1. Standards for Imaging Endpoints in Clinical Trials

2. Manufacturing of PET Radiopharmaceutical Products

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NIH CAMPUS, BETHESDA, MARYLAND

This presentation to FDA/SNM/RSNA Imaging Workshop is supported by the

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Integrating the Imaging Biomarker Enterprise: A Roadmap Proposal Developed by Stakeholders

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• Right treatment for right patient at right time
• Imaging biomarkers for cost-effective patient care
• Avoid trial and error treatment

Premise

- Images are inherently quantitative.

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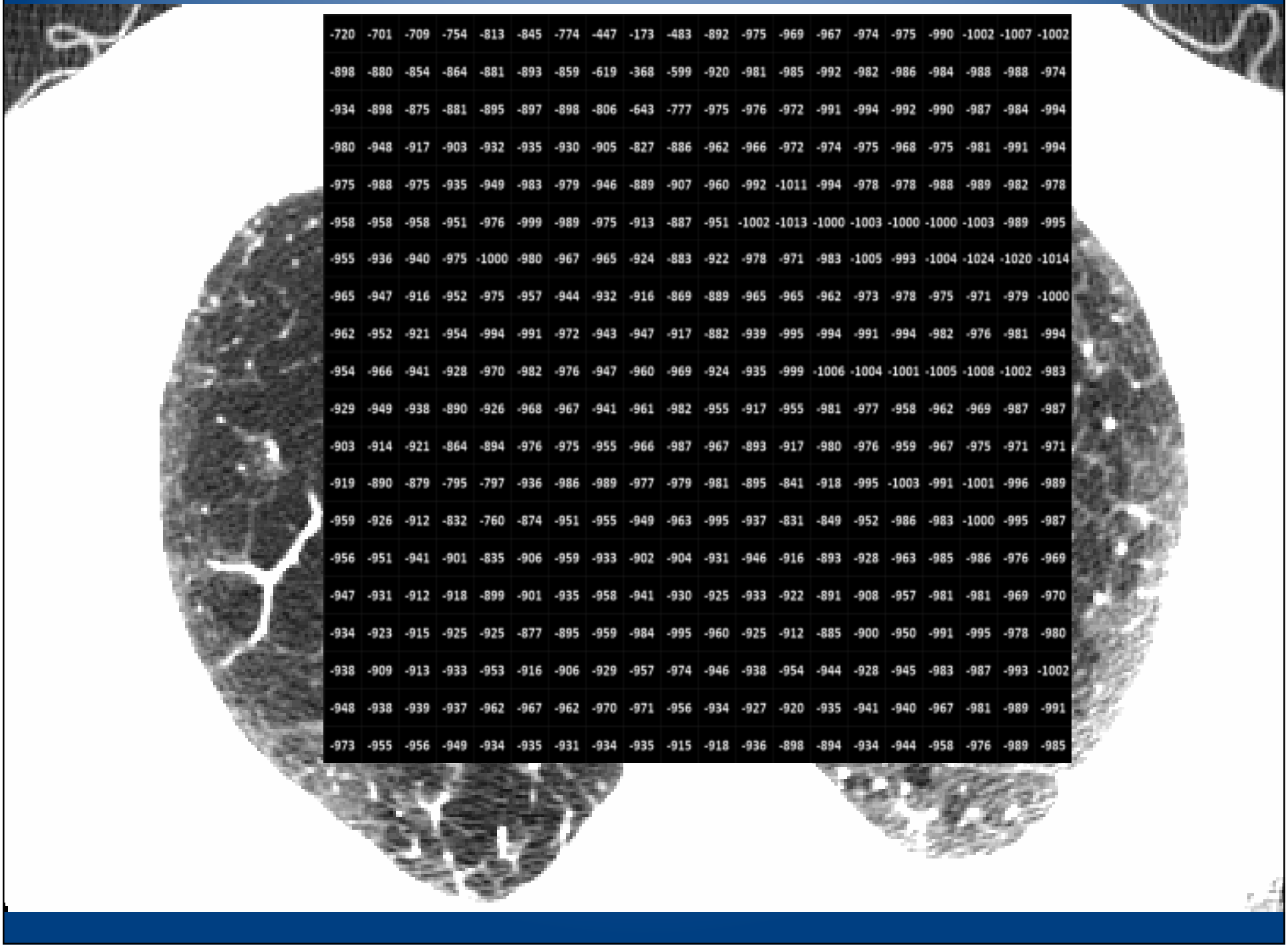
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Premises

1. Images are inherently quantitative.
2. Challenges are to:
   - Improve the relevant signal in each pixel/voxel
   - Extract the relevant numbers.

What quantification is possible with current imaging modalities?

- CT signal is proportional to density and has high spatial resolution.
  - Accurate morphologic measurements
  - Basic tissue characterization
  - Quantitative functional information with contrast
- PET [SPECT] signal is proportional to atomic decay events and has high sensitivity.
  - Radiopharmaceutical metabolism must be understood in order to relate signal magnitude to the labeled substance of interest.
  - SUV is semi-quantitative, but useful.

What quantification is possible with current imaging modalities (cont'd)?

- MR signals are complex: but they are quantitatively, although non-linearly, related to T1 and T2 relaxation phenomena, as well as proton density distribution.
  - With calibration and standardization, MRI techniques can be devised in which the gray scale is quantitatively meaningful
- Ultrasound signals are also complex: attenuation, refraction, reflection, bulk tissue properties and tissue elasticity all influence the recorded signal.
  - Quantitative distance, elasticity and Doppler measurements can be extracted.
- Optical methods vary. Quantification of photon properties similar to CT or PET.

RSNA Interests

- RSNA is interested in fostering more emphasis on quantitative imaging in clinical care
- Facilitating ***imaging as a biomarker in clinical trials*** helps RSNA move this agenda forward.

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A biomarker is:

(ideally) a measurement.

(less ideally) a qualitative observation.

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To advance QI, RSNA supports a group of related activities:

- Educate its membership about QI

(*Toward Quantitative Imaging*)

- Improve the radiology research infrastructure

(*CTSA-Imaging Working Group*)

- Promote inter-organizational communication about imaging biomarker activities

(*Imaging Biomarkers Roundtable*)

- Support efforts to improve the accuracy and precision of imaging biomarkers

(*Quantitative Imaging Biomarkers Alliance -QIBA*)

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Standardization and Optimization of Image Acquisition

Quality Control Concepts

Equipment and Software Standardization

Phantoms

QIBA Background

- Began May, 2008
- Mission: Improve value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time.
  - Build "measuring devices" rather than "imaging devices".

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Factors Affecting QIBA Scope

- **NIST definition of a measurement result:** "A measurement result is complete only when accompanied by a quantitative statement of its uncertainty. The uncertainty is required in order to decide if the result is adequate for its intended purpose and to ascertain if it is consistent with other similar results."
- **FDA:** "A biomarker must be qualified for its intended purpose"

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QIBA Committee Leadership

Steering Committee

Dan Sullivan, MD, Co-Chair (Duke; RSNA)
Andy Buckler, MS, Co-Chair (Buckler Biomedical LLC)
Kevin O'Donnell, PhD, Co-Chair (Toshiba)

PET/CT Quantitative Committee

Richard Frank, MD, PhD, Chair (GE Healthcare)
Richard Wahl, MD PhD, Co-Chair (Johns Hopkins)
Paul Kinahan, PhD, Co-Chair (University of Washington)
David Clunie, MBBS, Subcommittee Co-Chair (RadPharm)
Jeffrey Yap, PhD, Quality Control Metrics and Covariates Rationale Technical Subcommittee Chair (Dana Farber Cancer Institute)
Timothy Turkington, PhD, ROI Definitions Technical Subcommittee Chair (Duke University Medical Center)
Ling X. Shao, PhD, Software Tracking Technical Subcommittee Chair (Philips Healthcare)

COPD/Asthma Committee

Phil Judy, PhD, Chair (Brigham & Women's)
David Lynch, MD, Co-Chair (National Jewish)

CT Quantitative Committee

Andrew Buckler, MS, Chair (Buckler Biomedical LLC)
P. David Mozley, MD, Co-Chair (Merck)
Lawrence Schwartz, MD, Co-Chair (Memorial Sloan-Kettering Cancer Center)
Nicholas Petrick, PhD, Group 1A Subcommittee Chair (FDA)
Michael McNitt-Gray, PhD, Group 1B Subcommittee Chair (UCLA)
Charles Fenimore, PhD, Group 1C Subcommittee Chair (National Institute of Standards and Technology (NIST)
Anthony Reeves, PhD, Volcano (Cornell University)

MRI Quantitative Committee

Gudrun Zahlmann, PhD, Chair (Roche)
Sandeep Gupta PhD, Co-Chair (GEHC)
Ed Jackson, PhD, Co-Chair (MD Anderson Cancer Center)
Mark Rosen, MD, PhD, Clinical Test-Retest Subcommittee (UPenn)
Daniel Barboriak, MD, Data Simulation (Synthetic Data) Subcommittee (Duke University Medical Center)

fMRI Committee

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Jeffrey Petrella, MD, Co-Chair (Duke)
Joy Hirsch, PhD, Co-Chair (Columbia)

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QIBA Process

Quantitative Imaging Biomarkers Alliance

RSNA

- Identify sources of variability
- Collect “groundwork” data
- Devise mitigation strategies
- Write and promulgate “Profiles”.

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Result: QIBA Profiles

- A QIBA Profile is a document with 3 parts.
- It tells a user what can be accomplished by following the Profile. (Claims)
  - E.g. you will be able to detect volume changes of greater than 10% in Stage I lung cancer nodules which are 5mm in diameter or greater.

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QIBA Profile (2)

- It tells a vendor what they must implement in their product to state compliance with the Profile. (Details)
  - E.g. to comply, the scanner must be able to:
    - » scan a Mark-324 Chest Phantom, identify the smallest resolvable target, display the diameter of that target
    - » demonstrate resolving targets at least as small as 2mm diameter on the Mark-324 phantom
    - » scan patients according to the ACRIN NLST acquisition protocol
  - E.g. to comply, the quantification application must be able to:
    - » segment a nodule (automatically or manually), derive the volume, store it in a DICOM object
    - » run a user through a set of test data with known volumes and at the end display an accuracy score

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QIBA Profile (3)

- It may also tell the user staff what they must do for the Profile Claims to be realized. (Details)
  - E.g. to comply, the site CT techs must be able to:
    - » scan the patient within 10 minutes of contrast injection
  - E.g. to comply, the radiologist must be able to:
    - » achieve a score of 95% or better using their segmentation application on the LIDC test set.

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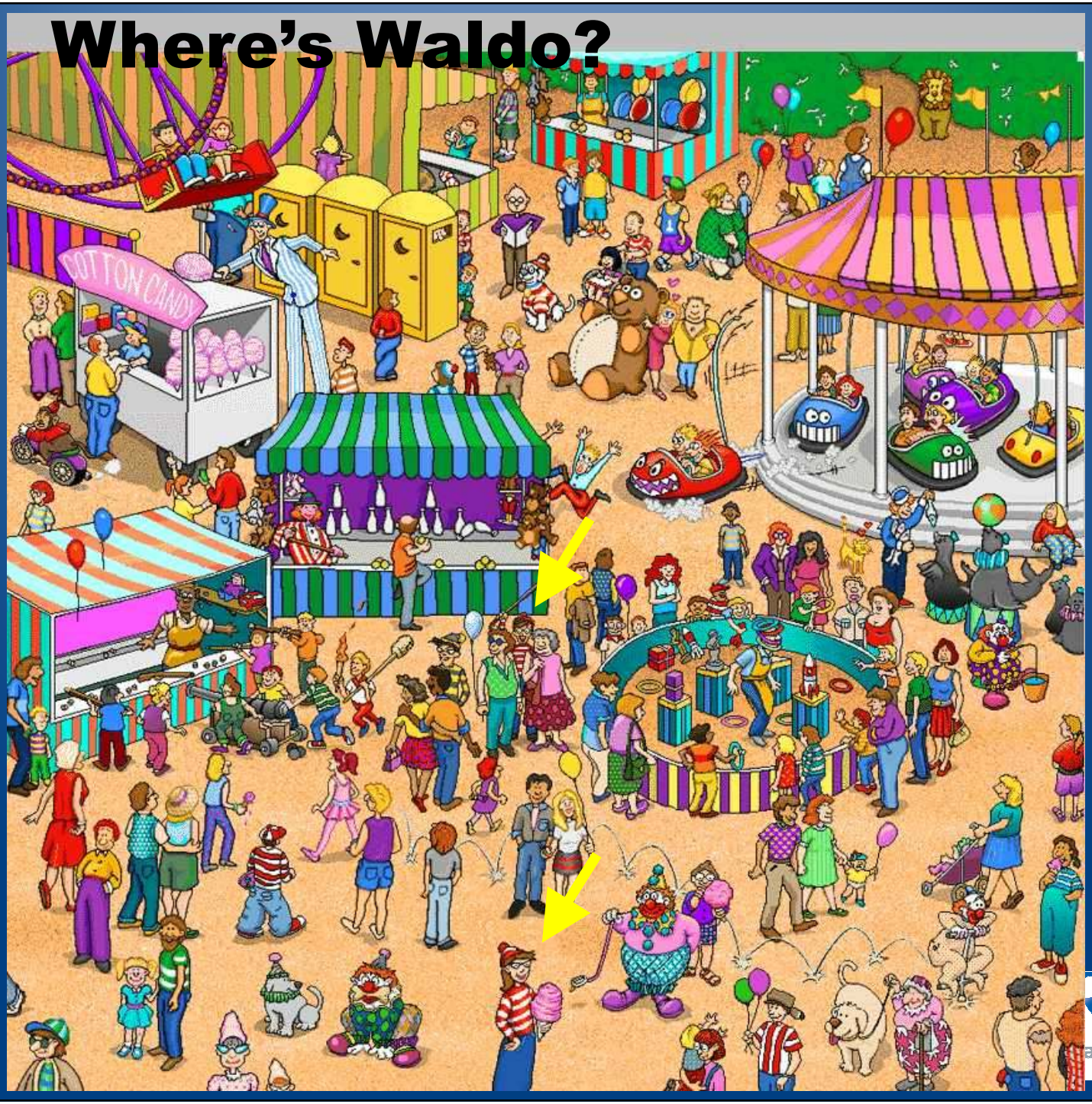
Image Interpretation

Independent Read Design

Delineation of sources of variability

Potential approaches for resolving variability

Where's Waldo?



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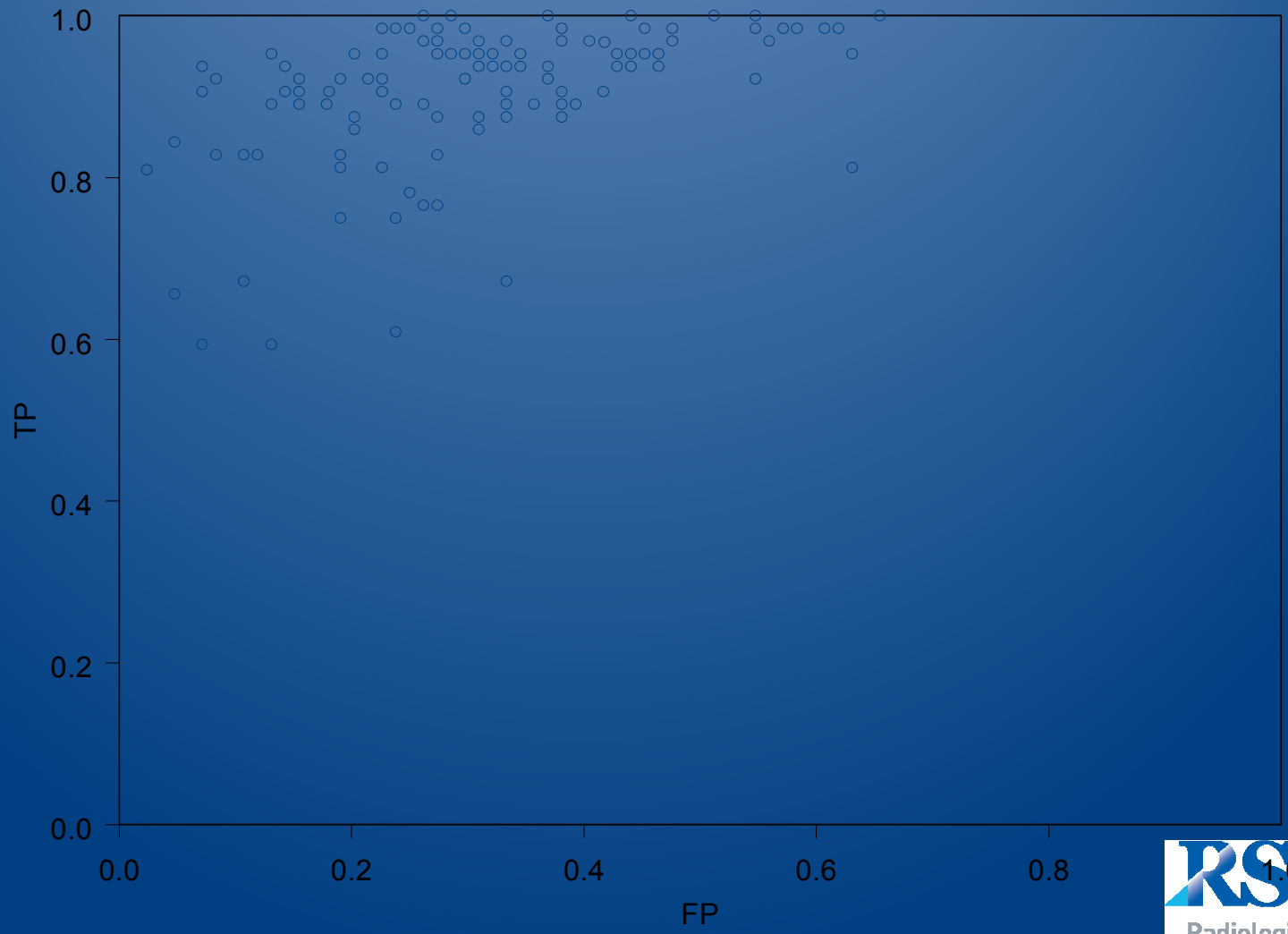
Operating points of 108 radiologists reading same mammograms



Beam, Layde, Sullivan Arch Intern Med 1996; 156:209-213

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Subjective Interpretations:

1. Necessary, because Artificial Intelligence (AI) has limitations.
2. The trained, experienced eye-brain system often can deal with the infinite biological variability better than AI, and …
3. … can normalize for many artifacts and machine variation better than AI.
4. But the variability inherent in qualitative interpretations is a huge problem. The addition of objective, quantitative information can help minimize that variability.

Management of Imaging Data

Acquisition
Display
Transmission
Storage
Analysis

CTSA Imaging Working Group

3 Subcommittees:

- Cores (Structure; Administration; Financing)
- Imaging Informatics (Integrate existing tools)
- Clinical Trials (UPICT – Uniform Protocols for Imaging in Clinical Trials)

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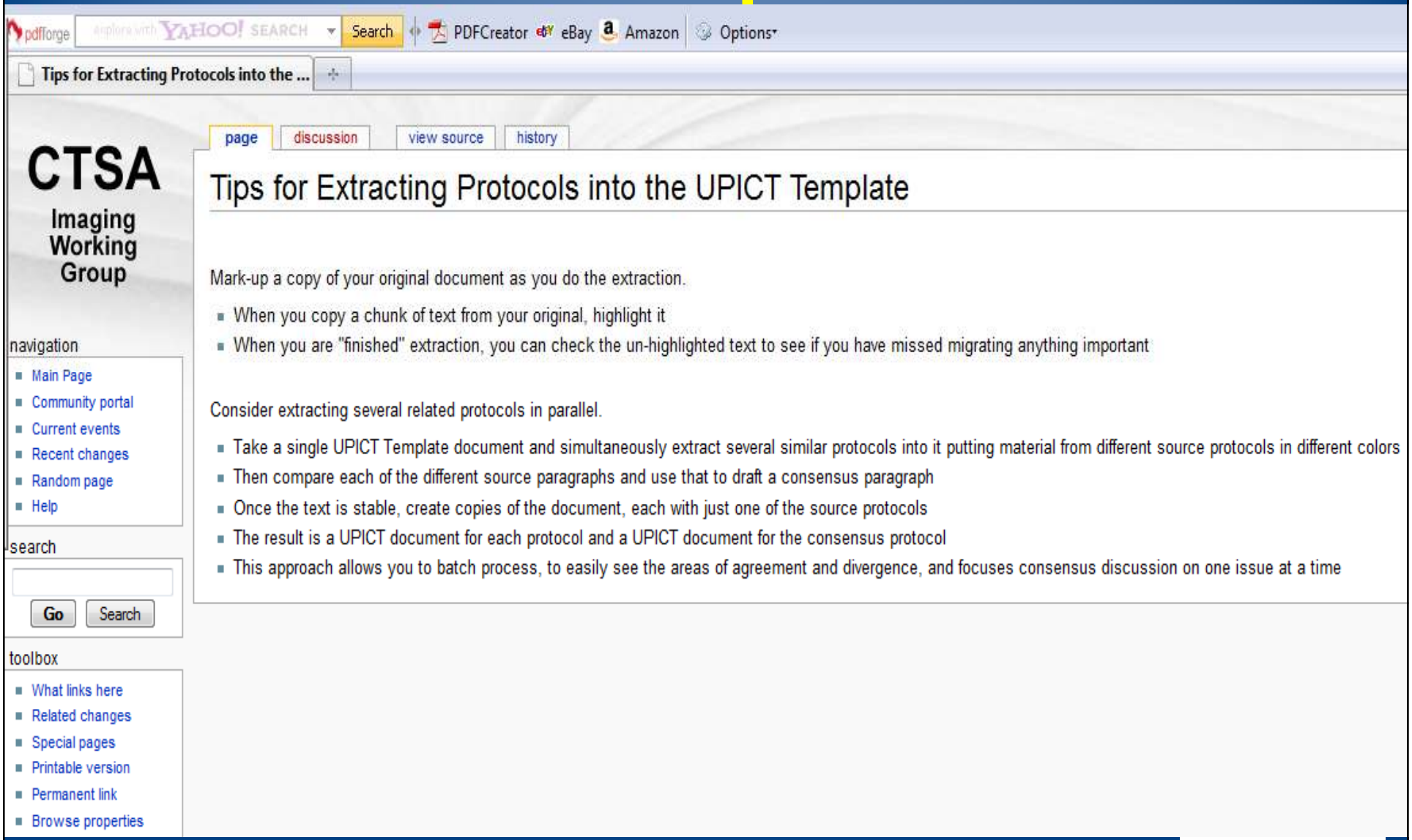
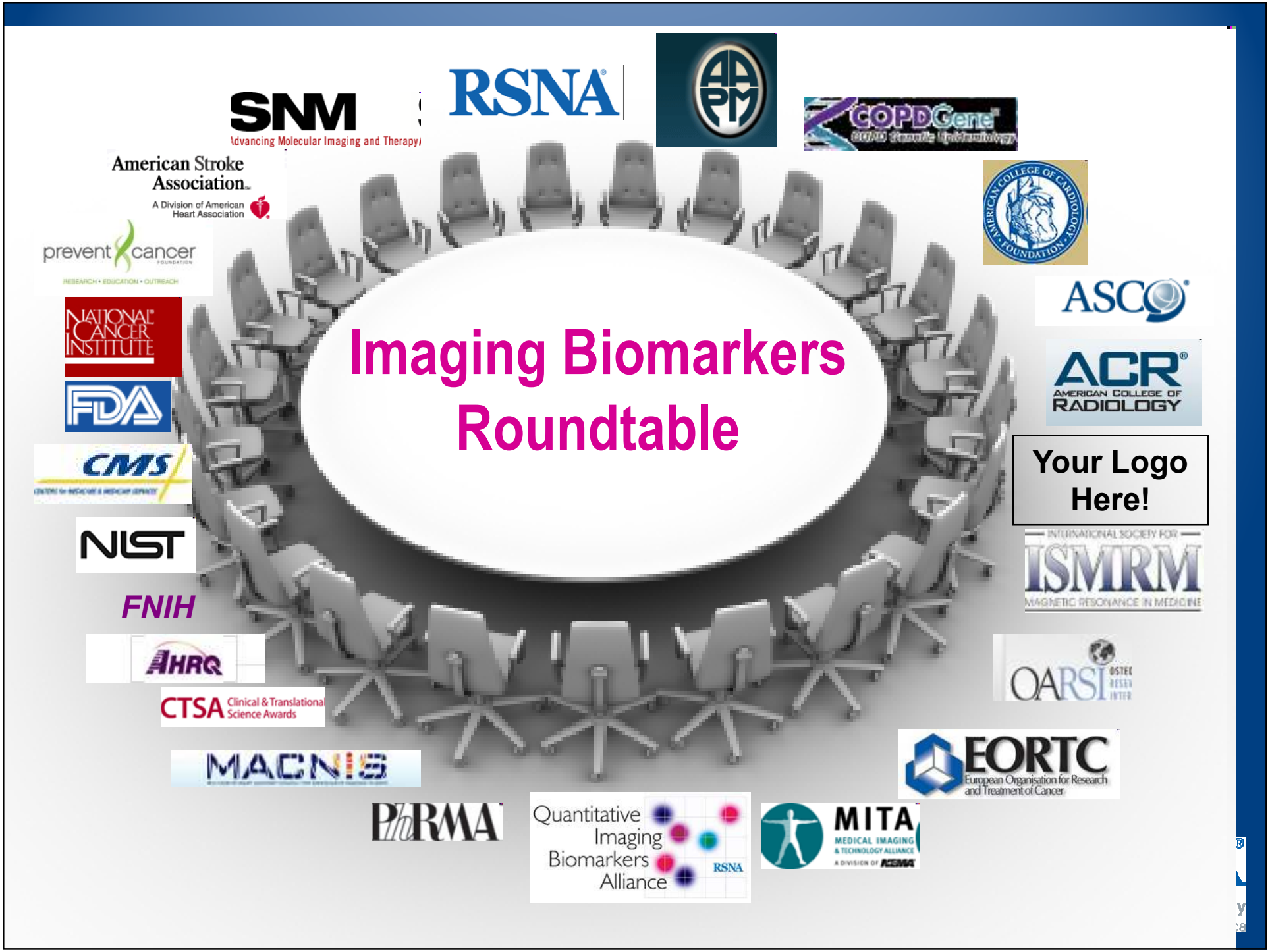
UPICT Template




SNM
Advancing Molecular Imaging and Therapy
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AAPM
COPDGene
American Stroke Association
A Division of American Heart Association
American College of Cardiology Foundation
prevent cancer
RESEARCH • EDUCATION • OUTREACH
ASCO
National Cancer Institute
ACR
American College of Radiology
FDA
Imaging Biomarkers Roundtable
CMS
Your Logo Here!
NIST
International Society for Magnetic Resonance in Medicine
ISMRM
FNIH
AHRQ
OARSI
CTSA Clinical & Translational Science Awards
MACNIB
EORTC
European Organisation for Research and Treatment of Cancer
PhRMA
Quantitative Imaging Biomarkers Alliance
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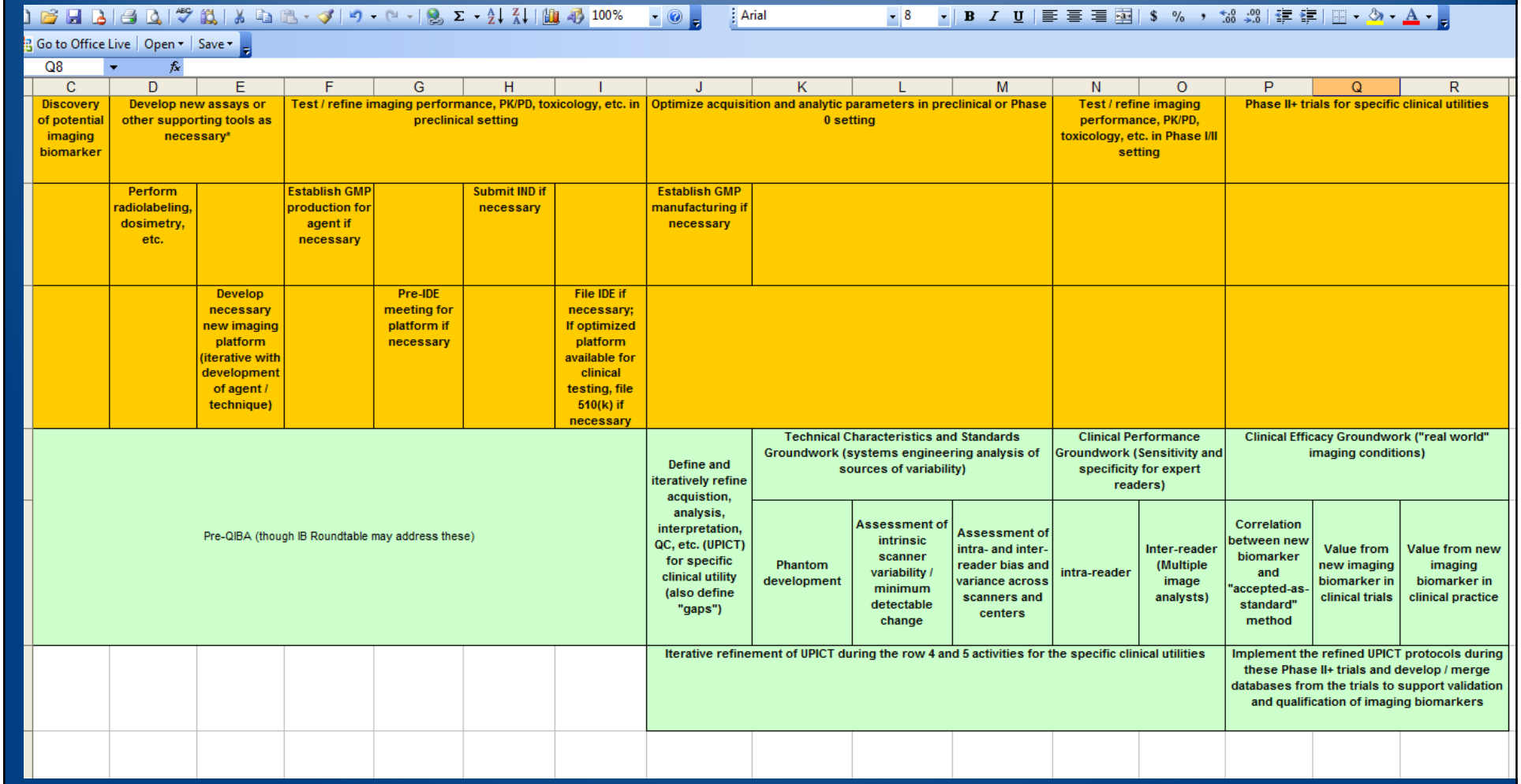
MITA
Medical Imaging & Technology Alliance
A Division of NEMA

Generic Roadmap



Discovery of potential imaging biomarker	Develop new assays or other supporting tools as necessary*		Test / refine imaging performance, PK/PD, toxicology, etc. in preclinical setting				Optimize acquisition and analytic parameters in preclinical or Phase 0 setting				Test / refine imaging performance, PK/PD, toxicology, etc. in Phase I/II setting		Phase II+ trials for specific clinical utilities		
	Perform radiolabeling, dosimetry, etc.		Establish GMP production for agent if necessary		Submit IND if necessary		Establish GMP manufacturing if necessary								
		Develop necessary new imaging platform (iterative with development of agent / technique)		Pre-IDE meeting for platform if necessary		File IDE if necessary; If optimized platform available for clinical testing, file 510(k) if necessary									
Pre-QIBA (though IB Roundtable may address these)							Define and iteratively refine acquistion, analysis, interpretation, QC, etc. (UPICT) for specific clinical utility (also define "gaps")	Technical Characteristics and Standards Groundwork (systems engineering analysis of sources of variability)			Clinical Performance Groundwork (Sensitivity and specificity for expert readers)		Clinical Efficacy Groundwork ("real world" imaging conditions)		
								Phantom development	Assessment of intrinsic scanner variability / minimum detectable change	Assessment of intra- and inter-reader bias and variance across scanners and centers	intra-reader	Inter-reader (Multiple image analysts)	Correlation between new biomarker and "accepted-as-standard" method	Value from new imaging biomarker in clinical trials	Value from new imaging biomarker in clinical practice
							Iterative refinement of UPICT during the row 4 and 5 activities for the specific clinical utilities						Implement the refined UPICT protocols during these Phase II+ trials and develop / merge databases from the trials to support validation and qualification of imaging biomarkers		

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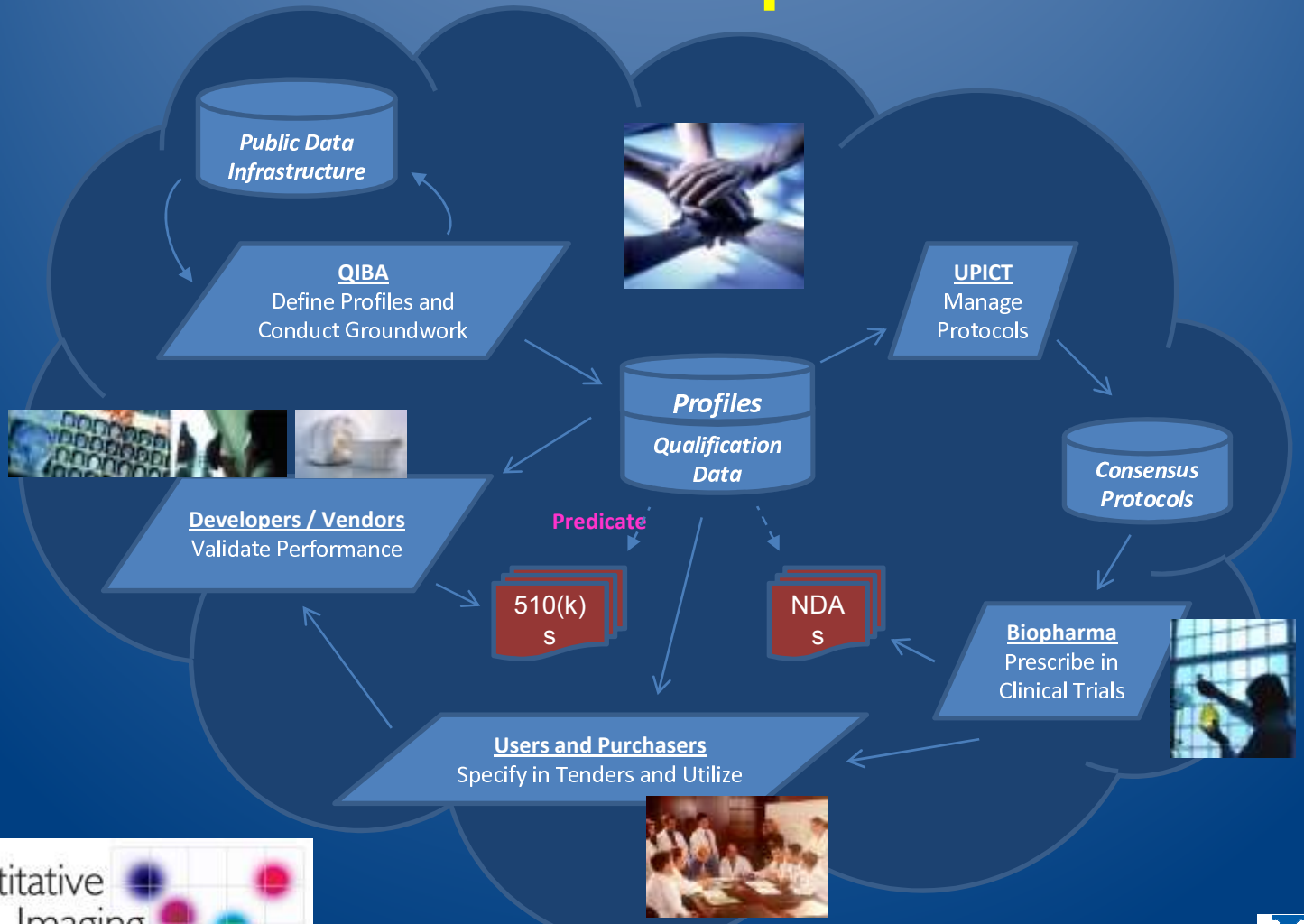
Integrating the Imaging Biomarker Enterprise



Quantitative Imaging Biomarkers Alliance
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FDA Approval Vs. Qualification

Approval (or Clearance) **is acknowledgement that, for the stated claim, the drug or device has been shown to have acceptable safety and effectiveness.**

Qualification **is acknowledgement that, within a stated context of use, the measurement can be relied upon to have a specific interpretation in drug development and regulatory decision-making.**

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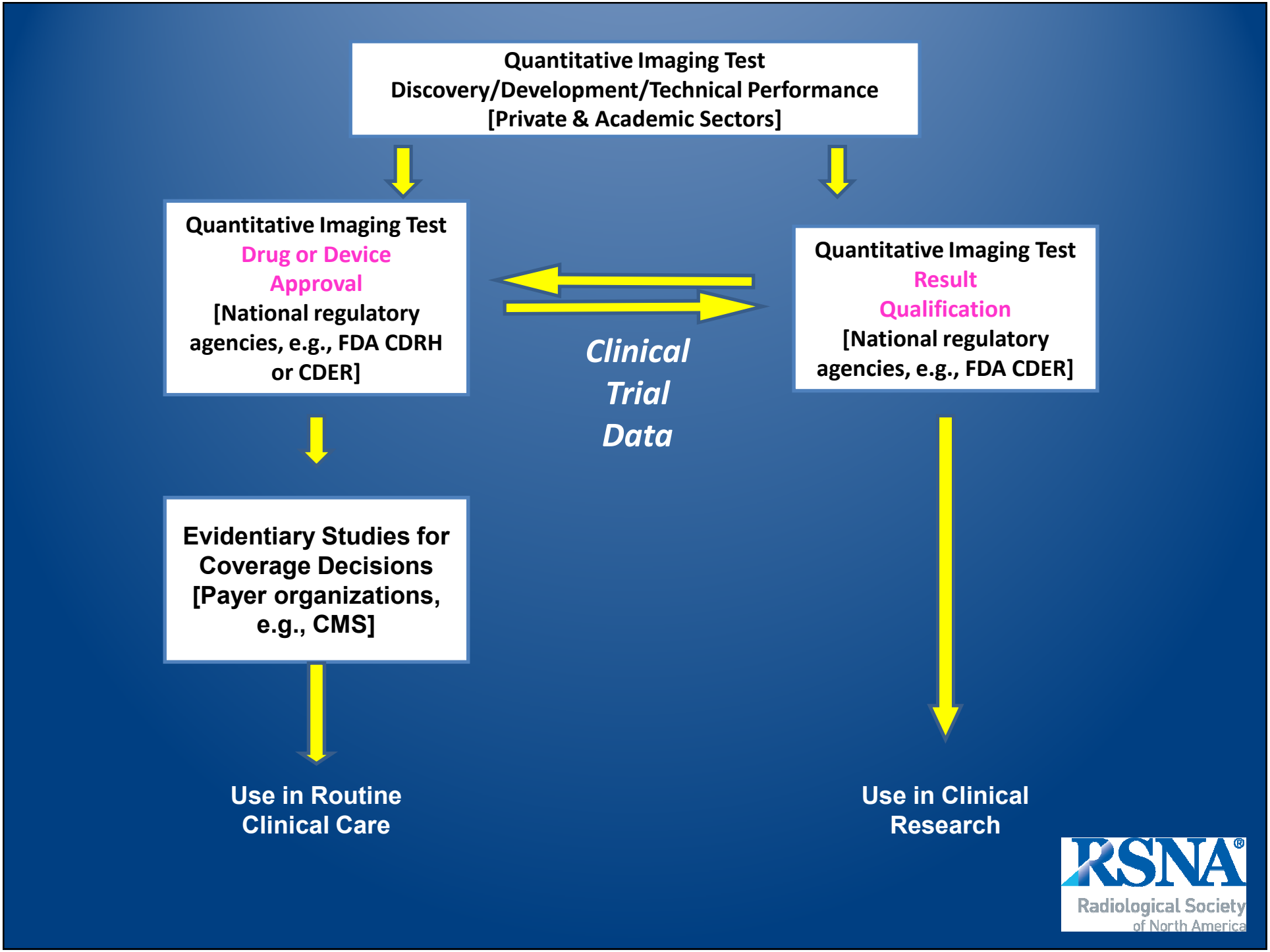
Quantitative Imaging Test
Discovery/Development/Technical Performance
[Private & Academic Sectors]
Quantitative Imaging Test
Drug or Device
Approval
[National regulatory agencies, e.g., FDA CDRH or CDER]
Quantitative Imaging Test
Result
Qualification
[National regulatory agencies, e.g., FDA CDER]
Clinical Trial Data
Evidentiary Studies for Coverage Decisions
[Payer organizations, e.g., CMS]
Use in Routine Clinical Care
Use in Clinical Research
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Proposed Imaging Biomarker Qualification Process

Sponsoring Collaborative

A) Declaratory information about the class of tests drawn from test validation sources.

B) Phantom and other controlled condition support material for “stand-alone” assessment and required initial and ongoing quality control specifics.

C) Implement and refine protocols for the intended use

D) Process map detailing steps contemplated to support qualification of the biomarker

E) Clinical Performance Groundwork to characterize sensitivity and specificity for readers using the imaging test when interpreted as a biomarker under limited conditions.

F) Clinical Efficacy Groundwork to qualify biomarker as a surrogate endpoint in "real world" imaging conditions

G) Draft advice guidance on incorporation of imaging biomarker into clinical trials.

H) Promote use of the imaging biomarker through education.

Request Letter

Briefing Document

Full Data Package

Signoff Letter

National Regulatory Agencies

CONSULTATION AND ADVICE PROCESS

1) Informal discussion of a potential biomarker sponsor with the Biomarker Qualification Coordinator (BQC).

2) Biomarker Sponsor submits to BQC a written request for qualification of an exploratory biomarker.

3) BQC evaluates qualification request.

4) Biomarker Qualification Management Team (BQMT) accepts or declines the sponsor’s request to proceed with qualification process.

5) Biomarker Qualification Review Team (BQRT) requests briefing document from biomarker sponsor.

6) BQ Project Manger schedules face-to-face meeting between the sponsor and the BQRT.

7) BQRT evaluates the briefing document and prepares for the Biomarker Qualification face-to-face meeting.

8) BQRT and Sponsor BQDS Meeting.

9) BQRT identifies and requests additional data from sponsor.

REVIEW PROCESS

10) BQRT receives full data package and review period begins

11) BQRT writes draft biomarker qualification review.

12) BQC routes the draft biomarker qualification reviews to all Offices

13) BQ Project Manager schedules the BQ review for presentation at a CDER Regulatory Briefing.

14) CDER Regulatory Briefing presentation and discussion is held.

15) CDER Office Directors make decisions to accept or reject the BQRT recommendations.

16) BQC drafts letter for sign-off by the Director of CDER communicating to the sponsor the results of the biomarker qualification.

Take-home Points:

1. Images are inherently quantitative.
2. Eye-brain system for visual analysis is very good for some things.
3. In practice, qualitative interpretations have been very useful.
4. However, the imaging field is systematically moving toward increasingly rigorous quantification.
5. Extracting quantitative information from images is challenging, but doable.

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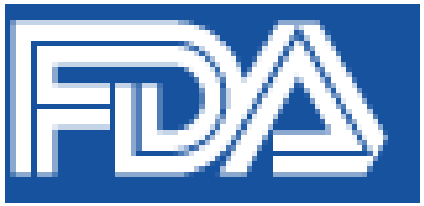

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