Quantitative Imaging Biomarker Alliance

RSNA's QIBA VOLUMETRIC CT: ROLLING TOWARDS QUALIFICATION

Lung Cancer Workshop VIII

2-3 May 2011

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PRINCIPAL LOGISTICAL AND FINANCIAL SUPPORT PROVIDED BY RSNA

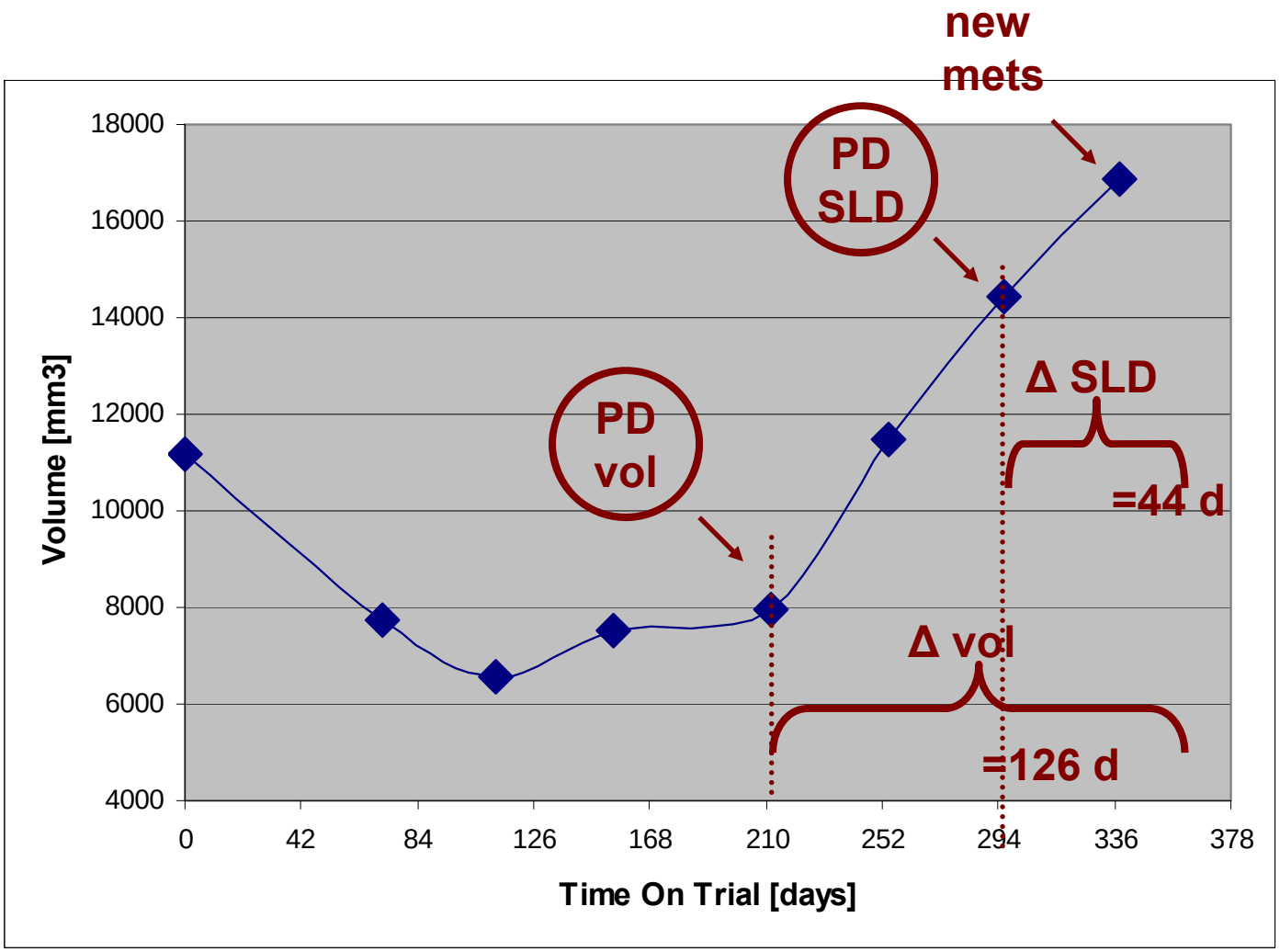
There are a Significant Number of Errors Made When Using Diameter Measurements

	Reader	Measure	RD Between 1st And 2nd Measures Median (Mean min–mean max)	Mean No. Misclassifications	% of Cases Misclassified
Response	Intra	RECIST	5.01 (0.00–44.44)	1.2 per reader	**3.64**
		WHO	8.87 (0.18–69.70)	1.0 per reader	**3.03**
	Inter	RECIST	10.07 (0.00–51.93)	4.9 per reader	**14.85**
		WHO	16.88 (0.97–71.95)	3.3 per reader	**10.00**
Progression	Intra	RECIST	5.30 (0.00–59.64)	3.0 per reader	**9.09**
		WHO	9.76 (0.18–126.76)	7.2 per reader	**21.82**
	Inter	RECIST	11.32 (0.00–116.91)	10.1 per reader	**30.61**
		WHO	20.56 (1.00–287.88)	14.3 per reader	**43.33**

Diameter measurements were proposed as a surrogate for volume at a time when there was no reasonable way to measure volumes.

Now that we can measure them, how much better can they do?

Longitudinal Volumetry Can Determine Outcomes Earlier than the Diameter Approximation

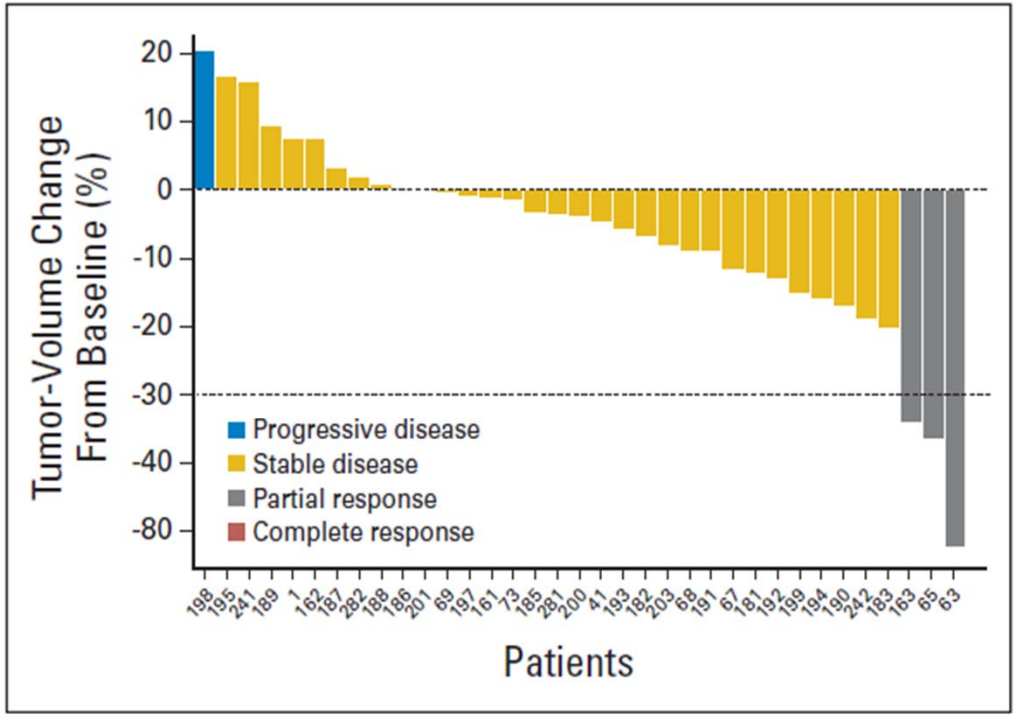


Volumetry 82 days earlier than diameters

This is Needed to Improve Clinical Trial Efficiency and to Improve Clinical Care

Make clinical trials more effective:

- **Better**
- **Tighter**
- **Faster**
- **Cheaper**



Altorki et al., J Clin Oncol 2010; 28:3131-3137.

Fig 2. Waterfall plot of central reviewer assessment of radiologic tumor response by Response Evaluation Criteria in Solid Tumors after treatment with preoperative pazopanib.

Technical Influences on Precision

- 2005: Zhao concluded that variance decreases with slice thickness, with volumetry being more dependant than LD.
- 2007: Petrou concluded that variations became no longer significant when reconstructed with thinner sections.
- 2009: Petrick and others at FDA concluded that adequately precise and accurate volume estimates are possible, at least when conducted at a single center.
- In 2009, McNitt-Gray and colleagues list a variety of technical factors that effect performance and early public data resources to study it.

Reader Agreement is Better for Volumetry than it is for Diameter Measures

- 2003: Revel concluded that two-dimensional CT measurements are not reliable in the evaluation of small noncalcified pulmonary nodules.
- In a 2004 follow up study, volumetry more reliable than diameters.
- In 2006, Marten concluded that intra-/inter-observer agreement on response assessment was significantly better for automated volumetry than for manual unidimensional measurements.

Clinical Significance is being Shown in an Increasing Number of Patients

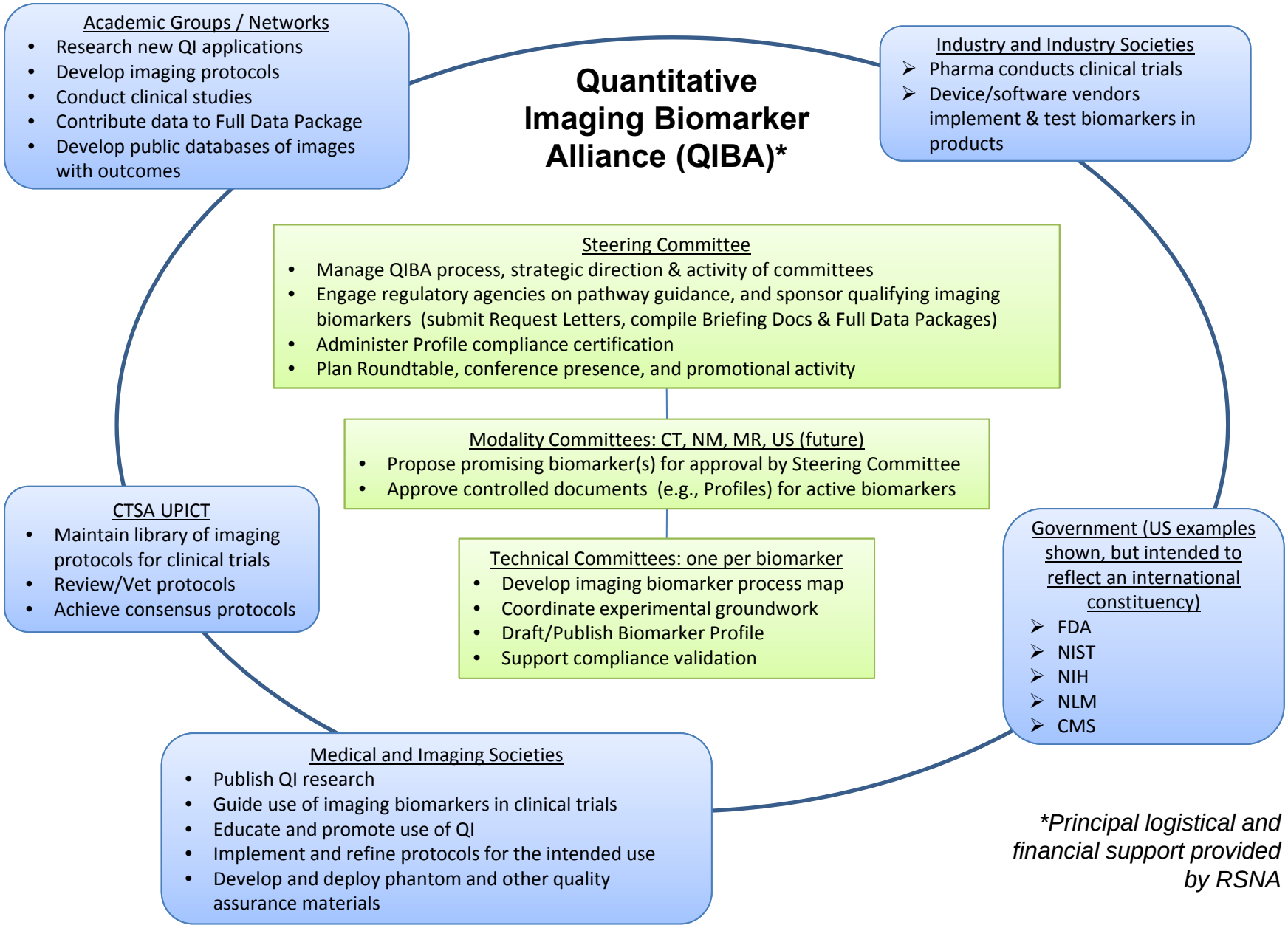
- 2006: Zhao reported a study where three to seven times the number of patients showed significant changes with volumetry vs. diameter measures.

  The same group found PPV of early volume response was 86% to predict the biologic activity of EGFR modulation.
- In 2007, Schwartz reported that volumetry predicted clinical response earlier than diameter by an average of 50.3 days.
- 2008: Altorki reported that 30 of 35 subjects with early stage lung cancer treated with Pazopanib had significant volume decrease, while only 3 met RECIST criteria for PR.
- 2009: van Klaveren reported that volumetry could spare a substantial fraction of patients with suspicious nodules from invasive diagnostic procedures and their associated morbidity.

Quantitative Imaging Biomarker Alliance

- Based on cross organizational meetings in 2006
- Kick-off November 2007, formal start May, 2008.
- Mission: Improve value and practicality of quantitative imaging biomarkers by reducing variability across devices, patients, and time.

Sound-bite version: Build "measuring devices" rather than "imaging devices."



**Principal logistical and financial support provided by RSNA*

Specific Aims

- Identify issues and refine quantitative volumetric CT measures to meet targeted levels of reproducibility for quantification of anatomical structures, such as neoplastic masses.

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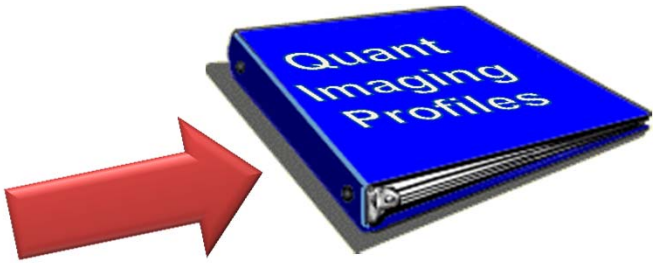
- Compare the performance of longitudinal volumetry with diameter measurements in cancer patients who are followed with serial CT scans.
- Qualify volumetric change for tumor assessment endpoints in evidence development and registration trials to accelerate evaluation and approval of novel treatment regimens and new anticancer drugs.

Specific Aim: Identify Issues and Refine CT Volumetry to Assess Response



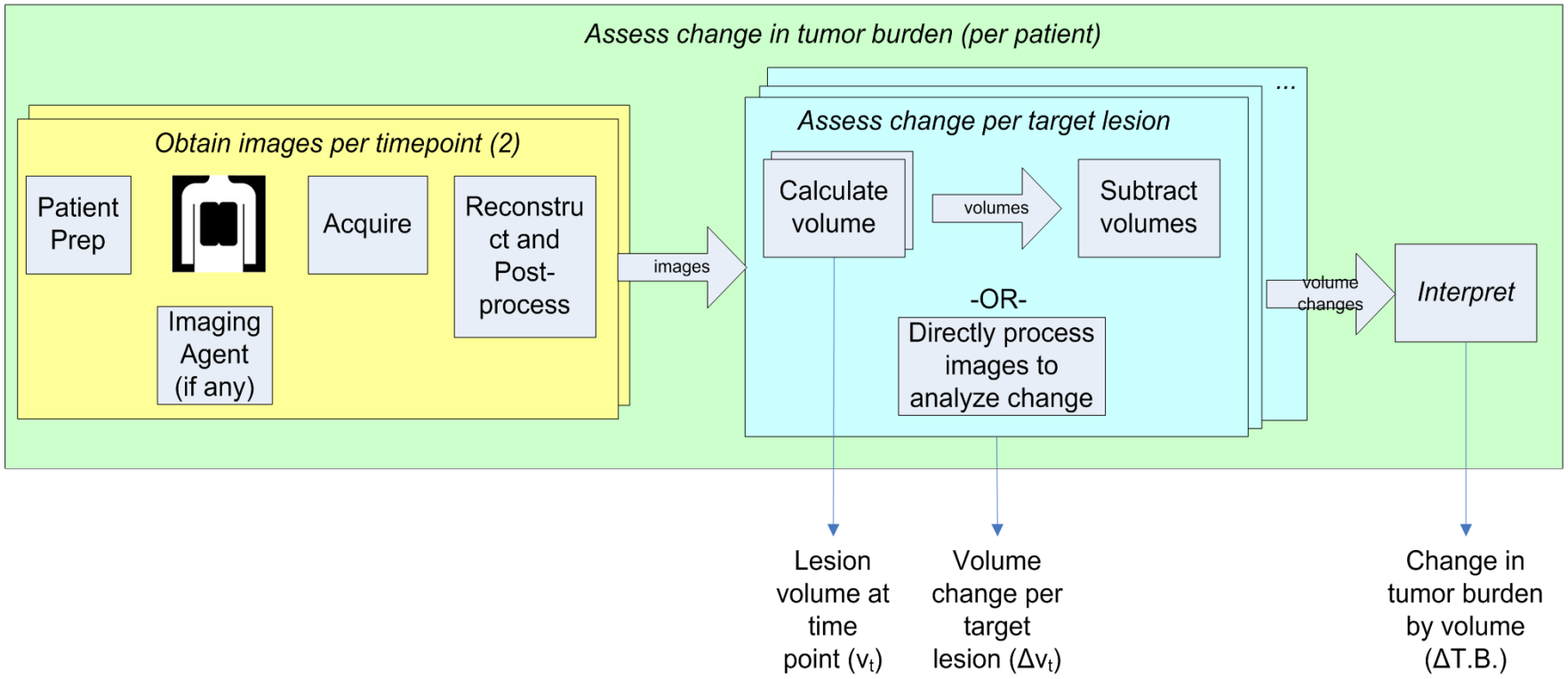
A UL-like certification reputation with customers and agencies

Matched to industry product development processes

Supported by archives of reference images for development and validation

Linked to a body of clinical evidence contributory to regulatory filings

We've put Together a Formal Description of the Assay…

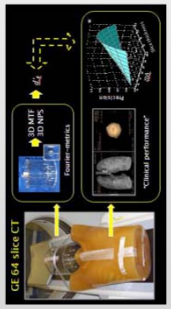


PROFILE Authoring and Testing

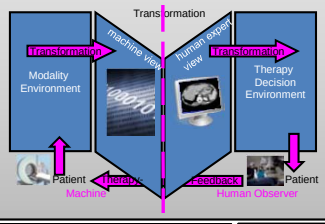
…and are Carrying Out Systematic Studies to Characterize its Performance

PROFILE Authoring and Testing

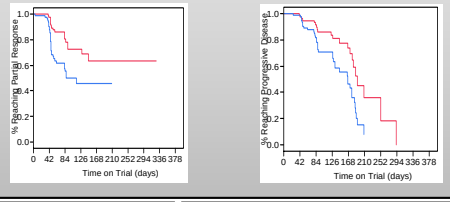
Explore figures-of-merit and QC procedures



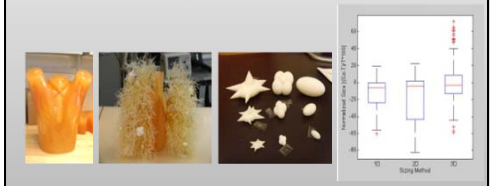
Inter-analysis technique (algorithm) variability



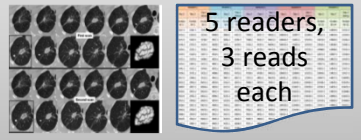
Correlation with clinical endpoints and outcomes



Intra- and inter-reader variability



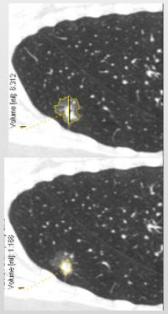
Minimum detectable biological change



Inter-scanner model, and -site variability

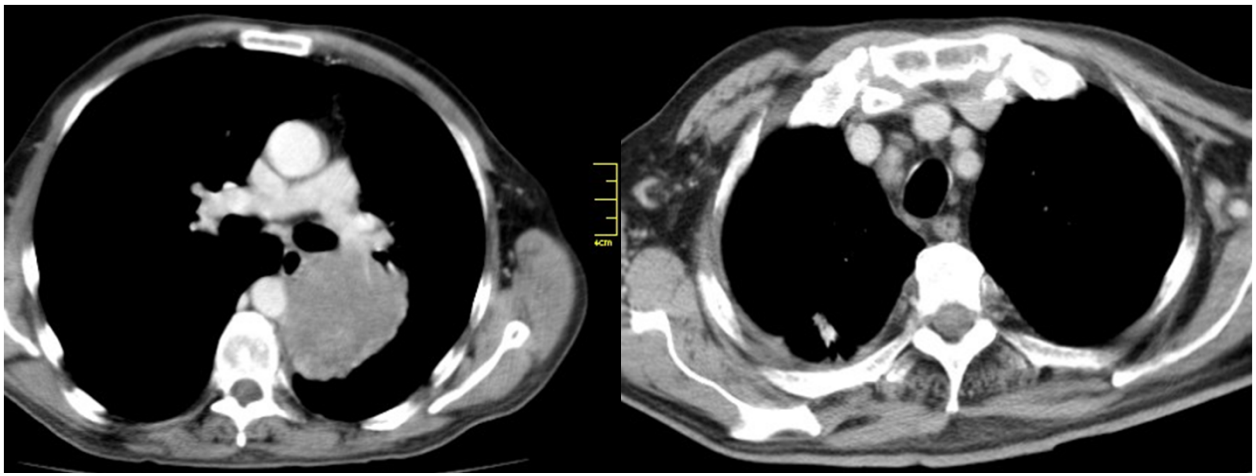
Performance-based branch / compliance procedure

Extend to other Lesion characteristics



Specific Aim: Compare the Performance of Volumetry with Diameter Measurements

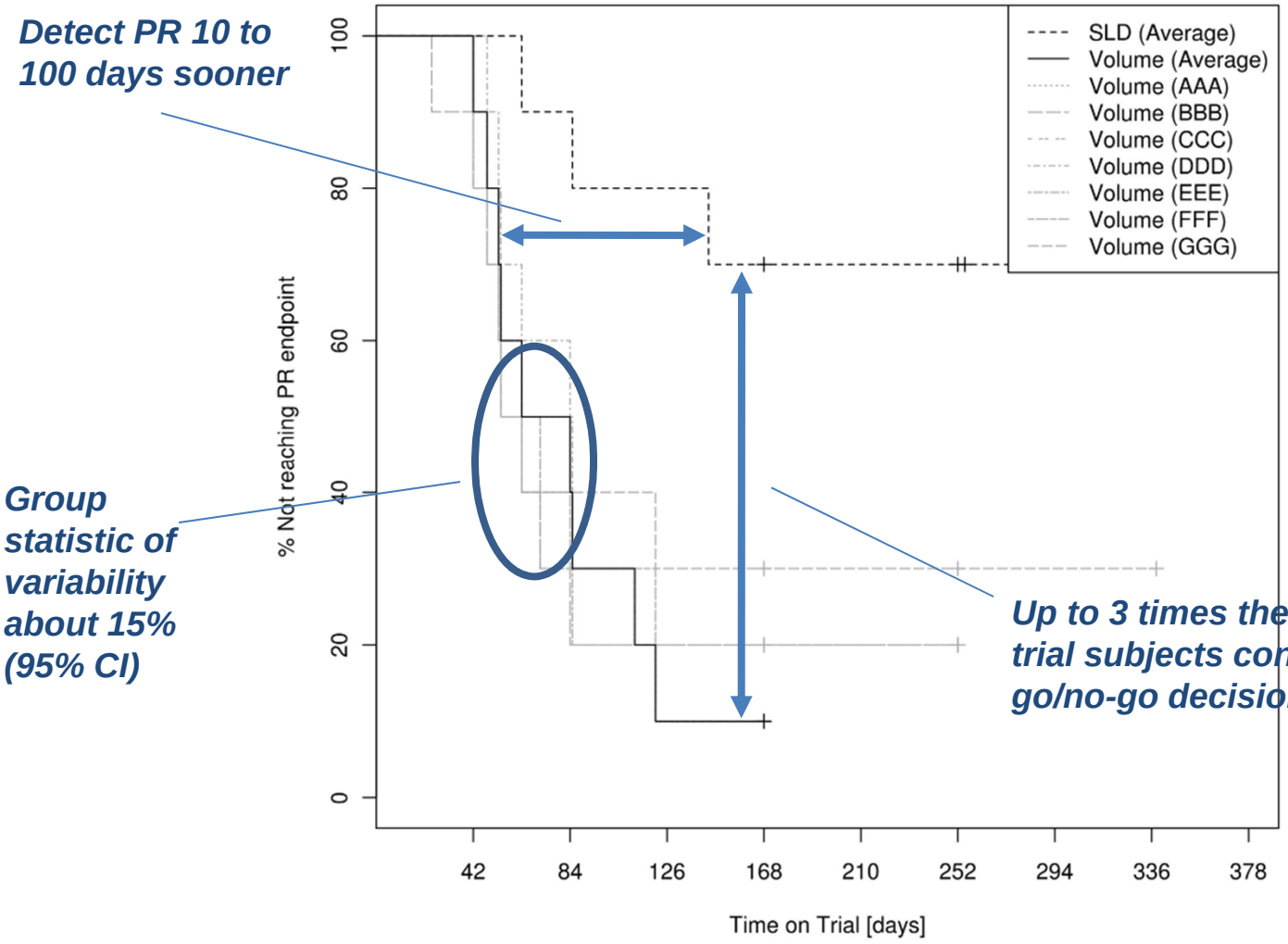
- Pilot study: in the context of advanced lung cancer, to estimate the precision and value of volumetric image analysis for monitoring treatment responses.



Left Panel: largest = 413 mL; *Right: smallest = 1.8 mL*

- First of potentially multiple retrospective re-analyses underway at Columbia: to retrospectively analyze tumor burden change in a multicenter Phase II/III clinical trial in metastatic colorectal cancer.

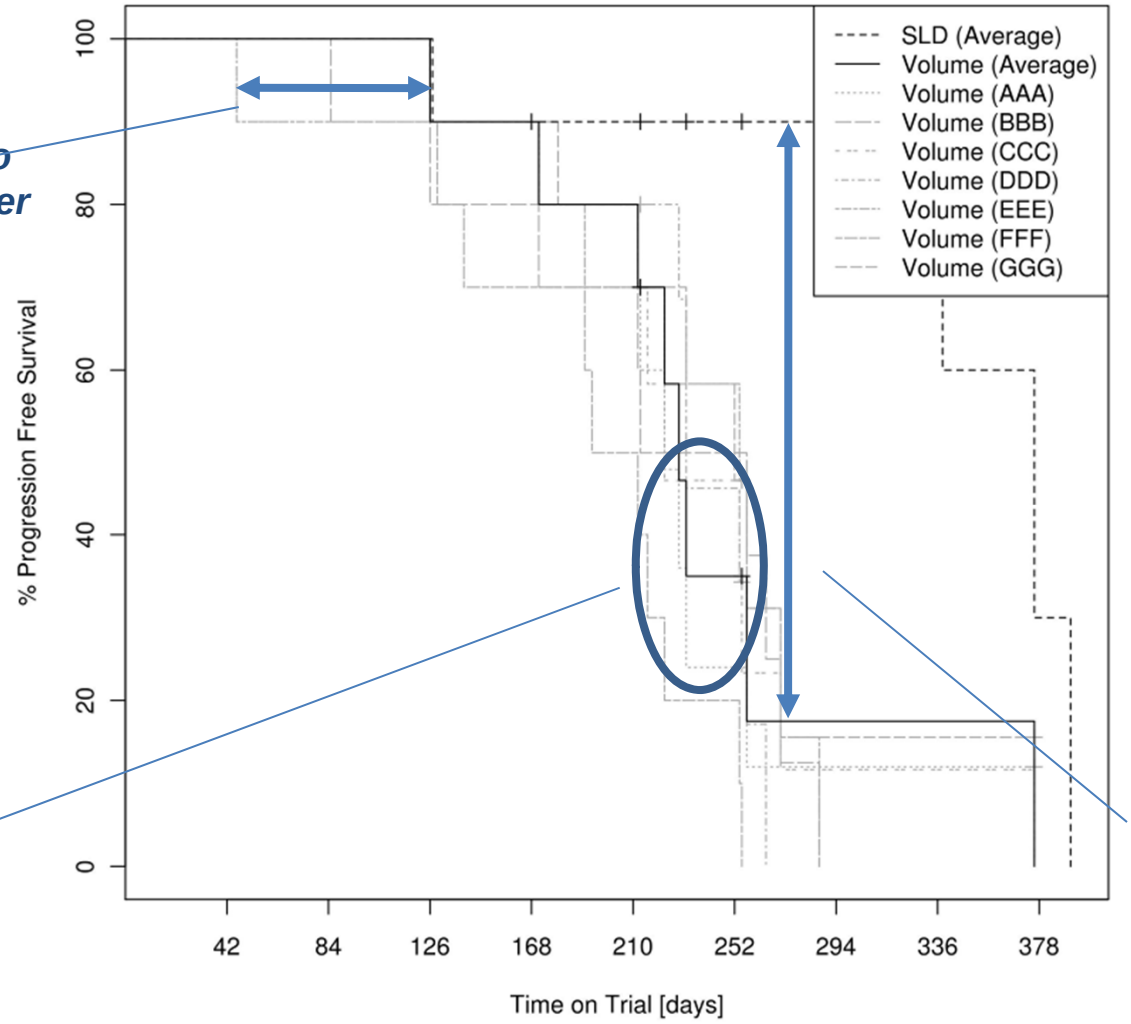
Objective Response Rate: Volumetry vs. Unidimensional (from the pilot)



p=0.002,

log rank test

Progression Free Survival: Volumetry vs. Unidimensional (from the pilot)



Detect PD 80 to 200 days sooner

Group statistic of variability about 25% (95% CI)

p=0.039,

log rank test

Up to 4 times the number of trial subjects contribute to the go/no-go decision

Current State of Literature (and Pilot) to Support Performance Claims

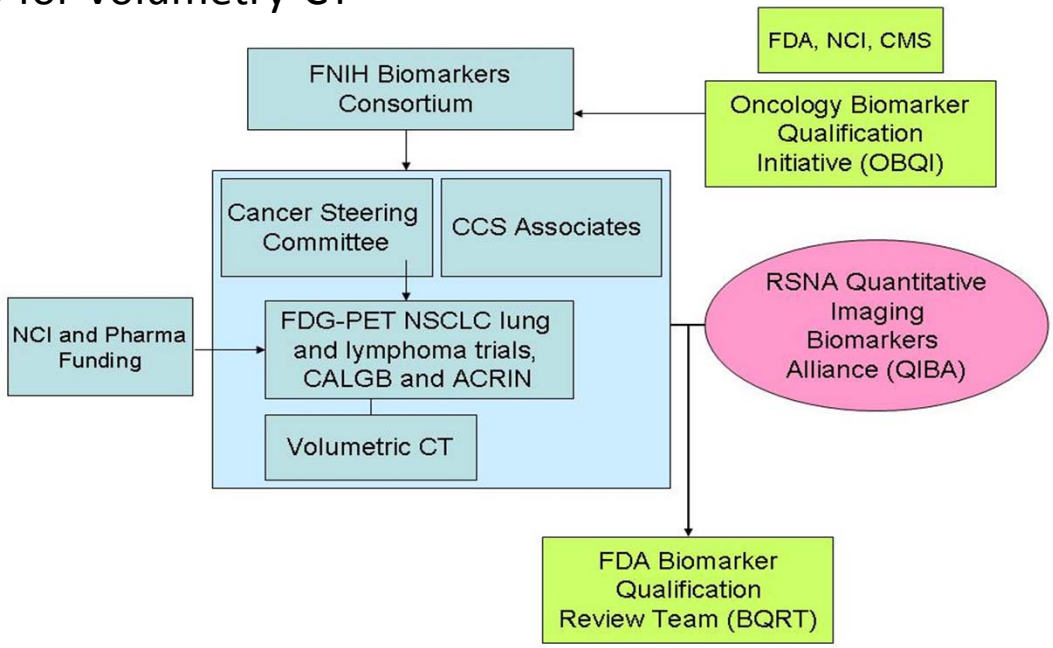
Slice thickness	RI	Nodule size	SD%	95% CI	Nodules	Patients	Year	Lead author
1.25	0.625	2-20mm		**7**	50	10	2004	Wormanns
1.25	0.625	2-5mm	19		105		2004	Kostis
1.25	0.625	5-8mm	11		105		2004	Kostis
1.25	0.625	8-10mm	8		105		2004	Kostis
2.5	1.25	5-18mm	3	**9**	54		2004	Revel
		2-21mm	20	**6**	50	10	2004	Wormanns
0.75	0.7	1-12mm	3		202	50	2006	Marten
1.25	0.625	2-20mm	13	**26**	50	29	2006	Goodman
		<10mm		**24**	218	20	2007	Gietema
1	0.75	1-10mm		**19**	4225	2239	2008	Wang
1.25	1.25	10-82mm		**14**	32	32	2009	Zhao
1	0.8	3-44mm		**26**	229	33	2009	Hein

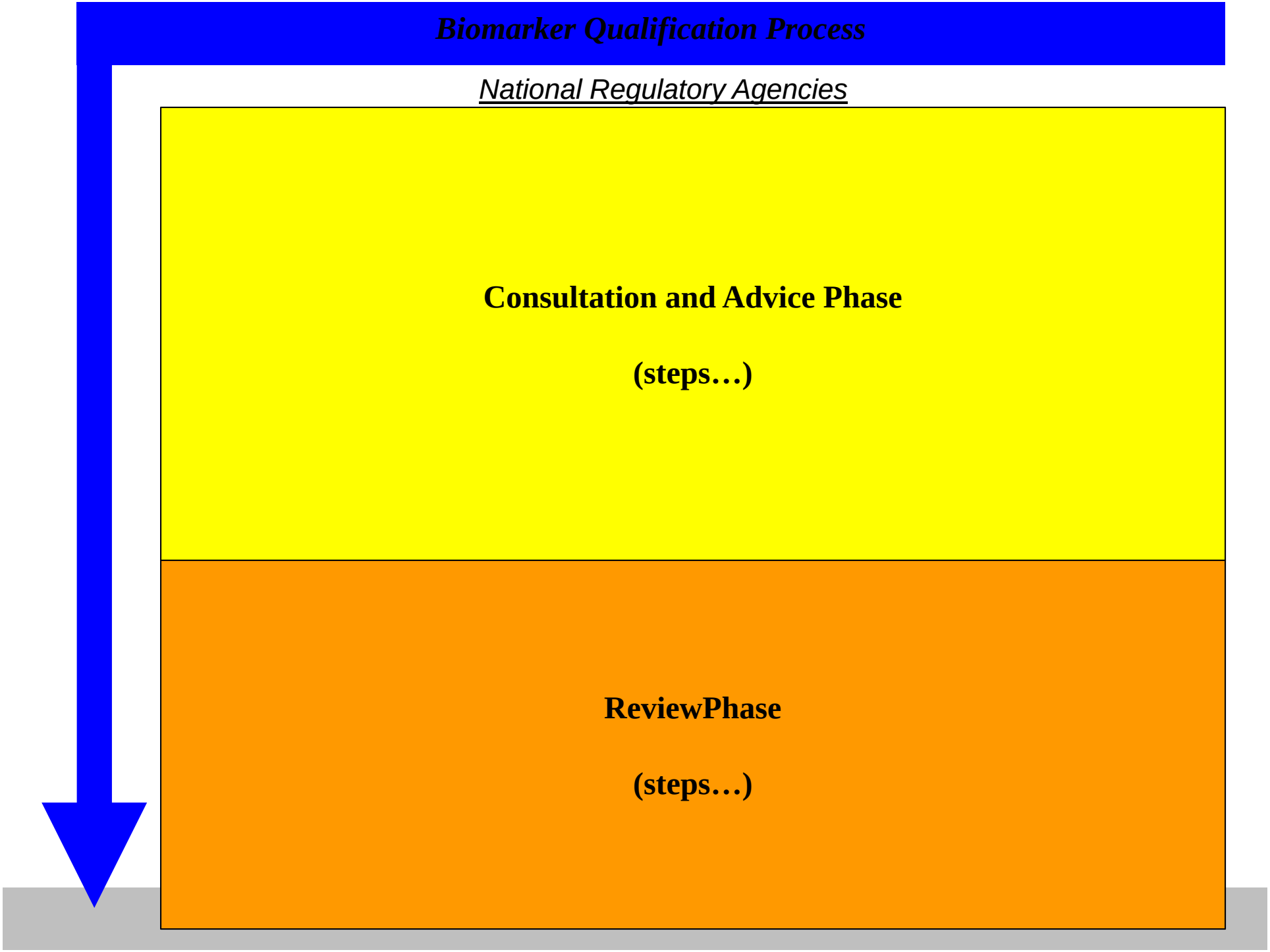
These are highlights of what we're incorporating into our Profile (with additional detail and support from our committee work)

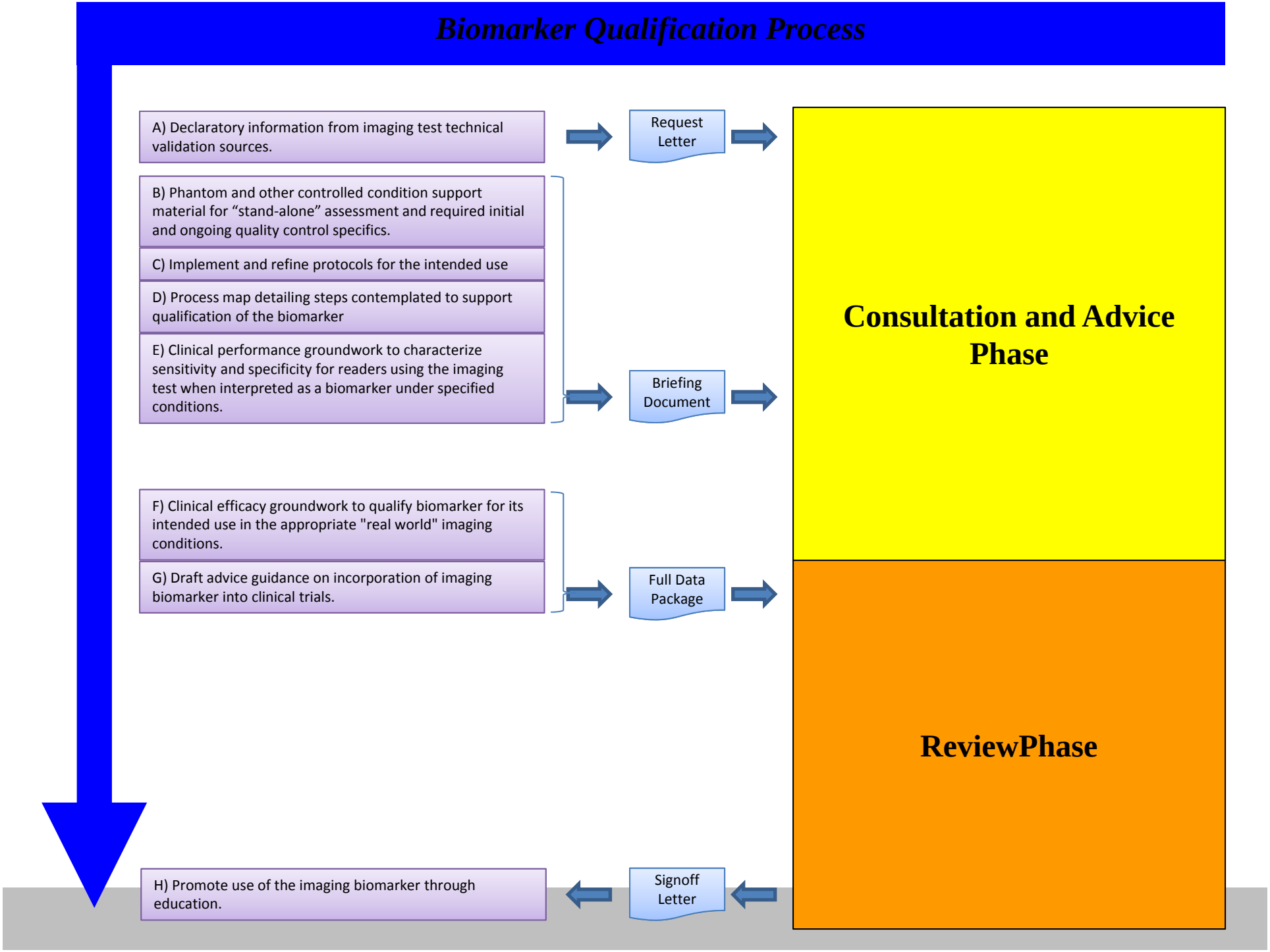
Specific Aim: Qualify Volumetry for Tumor Assessments in Clinical Trials

In partnership with FNIH Biomarkers Consortium and NCI:

- Requests tendered, Biomarker Qualification Review Teams formed, internal agency meetings underway.
- Briefing Documents:
  - FDG-PET has been submitted, meeting scheduled with BQRT this week
  - Presently completing BD for Volumetry-CT




Biomarker Qualification Process
National Regulatory Agencies
Consultation and Advice Phase
(steps…)
ReviewPhase
(steps…)


Biomarker Qualification Process
A) Declaratory information from imaging test technical validation sources.
Request Letter
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 specified conditions.
Briefing Document
Consultation and Advice Phase
F) Clinical efficacy groundwork to qualify biomarker for its intended use in the appropriate "real world" imaging conditions.
G) Draft advice guidance on incorporation of imaging biomarker into clinical trials.
Full Data Package
ReviewPhase
H) Promote use of the imaging biomarker through education.
Signoff Letter

Our Qualification Claim Positions Volumetry as Effective for Tumor Assessment

"Radiologic measurements of whole tumor volume are more precise (reproducible) than unidimensional measurements of tumor diameter. …

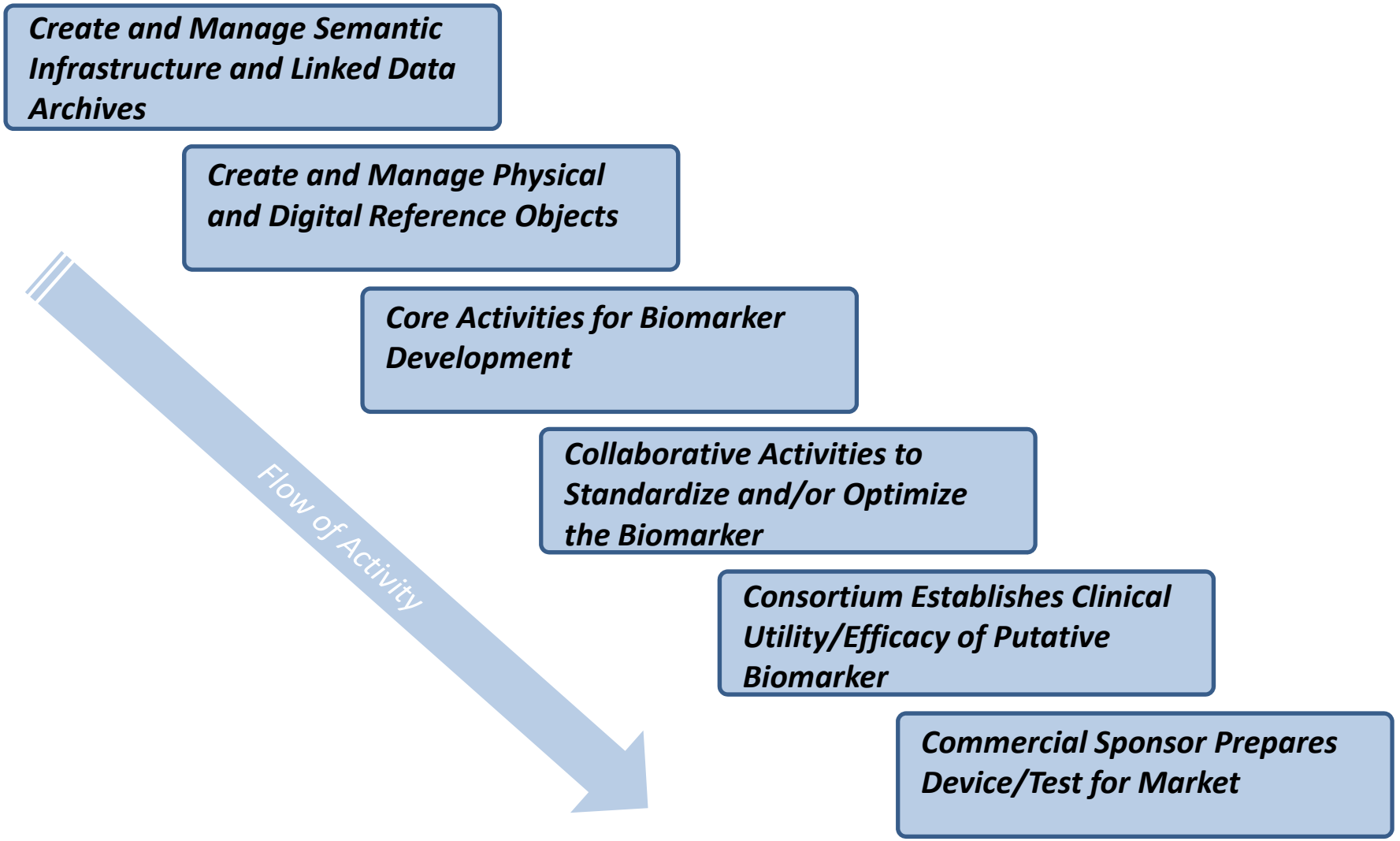
Tumor response or progression as determined by tumor volume can serve as the primary endpoint …

where outcomes based on radiologic assessment of tumors (e.g., PFS, TTP, and ORR) are currently accepted."

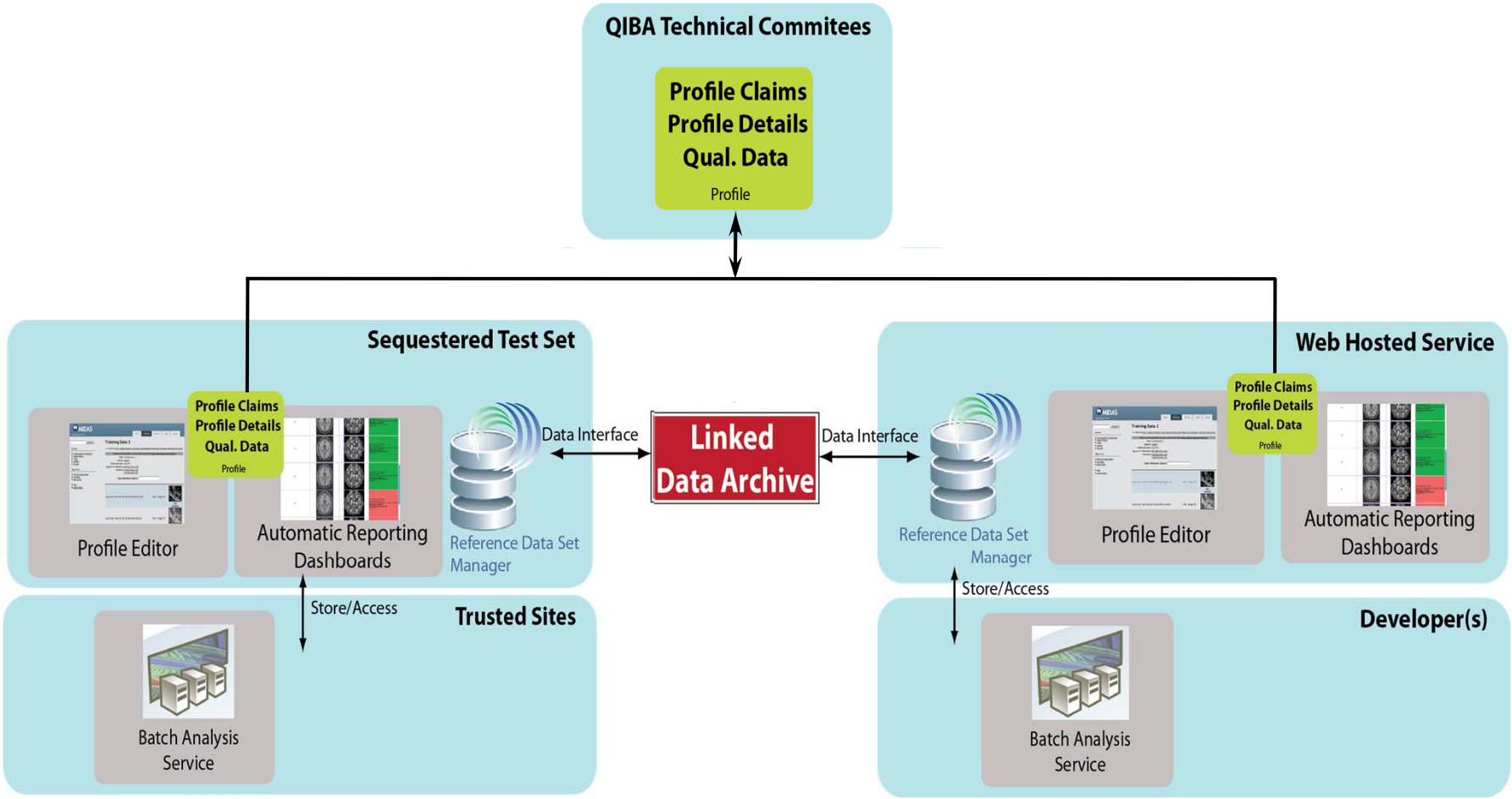
After Discussion with BQRT, we May Need to Collect More Evidence

- For example, to:
  - *Further establish the reproducibility of volumetric CT measurements, or*
  - *Compare volumetric measurements to unidimensional measurements, or*
  - *To establish threshold criteria for response categories based on volumetric measurements.*
- Request for data resources (as discussed at last workshop) has been submitted to first companies:
  - *Merck, Novartis, GSK, Pfizer, and Astra Zeneca.*
  - *Data would be analyzed from existing ongoing trials based on QIBA profiles.*
  - *A practical and demonstrable criterion may be that the early endpoint captures a substantial proportion of the treatment benefit.*
  - *A statistical analysis plan would be developed based on discussions with the BQRT.*

“Use Case” for Characterizing Performance and Creating Evidence for Filings



Capabilities to Support the Use Case are Being Developed



Summary and Conclusions

- Volumetry with CT seeks to improve tumor assessments vs. using diameters.
- The Volumetric CT Committee of QIBA is working to define Profiles, conduct groundwork, and aggregate evidence.
- We are partnered with the FNIH Biomarkers Consortium and the NCI to qualify the marker with CDER at FDA.
- We are developing means for amassing image archives and services for characterizing performance of QI techniques through NIST MSE program.
- If successful, we will increase availability of volumetry-based tumor assessment for:
  - *reduce number of subjects enrolled per trial*
  - *decrease time on study per subject*
  - *speed the delivery of new treatments to patients with unmet medical needs*
  - *positively influence patient management*
- Doing so should build value for all stakeholders

The QIBA CT Team

See speaker notes for full list of individual names

ActiViews Inc.
Amgen
AstraZeneca
Beth Israel Deaconess Medical Center
BioClinica, Inc.
Biomedical Systems
Boston Medical Center
Breast Health Management, Inc
Brigham and Women's Hospital
Bristol-Myers Squibb
Buckler Biomedical LLC
CCS Associates, Inc.
Columbia University
Definiens
Duke University
FDA
GE Healthcare
Glenfield Hospital, UK
Harvard Medical School
Haukeland Univ Hospital
Henry Ford Health System
Imagepace
Intio, Inc.
Iowa Comprehensive Lung Imaging Center
Johns Hopkins University
Kitware, Inc.
Leiden Univ Med Ctr
Lung Cancer Alliance
Mallinckrodt Institute of Radiology
Massachusetts General Hospital
MD Anderson Cancer Center
Median Technologies
Merck
Merge Healthcare
Millennium Pharmaceuticals
MITA (NEMA)
Mount Sinai Hospital
MSKCC
National Jewish Health
NCI NIH Cancer Imaging Program
NIST
Perceptive Informatics, Inc.
Philips Healthcare
RadPharm
Roswell Park Cancer Institute
Rush University Medical Center
Siemens
Stanford University
TeraRecon, Inc.
The Phantom Laboratory, Inc.
Toshiba
University Medical Imaging
University of Alabama at Birmingham
University of British Columbia
University of California, Davis
University of California, Los Angeles
University of Chicago
University of Colorado, Denver
University of Illinois at Chicago (UIC)
University of Iowa
University of Maryland
University of Pennsylvania
University of Pisa
University of Utah
University of Virginia Health System
University of Wisconsin-Madison
VIDA Diagnostics, Inc.
Weill Cornell Medical College

Joint Imaging Biomarker Qualification Committee Members

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- Denise Aberle, MD, UCLA
- Monica Bertagnolli, MD, Brigham &Women's Hospital. CALGB
- Ronald Boellaard, PhD, Nuclear Medicine, VU Medical University, Amsterdam
- Andrew Buckler, Buckler Biomedical, LLC
- Laurence P. Clarke, PhD, NIH/NCI/DCTD Cancer Imaging Program
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- Gundrun Zahlmann, MD, PhD, Roche, Inc.

NIST Project Acknowledgements

- Partners:
  - Kitware, Inc.
  - Information Technology Laboratory of (ITL) National Institute of Standards and Technology (NIST)
- In coordination with:
  - Quantitative Imaging Biomarker Alliance (QIBA)
  - Imaging Workspace of caBIG
  - Stanford Center for Biomedical Informatics Research (BMIR)