Quantitative Imaging Biomarker Alliance

WHY QIBA:
MR SPECIFICS

Corporation Visit

Autumn 2010

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PRINCIPAL LOGISTICAL AND FINANCIAL SUPPORT PROVIDED BY RSNA

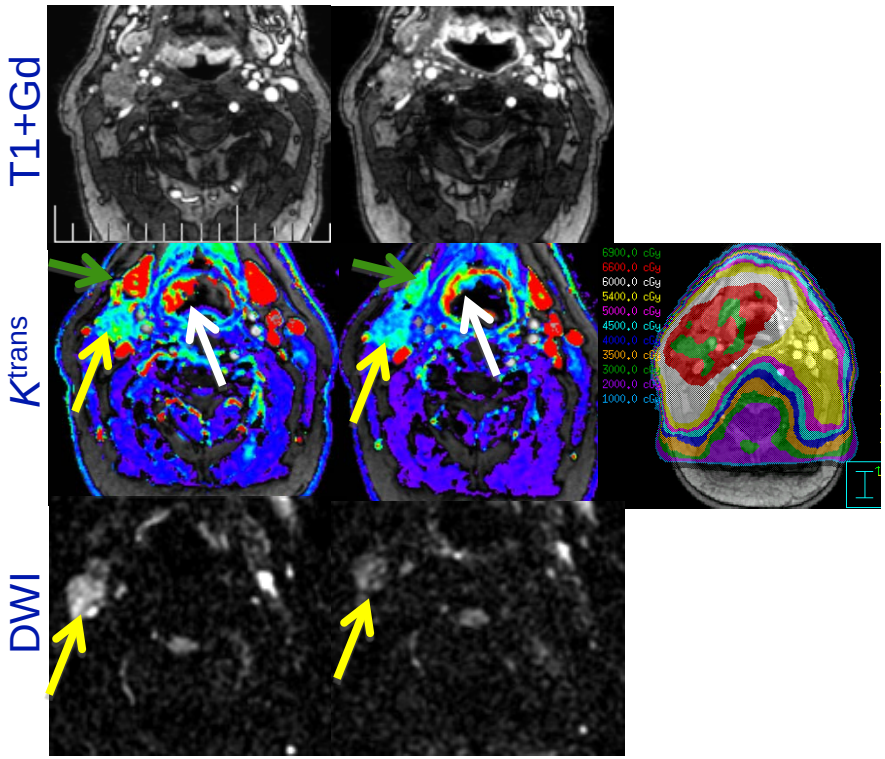
Our Team

ACR / ACRIN
AMAG Pharmaceuticals, Inc
AstraZeneca
Avotec, Inc
Beth Israel Deaconess Medical Center
BioClinica, Inc.
Biomedical Systems
Brigham and Women's Hospital
Buckler Biomedical LLC
CHOP
Columbia University
Duke University
FDA
GE Healthcare
Hologic, Inc
iCAD, Inc
Imagepace
Indiana University
Institute for Medical Image Computing
Johns Hopkins University
Lehigh Valley Diagnostic Imaging
MAC
Mallinckrodt Institute of Radiology
Massachusetts General Hospital
Medical College of Wisconsin
Medical Numerics
Merck
Merge Healthcare
MITA (NEMA)
Moffitt Cancer Center
NCI
NIBIB
NIH
NIST
NordicNeuroLab, Inc.
Novartis
Ohio State University
Perceptive Informatics, Inc.
Pharmtrace
Philips Healthcare
Prism Clinical
Quiron Hospital, Valencia, Spain
Radboud University Medical Center, Nijmegen
RadPharm
Roche
Siemens Medical
State University of New York
Temple
TeraRecon, Inc.
The Institute of Cancer Research
Univeristy of Pennsylvania
University of Alabama at Birmingham
University of California, Davis
University of California, San Diego
University of Chicago
University of Michigan
University of Pennsylvania
University of Southern California
University of Texas Health Sciences Center, San Antonio
University of Texas M.D. Anderson Cancer Center
Vanderbilt University
VirtualScopics, Inc.

See speaker notes for full list of individual names

Quantification Builds on the Proud History of Innovation in MR

- Technical advances help us move from "qualitative image *information*" to "quantitative image biomarker *measurements*"
- Quantitative imaging biomarker data can be used to 1) provide improved differential diagnosis and staging, and 2) optimize both the delivery and assessment of personalized therapies
- Examples:
  - Early response assessment
  - Adaptive therapy
  - Optimized delivery of combination therapies



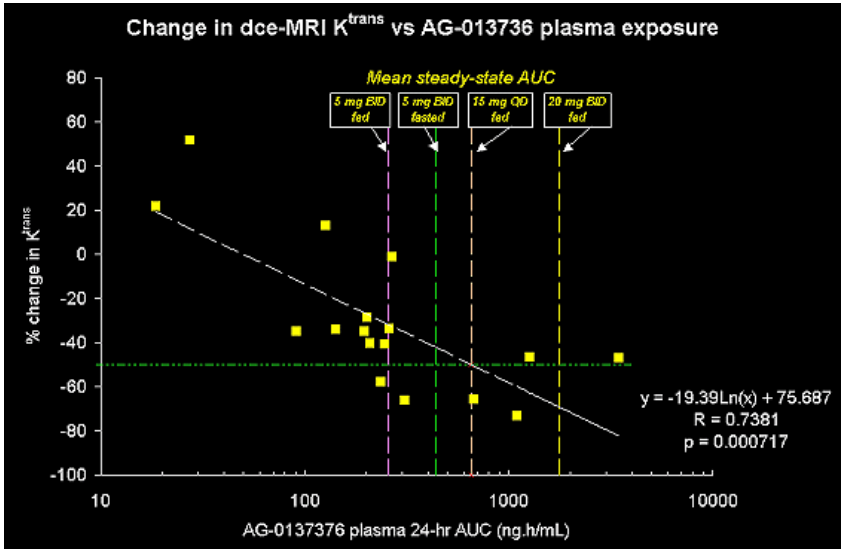
Adaptive Radiation Therapy
- tumor and normal tissue response -

Quantitative MR Applications Measure Disease more Precisely

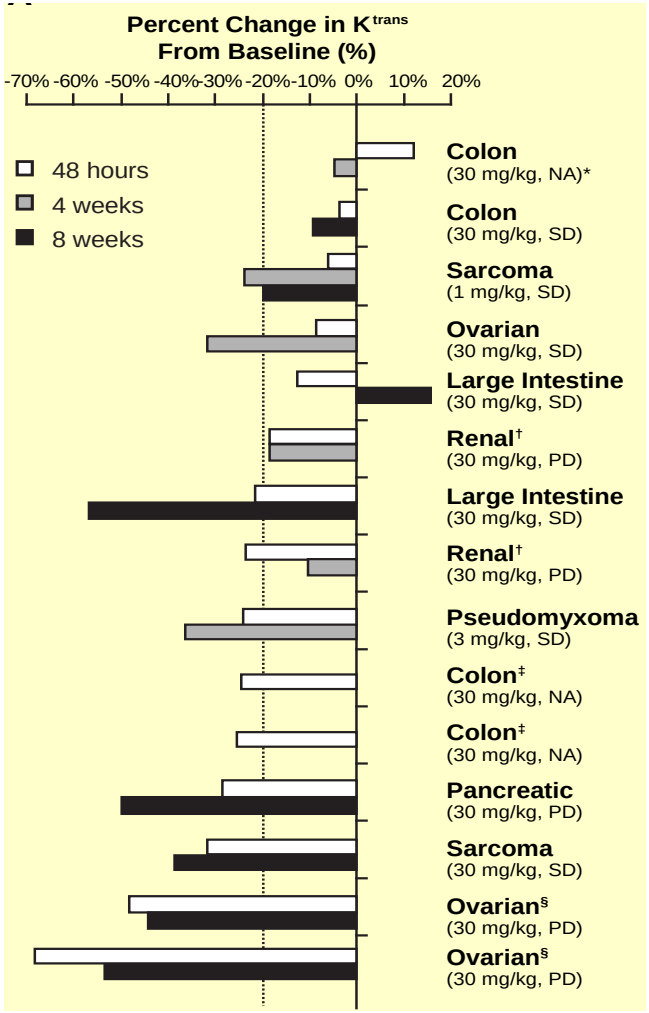
- Clinical research, Clinical trials, and Drug discovery
- Assessing individual response to therapy
- Guidance for real time, *e.g.*, MR-guided thermal therapy, or adaptive therapy, *e.g*. MR-guided adaptive radiotherapy

Already in use in single- and multi-center Phase I/II clinical trials

Increasing use clinically



Liu, *et al*., J Clin Oncol 23:5464, 2005.



Herbst *et al*., J Clin Oncol 27:2557, 2009

Quantification Increases the Utility and Value of Imaging

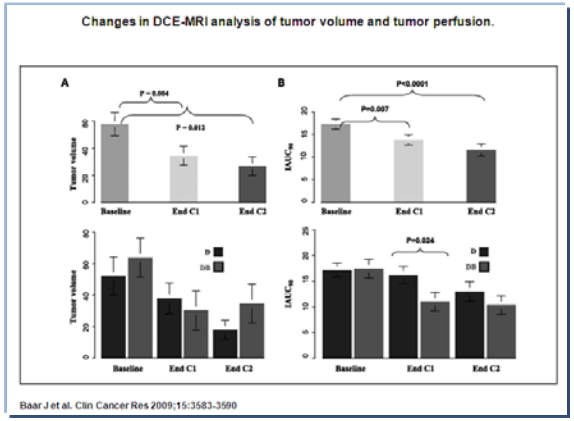
Biomarkers often follow Therapy into the clinic as diagnostics for better therapy monitoring by:

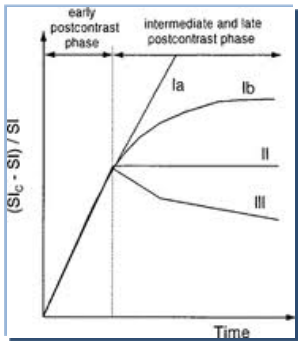
(A) Making clinical trials more effective:

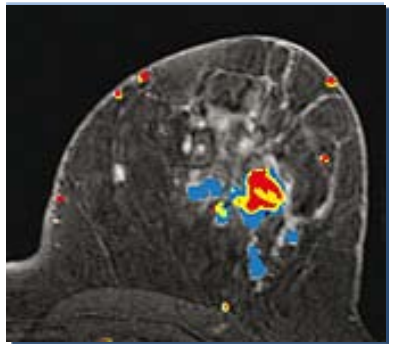
- **Faster** (Window trials—quantitative endpoint); **Cheaper** (two to three weeks of drug exposure); **Better** (Phantom calibration, standardize method, open source reference tools, defined molecular targets, tailored delivery systems) ; **Tighter** (variance); **Standardized** (Protocols, Profiles)

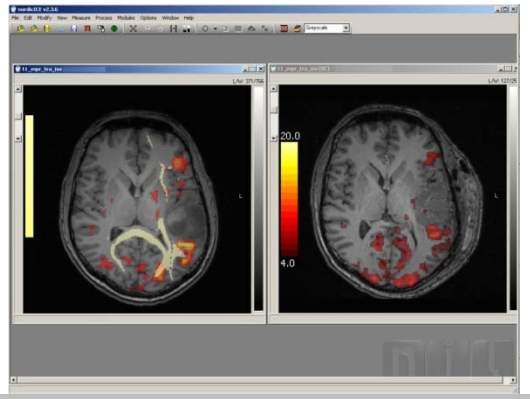
(B) Making care more personalized to patient:

- **Clinically proven** detection and longitudinal quantification for follow-up
- Quantitative imaging biomarker measures incorporated into **adaptive therapy**
- Moves imaging from diagnostics and staging to **therapy monitoring**









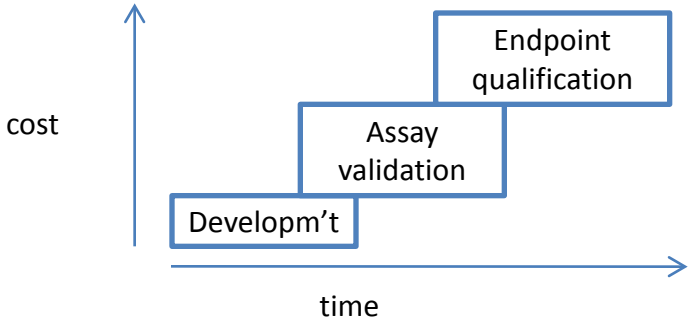
Technical as well as Business Obstacles Impede Realization of the Opportunity

- Technical factors
  - Vendor-specific pulse sequence implementations
  - Field inhomogeneity
  - Surface coil intensity variation
  - Off-resonance & dielectric effects
  - Image artifacts and noise
  - Signal non-linearity with respect to agent concentration
  - Lack of standardization (phantoms for contrast response assessment, *etc*.)
  - Quantitative imaging not business model ("upgrade dilemma")
- Physical factors
  - Scan acquisition parameters
  - Image reconstruction parameters
  - Choice of contrast agents
  - ROI subjectivity
  - No standardized data analysis models or test data
- Biologic factors
  - Patient gross motion (voluntary & involuntary)
  - Respiratory motion
  - Cardiac motion/cardiac output

Efforts by individual manufacturers to qualify quantitative imaging applications:

- *Are more costly, and*
- *Run over longer time periods…*

…than the business model of device and software manufacturers generally support.



These issues are exacerbated by lack of clarity in regulatory and reimbursement policy which increase the risk while decreasing the incentive

Even when individual companies do these steps, community need for standards required to address multi-vendor reproducibility are not accounted for.

Example drill down: *IAUC*/K^{trans} using DCE-MRI

- DCE – MRI: quantitative analysis of dynamic T1 contrast enhanced images
- Use cases:
  - Clinical trial related
    - UC1: pharmacodynamic investigations (*e.g.*, K^{trans}) in early phase clinical trials
    - UC2: biological effect assessment as predictive biomarker
    - UC3: heterogeneity of disease/response
  - Clinical routine use (future)
    - UC4: diagnostic decision making
    - UC5: therapeutic progress assessment in a clinical environment
    - UC6: therapy guidance / adaptive therapy

- DCE-MRI is not routine standard of care, but increasingly used clinically
- Current radiological practice is not quantitative
- Manufacturers have different implementations of pulse sequences that result in wide range of contrast response characteristics
- Manufacturers have nothing to compare to
- Economic challenge to manufacturers in supporting clinical trial applications vs clinical routine

- DCE-MRI is used in early phase clinical studies
- There is increasing interest in clinical use as well
- The diversity in technical solutions will remain due to the lack of economic benefits to the vendors. The task is to come up with solutions to harmonize image biomarker results across vendors.
- Image quality is a major issue for all quantitative imaging
- Manufacturers are focusing on technology not biological validation. We have to deal with it for almost all exploratory types of activities.

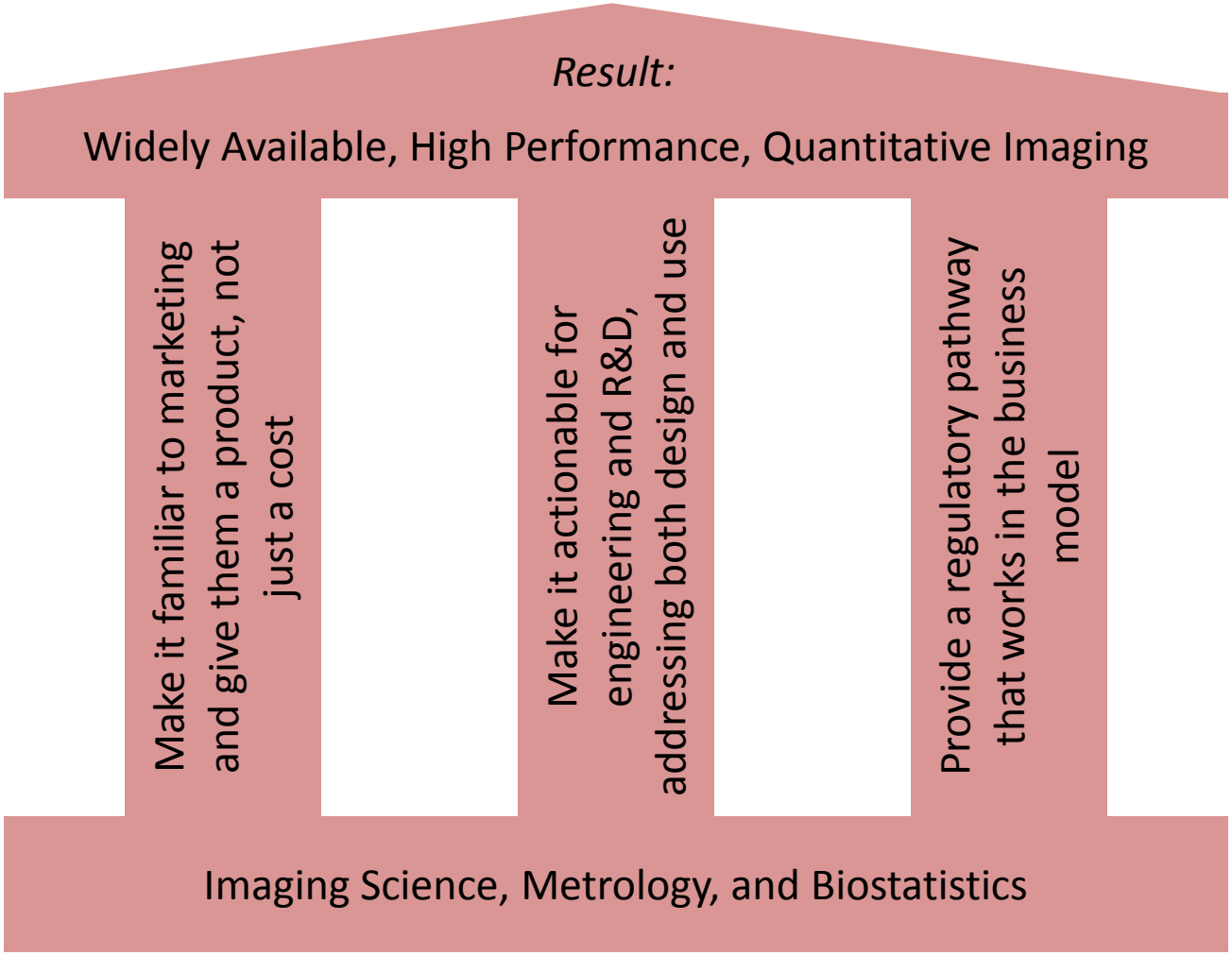
Example drill down: PreSurgical Mapping using BOLD fMRI

- BOLD fMRI: quantitative analysis of EPI image sequences used in conjunction with functional imaging stimulus paradigms
- Use cases:
  - Clinical routine
    - UC1: diagnostic assessment in surgical and/or treatment planning (e.g. tumor, epilepsy)
    - UC2: risk assessment in decision making
    - UC3: therapeutic progress assessment in a clinical environment (e.g. stroke recovery, TBI)
  - Clinical trials (future)
    - UC4: biological effect assessment as predictive biomarker, therapeutic progress

- BOLD fMRI is not standard of care in clinical practice but employed increasingly
- CPT codes introduced (2007) – positive growth in reimbursement and adoption
- Methodology evolved via neuroscientists, neuropsychology – relatively new to radiology practice
- Current radiological practice is not quantitative
- fMRI not yet used in clinical trials

- Manufacturers provide technical solutions for implementation - variability in defining parameters (# volumes and TR)
- Required peripheral equipment not routinely provided by MR vendor – requiring integration of 3rd party technical solutions (stimulus presentation)
- Variability in analysis protocols – QC measures available from manufacturers (MR and SW)
- Economic challenge to manufacturers – volume is not there

QIBA Addresses the Obstacles, Enabling Profitable New Products



QIBA Profile Content

User Perspective

Will it do what I need?

What/who do I need to get started?

What do I have to do (procedures, training, performance targets) to achieve the Claims?

Claims:

"Detect tumor response with twice the sensitivity of RECIST in the Lung"

Details:

Actors Table

- CT Acquisition System
- Measurement Software
- Radiologist

Activity Definitions

- Calibration / QA
- Patient Preparation
- Image Acquisition
- Reconstruction
- Post-Processing
- Analysis / Measurement
- Reading / Interpretation
- …

Vendor View

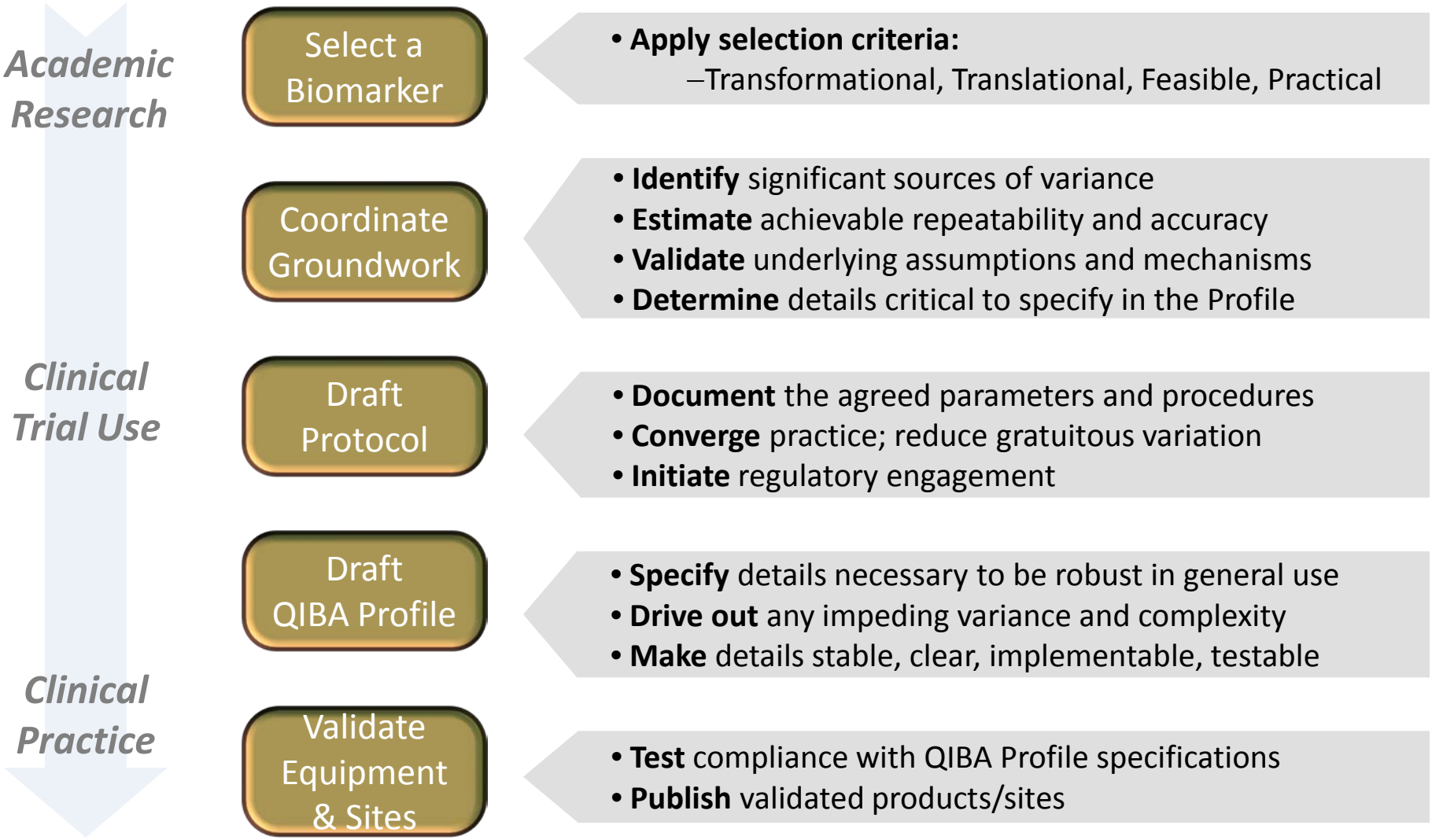
Why do you want me to do this?

Which of my products are affected?

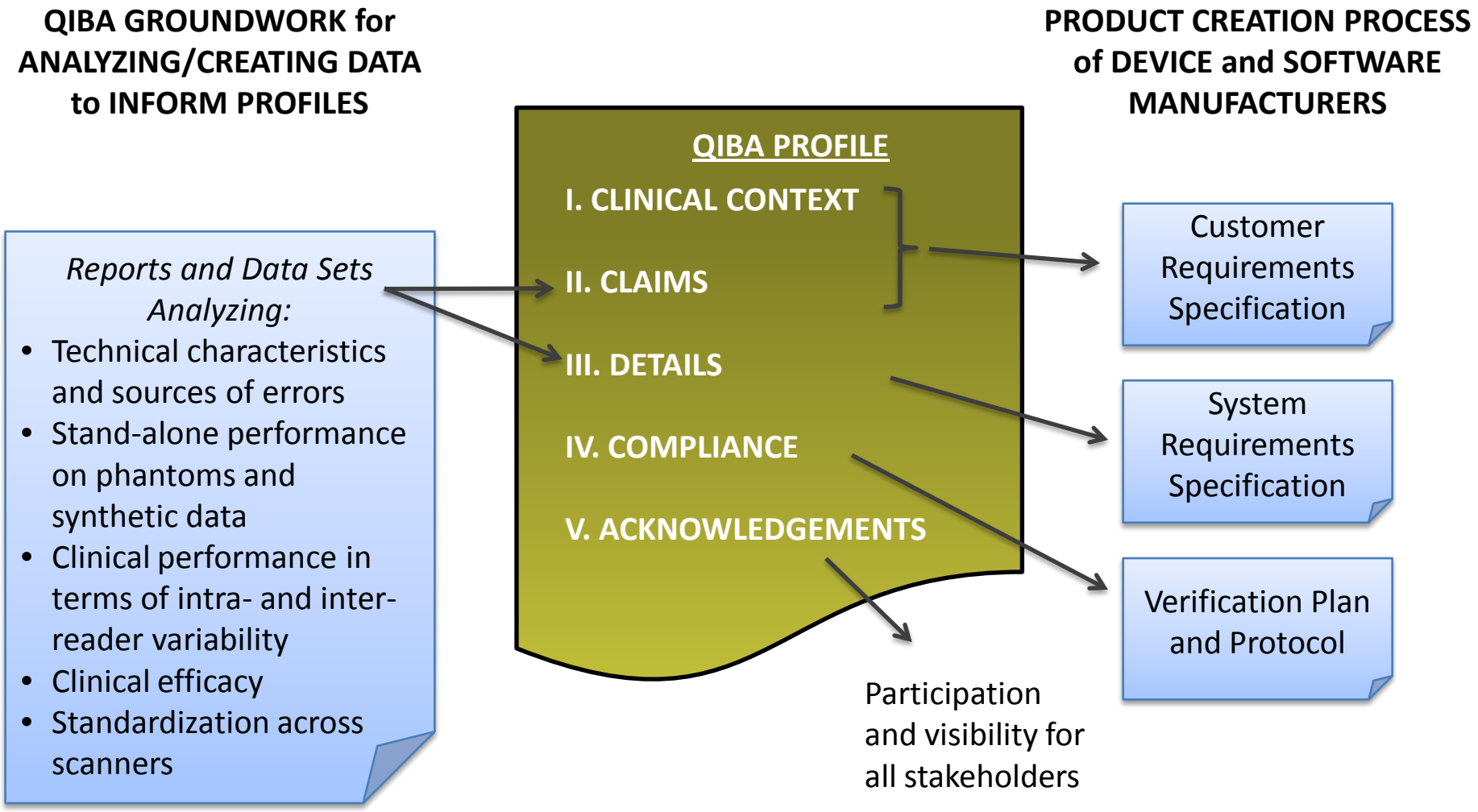
What do I have to implement; (features, capabilities, performance targets)

How will I be tested?

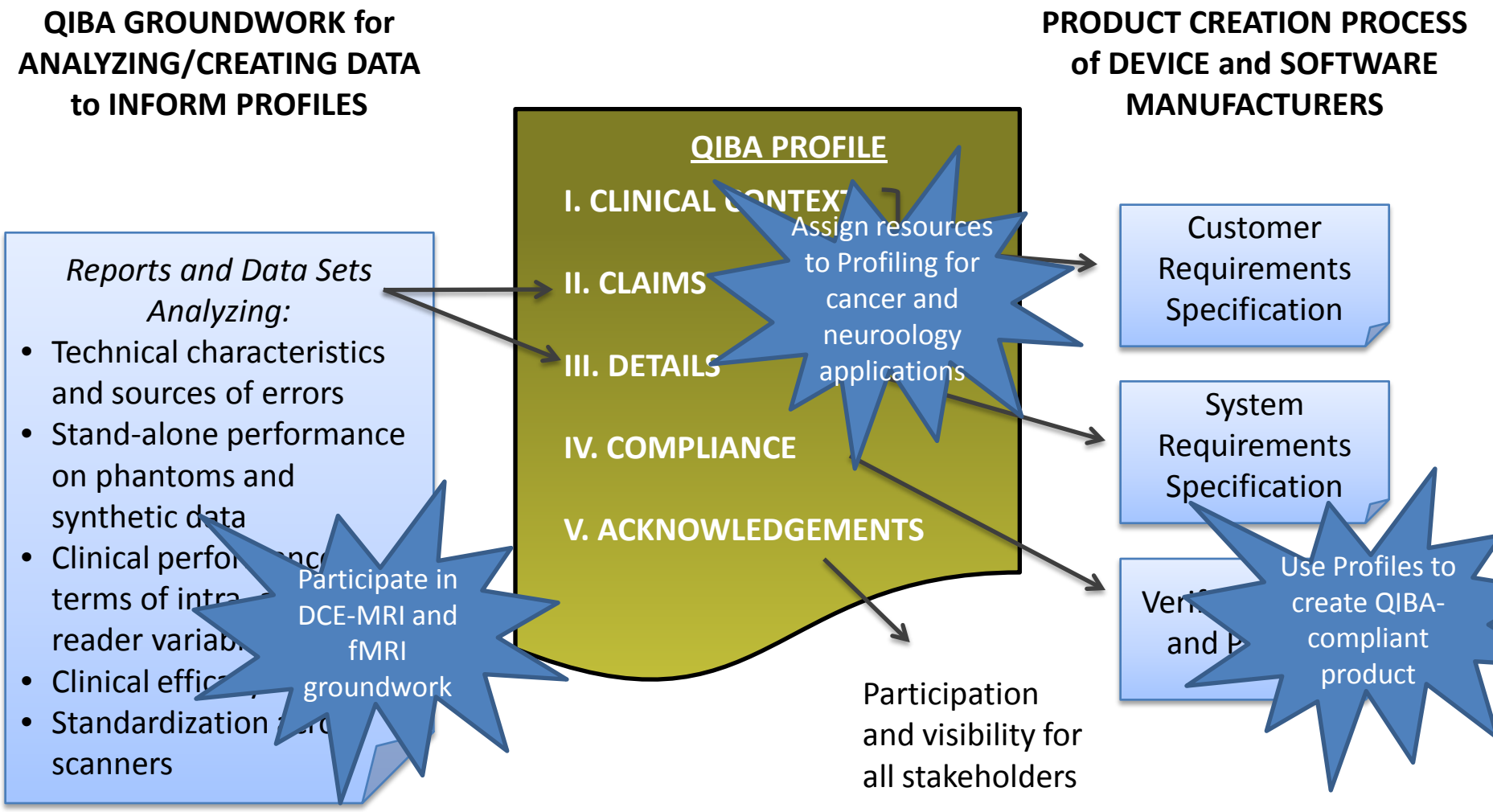
QIBA "Industrializes" QI



QIBA Leverages Resources and Bridges Perspectives Across Communities



Our Offer – and our Request – is to Increase your Engagement with Us



To be specific, for DCE-MRI and BOLD fMRI, we are requesting:

- Assist with collaborative groundwork activities:
  - Participate in experimental studies for characterizing performance.
  - Review requests and provide feedback on standardizing acquisition system characteristics.
- Apply engineering resources to help refine QIBA profiles:
  - Assist with the engineering analysis being performed to arrive at requirement levels and functional specifications.
  - Assist with the writing of QIBA profile claims.
- Prepare for future product development and marketing:
  - Review QIBA profiles and current product performance claims.
  - Perform QIBA studies and internally validate QIBA compliance.
  - Obtain approval to claim QIBA compliance.

We can't do it alone, you can't do it alone. We need to do it together.

- Utilization of imaging grows as it is used for monitoring response and adapting therapy.
- Technical as well as business obstacles impede commercialization.
- QIBA addresses these obstacles, accounting for individual stakeholder value propositions.
- The commercialization model is similar to IHE, including relationship to product creation process.
- Collaborative resources in precompetitive model address the science and provide critical mass as well as cost sharing for regulatory data collection.
- We invite you to join us in making the critical step of defining Profiles.
- New products compliant with the outputs of this process will fuel a virtuous cycle of innovation in this next generation of imaging, rewarding all participants.