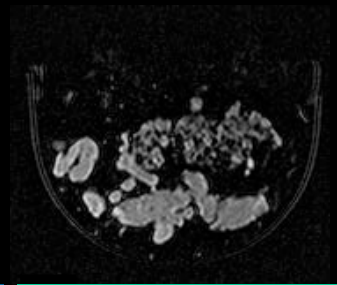
Human MRI

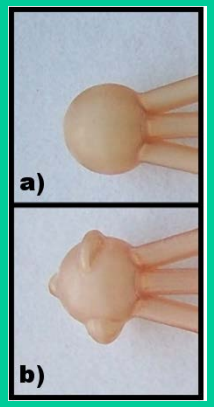


State-of-the-Art

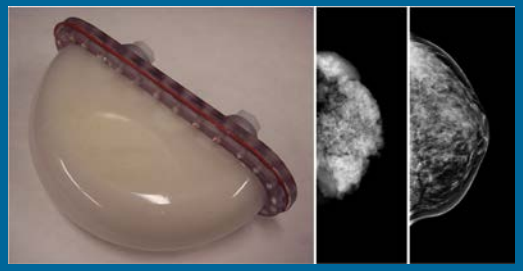


MRI of DIAM phantom





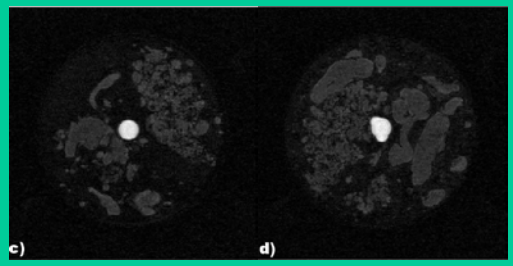
Compressed version of DIAM phantom



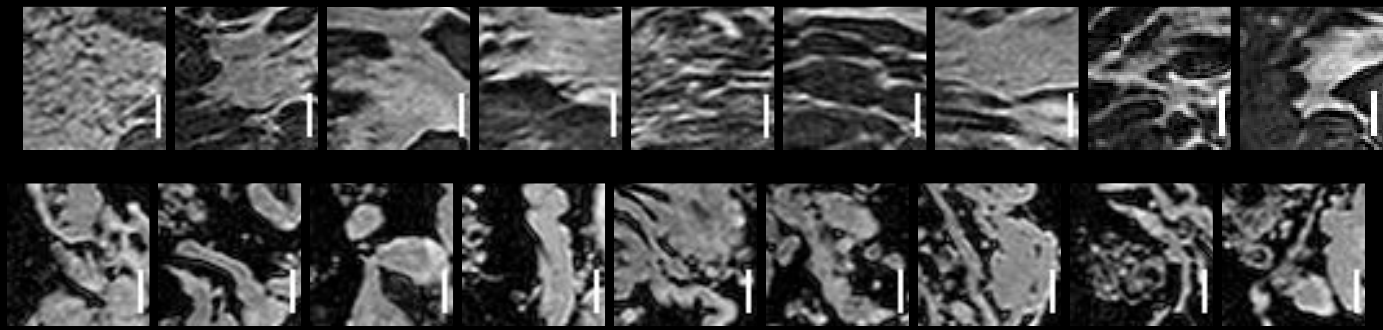
FFDM images of human breast and DIAM phantom

Dynamic lesions

Coronal Images with Lesion:
c) Sphere
d) Lobulated



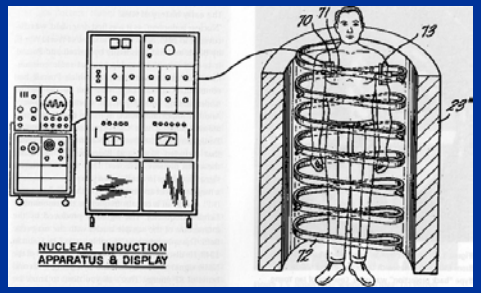
3.5 x 3.5 cm regions-of-interest taken from images of humans (top) and phantoms (bottom).



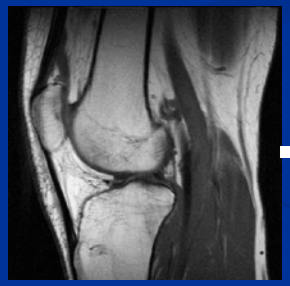
Open Source Simulation Tools

Computational modeling is an important tool for the understanding and evaluation of every stage of the imaging chain

Object



Imaging Hardware



Reconstruction

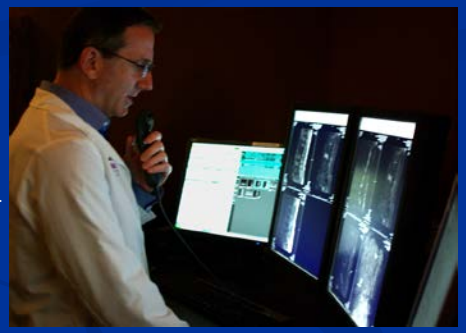
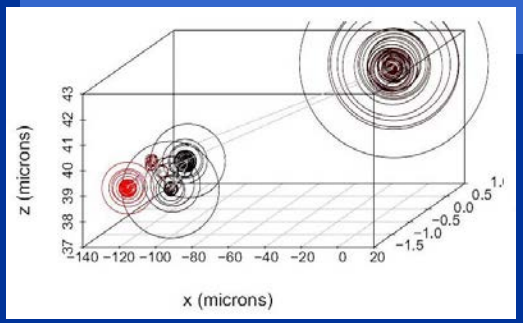


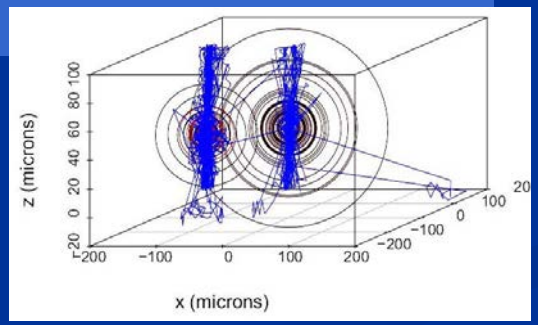
Image Display
Reader Interpretation

FDA/CDRH open source software tools: Models for imaging systems and patients

MANTIS: **M**onte Carlo x-r**A**y electro**N** and op**T**ical **I**maging **S**imulation

- Unique Monte Carlo for g, x, e, and optical photons.
- Open source and validated for noise and blur.
- Accurate physics models in range 50 eV – 1 GeV.
- Simultaneous scoring of images and location-specific dose.
- Over 400 downloads in 5 continents

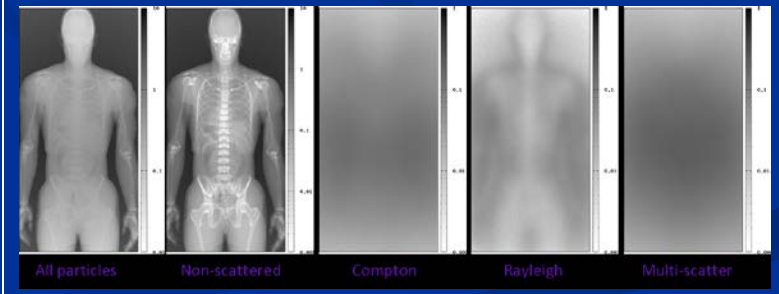




Particle paths in 3D columnar CsI: Energy depositions from single x ray (39.5 keV) with optical photon paths in blue.

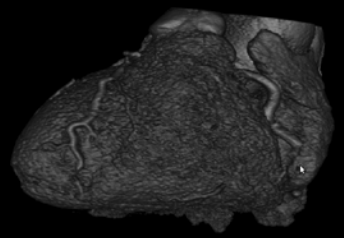
- Accurate measures of dose for new systems

- Optimized patient-specific imaging strategies



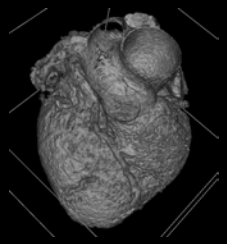
http://code.google.com/p/mantismc/

In Silico Heart Phantom: Development tool for evaluation of cardiac imaging methods



CT Scan

=

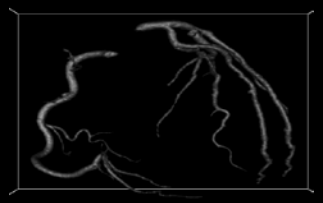


Envelope

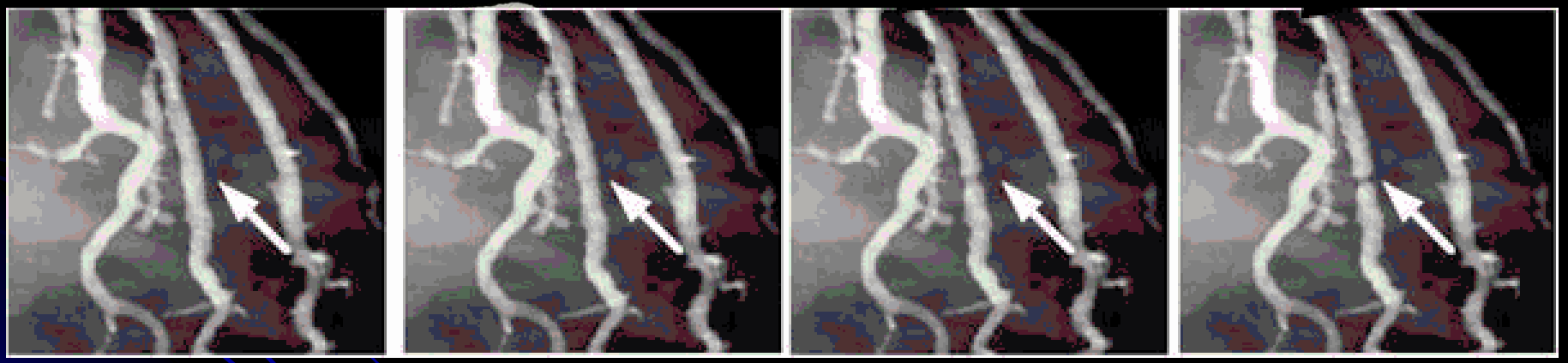
+

Ventricle

+



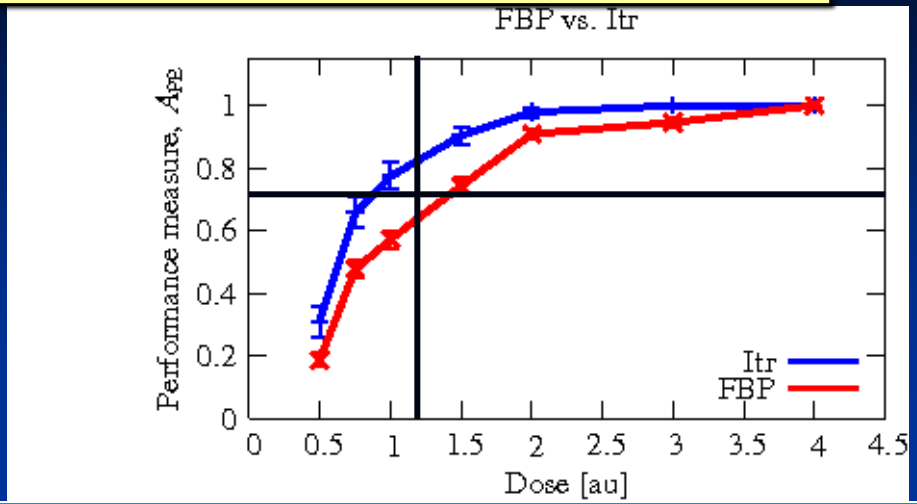
Coronary Artery

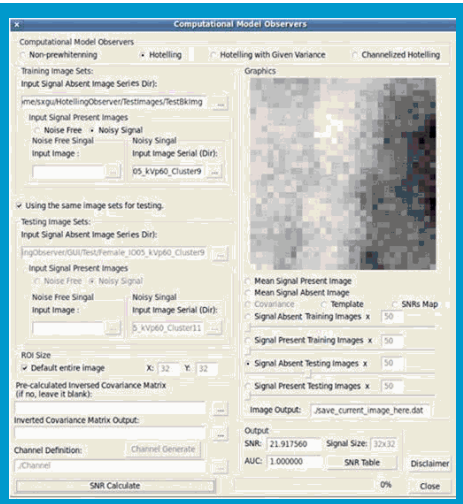


http://code.google.com/p/hades/

Iterative Reconstruction in CT

- Incorporation of all aspects of the imaging process in the reconstruction
- Significantly more information/photon
- Joint FDA-MITA task group developing framework for validation of claims:
  - Phantoms as stand-ins for the patient
  - Software for automated assessment
    - Rapid system evaluation without confounding factors of display and human inefficiency and variability
  - Statistical tools for measuring performance





MUMOC: Multiple Model Observer Calculator
Software tool (CDRH public resource)
for assessing image quality
http://code.google.com/p/mumoc/

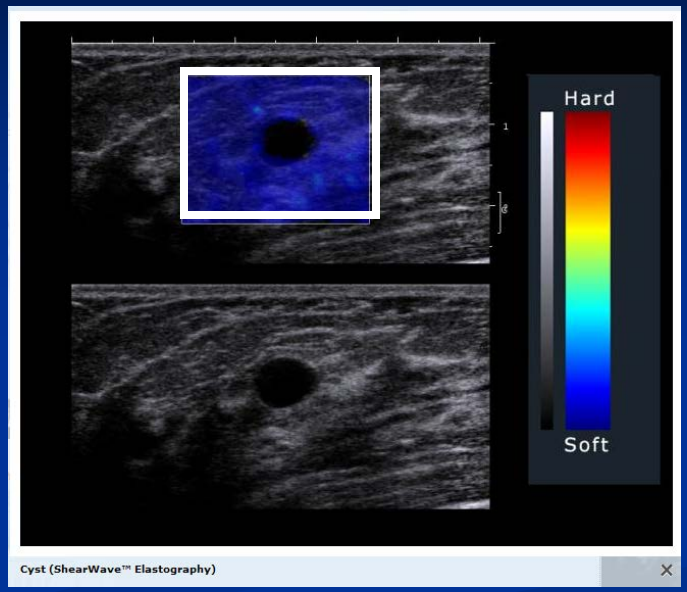
Quantitative Ultrasound

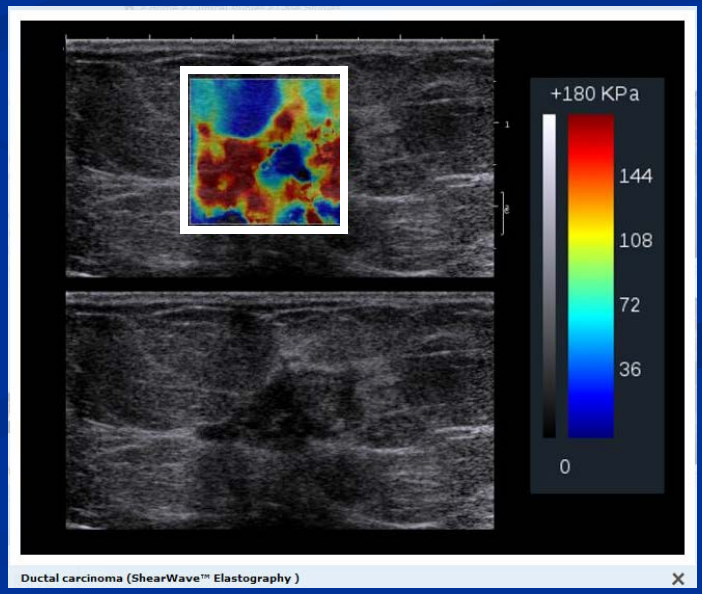
- A cyst (top) and a ductal carcinoma (bottom) may both appear dark on conventional gray-scale ultrasound.

- Ultrasound Shear Wave Speed (SWS), which is related to tissue stiffness, has been used to evaluate liver fibrosis and cancer.

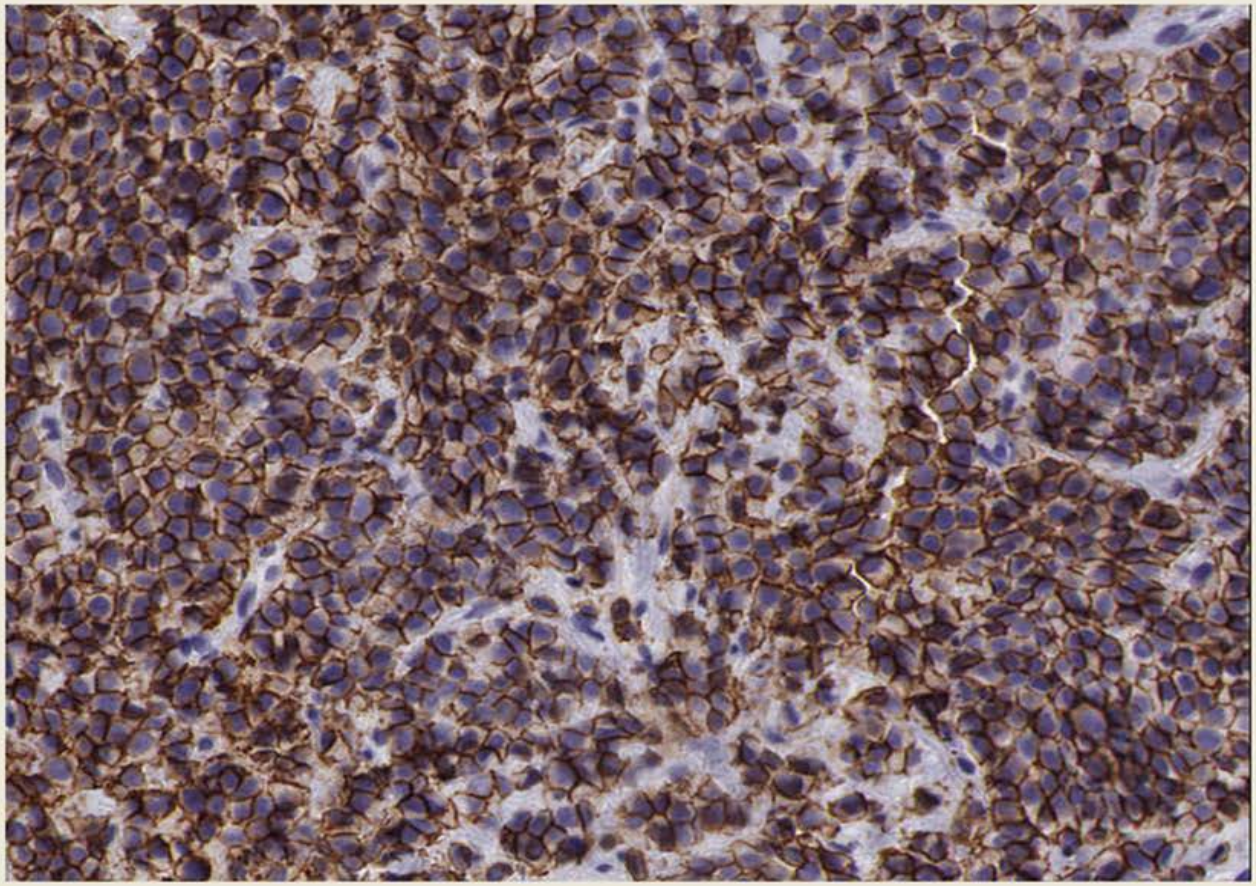
Quantitative Ultrasound

- The SWS color-overlay image reveals the stiffer nature of the ductal carcinoma (orange and red).
- The current challenge is to advance from images of relative SWS to quantitative measurements of SWS that may be compared against an absolute scale.
- CDRH scientists are working as part of the QIBA Ultrasound Shear Wave Speed Technical Committee to help advance this aim.





HER2 Assessment: computer-aided



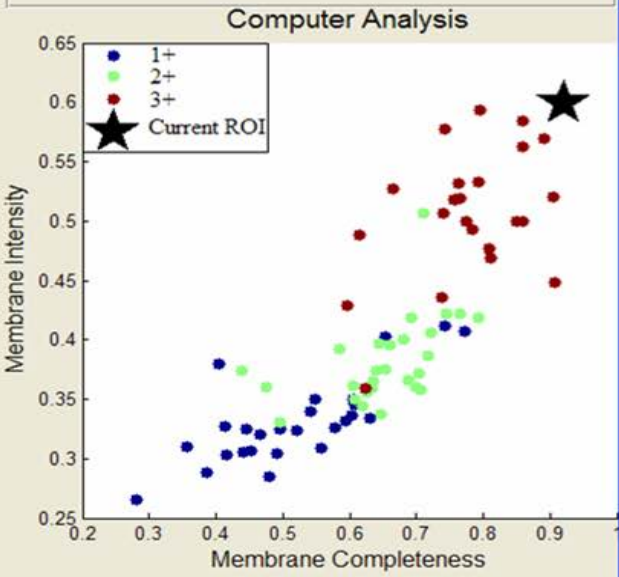
1+ | 2+ | 3+

Score: 3

Rating: 97

Pause | Next

ROI 1/500



The graph depicts computer score of slides and where the ROI viewed lays. Slides of the same score tend to group, however, the score is based on a pathologist score and as such, is not always accurate

Masmoudi, *et al*., "Automated quantitative assessment of HER-2/neu immunohistochemical expression in breast cancer," *IEEE Trans. Med. Imag.* 28:916, 2009.

Gavrielides, *et al*., "Observer variability in the interpretation of HER2/neu immunohistochemical expression with unaided and computer-aided digital microscopy," *Archives of Path. Lab. Med.* 135:233, 2011.

CDRH Network of Experts

- Vetted network of outside scientists, clinicians and engineers who will provide rapid access to scientific, engineering, and medical expertise to supplement existing knowledge and expertise within CDRH.

- Three external organizations in the current pilot program:
  - American College of Cardiology
  - American Institute for Medical and Biological Engineering
  - The Society of Thoracic Surgeons

- Draft SOPs are available online:
  - Network of Experts - Expert Utilization Standard Operating Procedure
  - Network of Experts - Expert Enrollment Standard Operating Procedure

Essentiality of Resource Sharing: Harnessing the Greater Network

- All data – longitudinal, multimodality, w/outcomes
  - New culture of sharing can break down the privacy wall
  - Give-A-Scan is a great step toward this!
- Raw data off imagers – cultivate patient demand
  - Publicize current barrier to innovation.
    Widespread patient demand for access to their data might be tipping point?
- Software, phantom designs/recipes, reader data…

Quantitative Imaging is Measurement Science

- Many aspects of it – particularly the statistical, foundational ones – are mature, especially for disease detection and binary classification tasks.
- Facilitation of innovation complements FDA's mission of promoting and protecting public health
- Patients, clinicians, scientists, and regulators all have significant roles to play
  - Resource sharing (data, software tools, phantoms, etc.)
  - Collaboration and consensus development

Acknowledgments

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- Xin He
- Robert Jennings
- Iacovos Kyprianou
- Eugene O'Bryan
- Rui Peng
- Nick Petrick
- Lucretiu Popescu
- Berkman Sahiner
- Frank Samuelson
- Diksha Sharma
- Keith Wear
- Rongping Zeng