NCI: Development of International Resources as Required for Personalized Medicine

Clinical Model: Measurement of Response to Therapy Using Imaging as a Biomarker

Strategy: Funding Agency Perspective

Larry Clarke

Imaging Technology Development Branch (ITDB)

Cancer Imaging Program (CIP)

Division of cancer Treatment and Diagnosis (DCTD)

HISC Canberra Australia

Aug 21st 2009

Personalized Medicine: Clinical Model

- The next generation of electronic health care (ehealth) will most certainly include a strong emphasis on molecular based screening, diagnosis, and treatment methods as ways to facilitate personalized.

- One rapidly maturing medical discipline in personalized medicine strategies is in vivo functional and molecular imaging.

- Imaging has the potential to take the lead in integrating informatics and clinical decision-making software tools, creating the role of imaging as a biomarker

Personalized Medicine: Clinical Model

- NCI is exploring an integrated approach for creating reference standards for both data and software tool interoperability and clinical decision software tools.

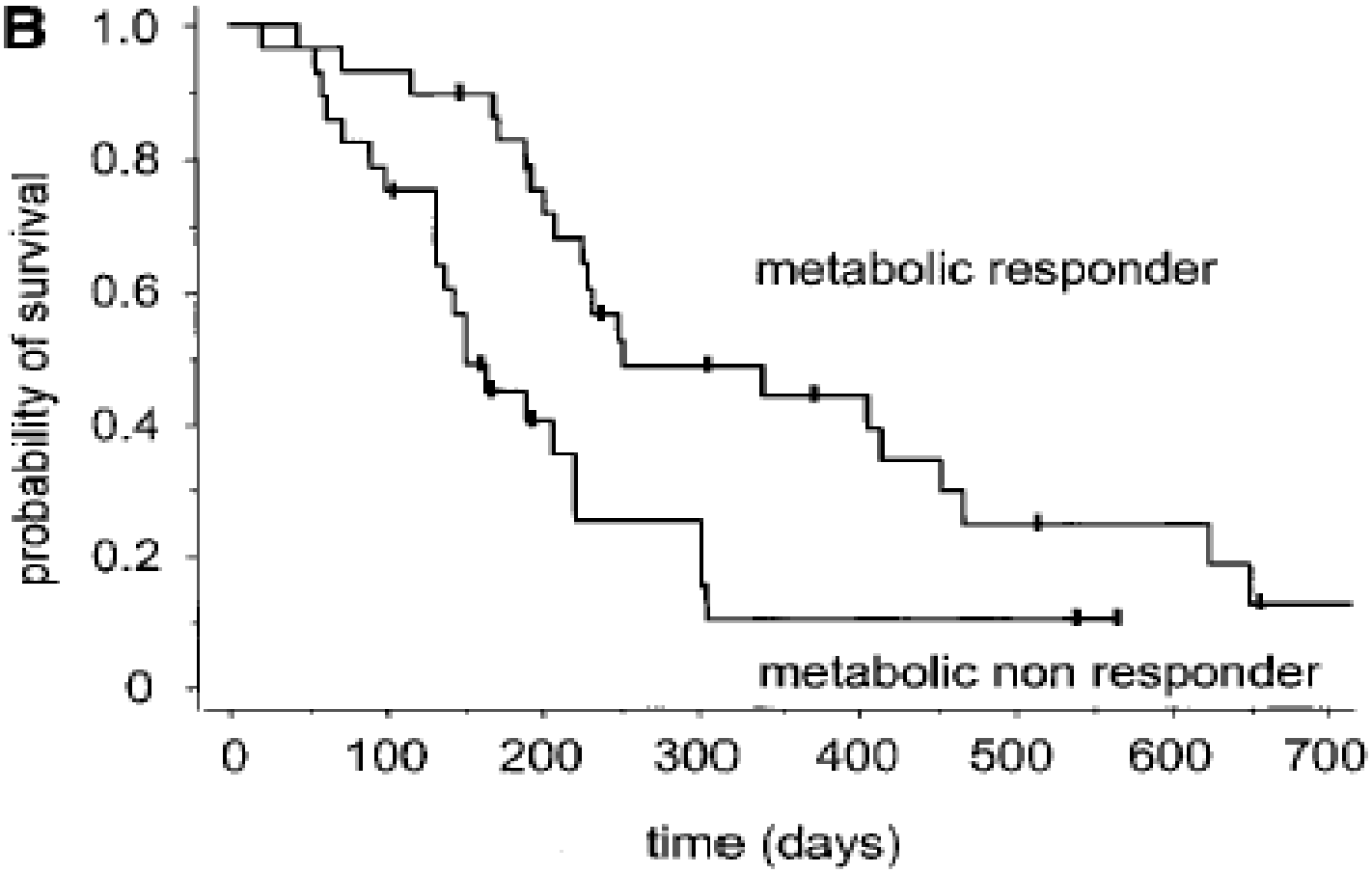
- Goal of this presentation is to describe
  - NCI initiatives in this area
  - Potential collaboration with Australian researchers
  - Potential leveraging of resources with Australian funding agencies

Clinical Model: Measurement of Therapy Response in Biomarker Clinical Trials

- **Challenges: Data Complexity-Measurement Uncertainty**
  - **Multi-Modality-Molecular Imaging (PET-CT, MRI-PET,..)**
  - **Multi-dimensional and heterogeneous data**
  - **Resolution scale: cell to organ level**
  - **Physical measurement uncertainty –imaging platform dependent**
  - **Biological variability- impacts measurement uncertainty**
  - **Need for quantitative methods for analysis ..as opposed to observer based measurements of change over time.**

- **Barriers: Convert data to knowledge, absence of reference standards or consensus for:**
  - **Image data collection-analysis across imaging platforms**
  - **Data query and inter-operability of validation tools**
  - **Image data and meta data integration with other laboratory assays**
  - **Standards for validation of performance of clinical decision tools**

Example: Prediction of overall survival after chemo in patients with NSCLC by FDG-PET



Weber WA et al. J Clin Oncol 2003.

Scope of Presentation: 4 topics

1. caBIG : Imaging workspace and open source tools

2. Web accessible reference image database resources
   - Phantom Studies
   - Clinical trial image data collections
   - Archives: Data integration

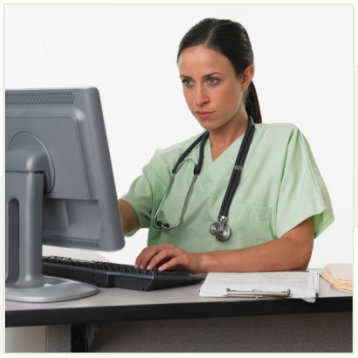
3. NCI international funding initiatives:
   - R01: Investigator Initiated grants
   - Research networks
     - Current generation of imaging platforms
     - Next generation of imaging platforms

4. Integrated approach to development of informatics and imaging standards

1. NCI Contract: caBIG® Core Principles

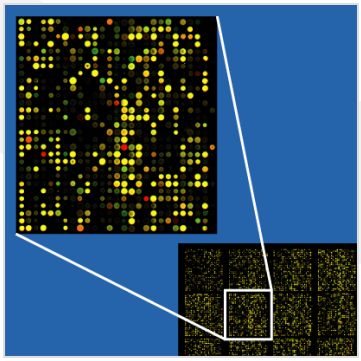
- **Open Access** – caBIG® is open to all, enabling wide-spread access to tools, data, and infrastructure
- **Open Development** – Planning, testing, validation, and deployment of caBIG® tools and infrastructure are open to the entire research community
- **Open Source** – The underlying software code of caBIG® tools is available for use and modification
- **Federation** – Resources can be controlled locally, or integrated across multiple sites

1. caBIG Path to Personalized Medicine
Major Challenge: Data Integration

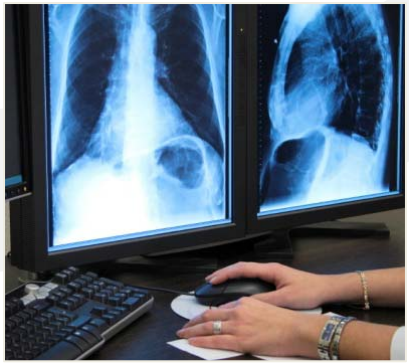


Clinical Data and
Trials Management

Biospecimen
Management



Molecular
Characterization



In Vivo
Imaging

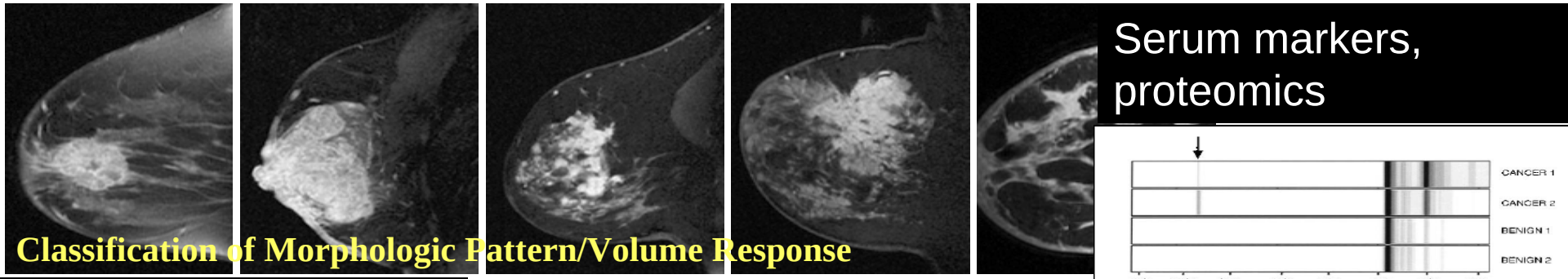
Clinical Study

Anthracycline

Taxane

Surgery & RT

Tam if ER+

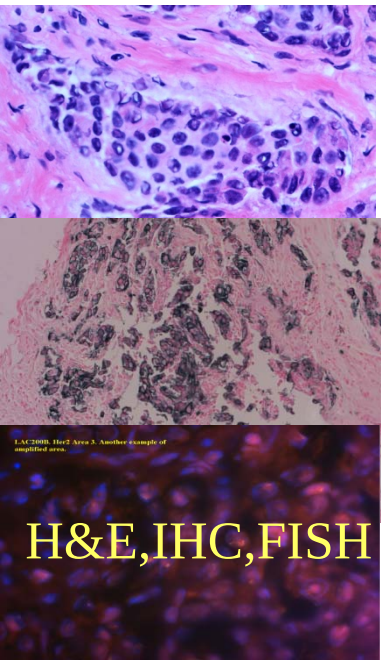


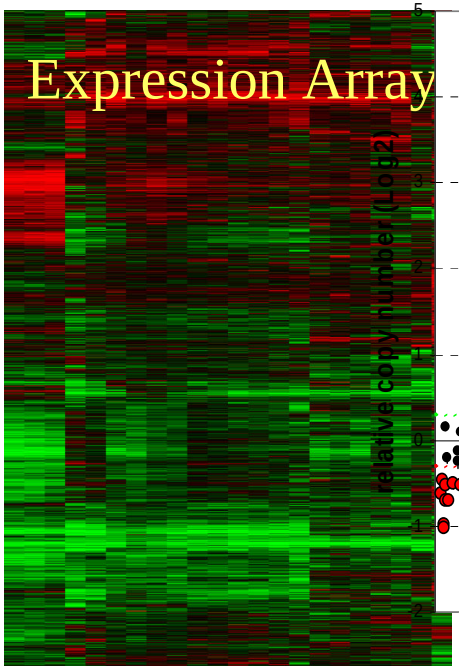
Classification of Morphologic Pattern/Volume Response

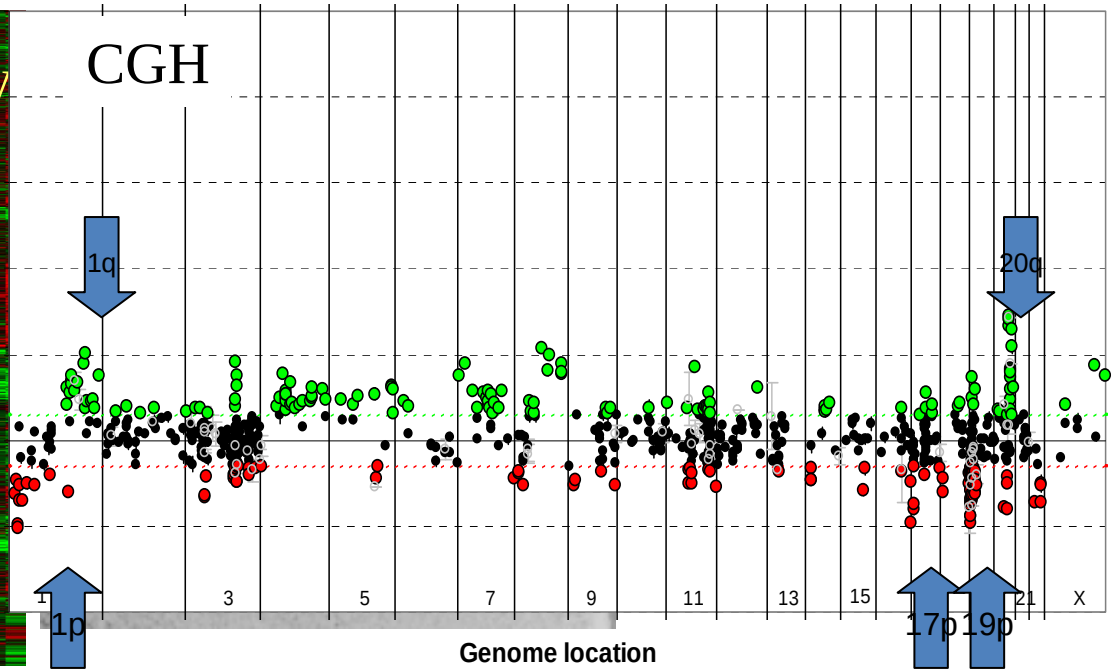
Serum markers, proteomics

Fig. 1. Proteomic spectra. Representative surface-enhanced laser desorption ionization time-of-

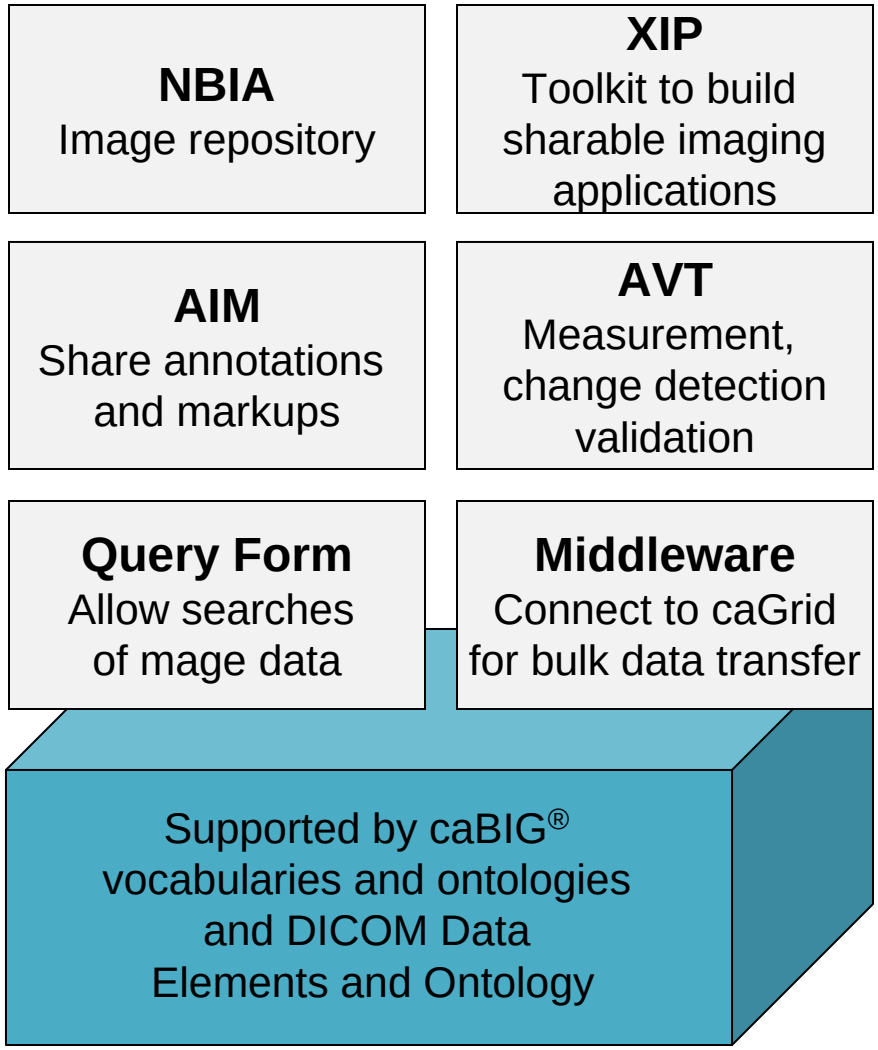
Tissue: Core or Surgica







1. NCI caBIG Imaging Workspace



- **Digital Imaging and Communications in Medicine (DICOM) is a standard for handling, storing, printing, and transmitting information in medical imaging.**
- **caBIG® Imaging tools are DICOM-compliant and allow for the annotation, visualization, and sharing of data.**
- **Specialists can select any or all of the tools to meet research or clinical needs**

2. NCI Contract: RIDER Database Resource

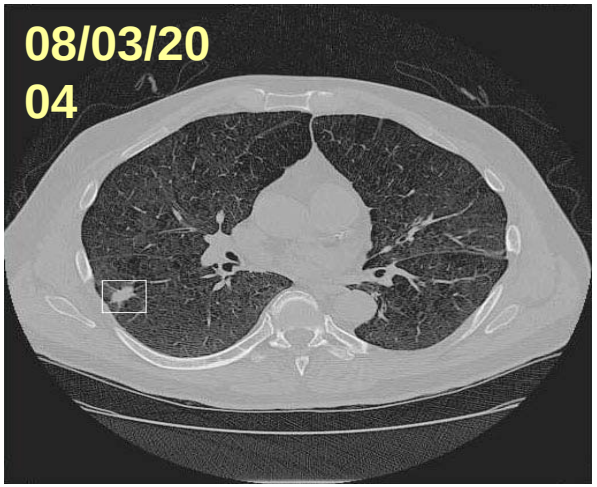
Public Resource of Image and Meta Data: CT, PET CT, DCE- DW MRI

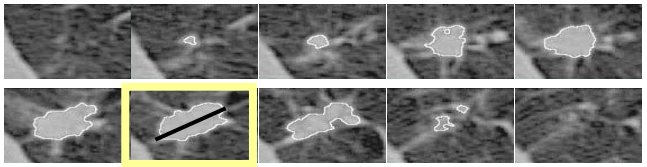
Repeat and longitudinal phantom and patient data-with results

Open architecture platform, inter operable validation tools: annotation, validation, statistical analysis

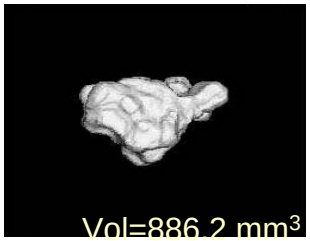
<u>Open Science: Benchmarking data collection-analysis tools</u>

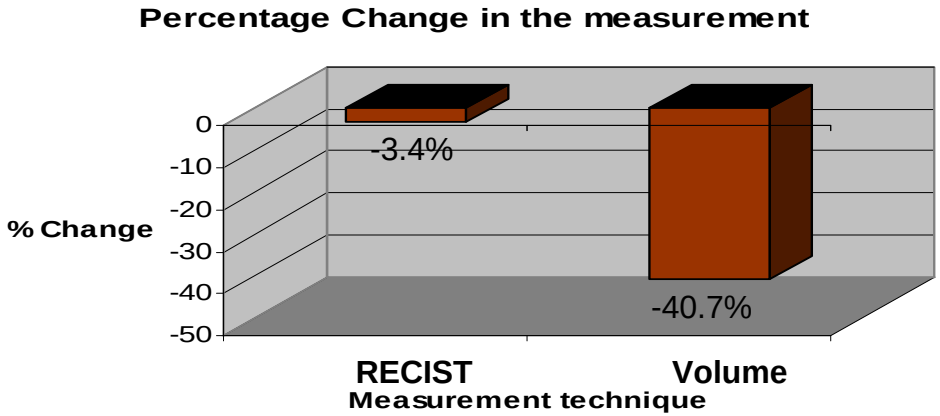
2. CT Lung: Measurement of Response to Therapy over Time

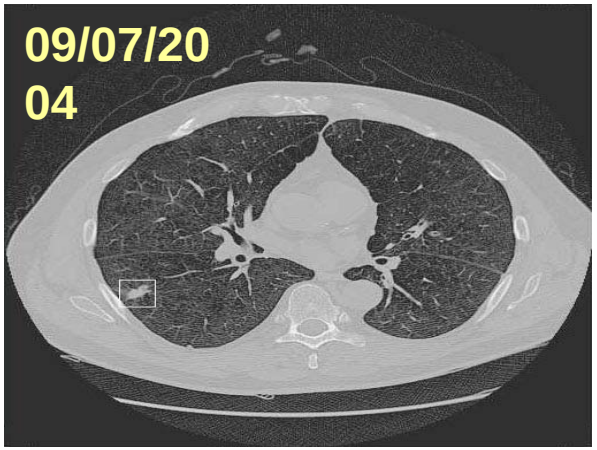


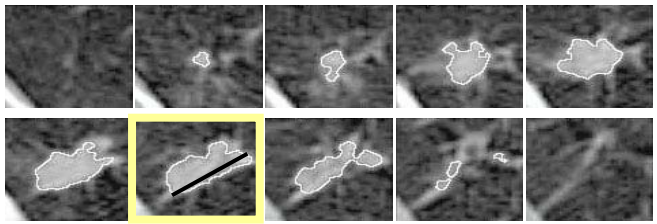


Diameter=17.7 mm

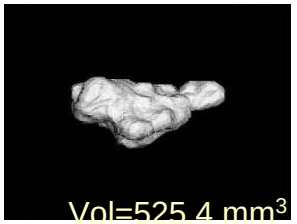






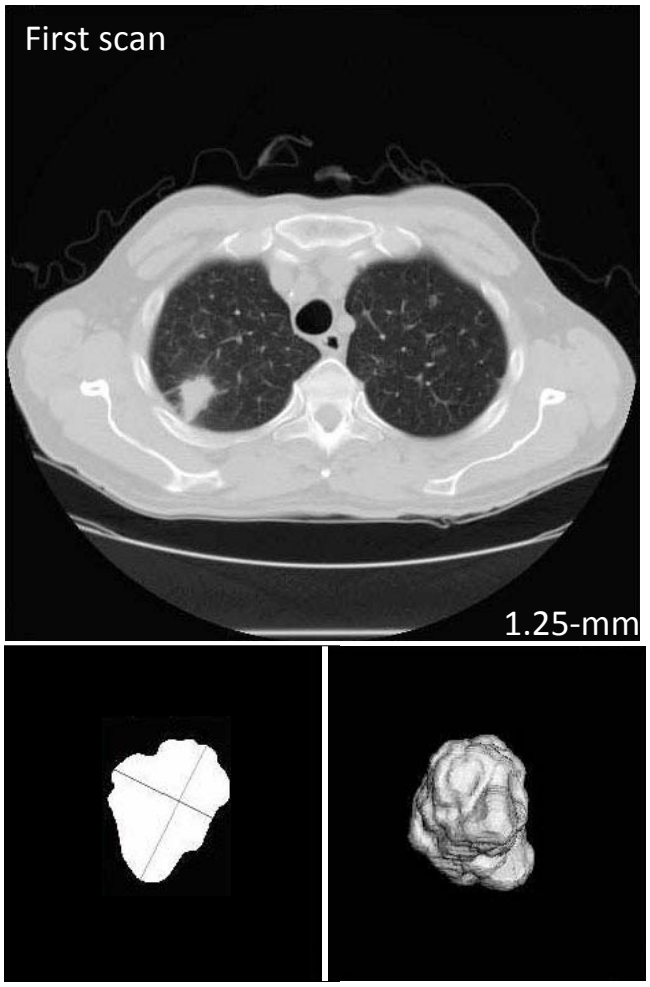


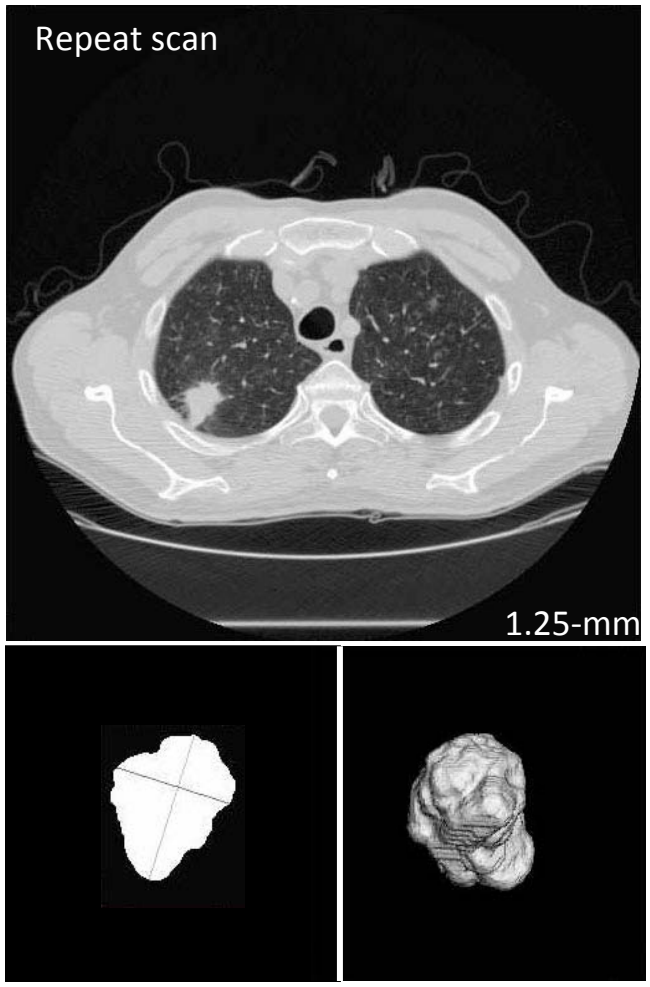
Diameter=17.1 mm



MSKCC DATA

2. Same-day repeat CT Study: Minimum Change

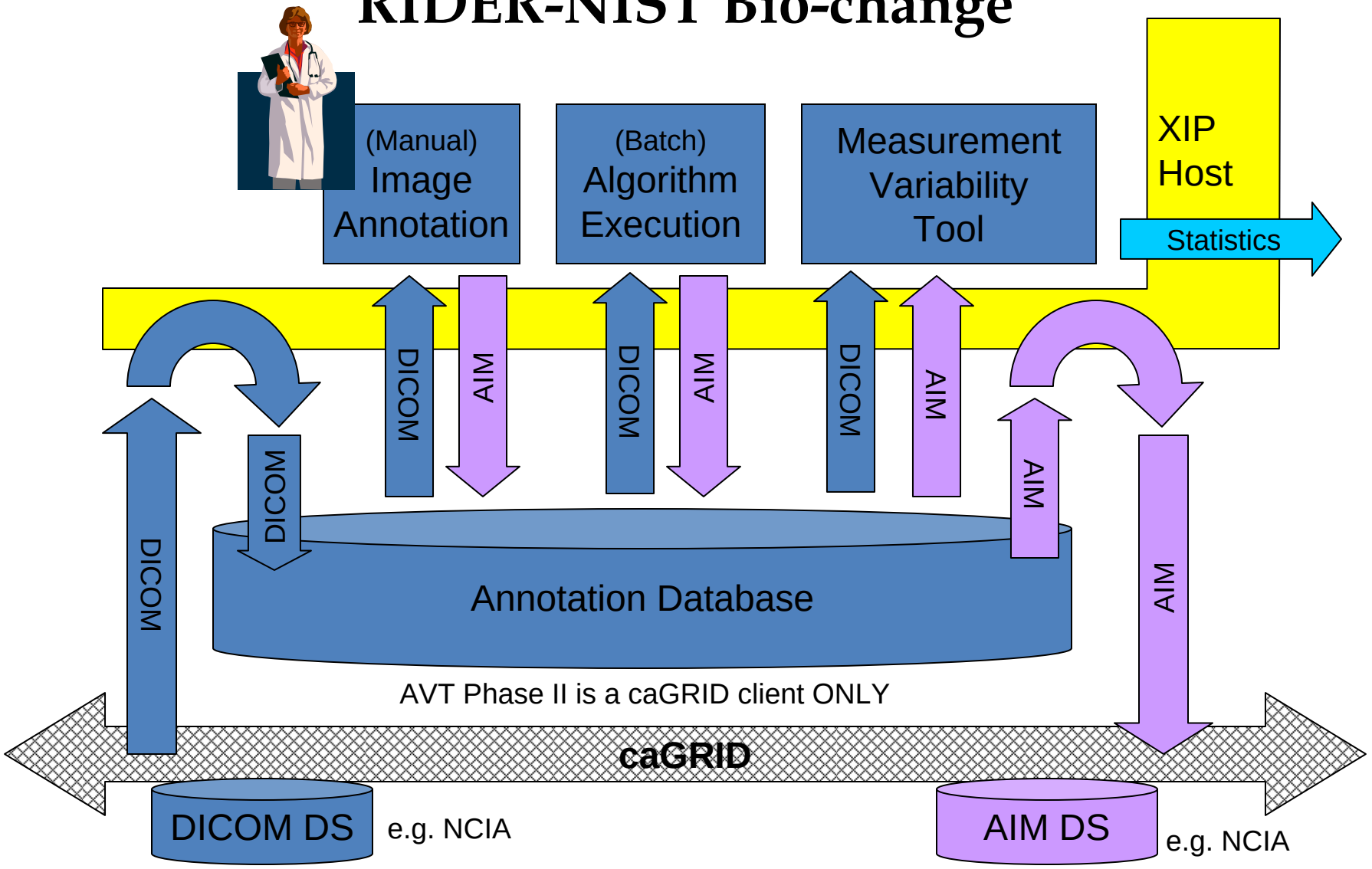




	First scan	Second scan	Relative Difference
Unidimension (mm):	27.6	27.8	0.7%
Bidimension (mm^2):	552	597.7	7.9%
Volume (mm^3):	4957.1	4852.3	2.1%

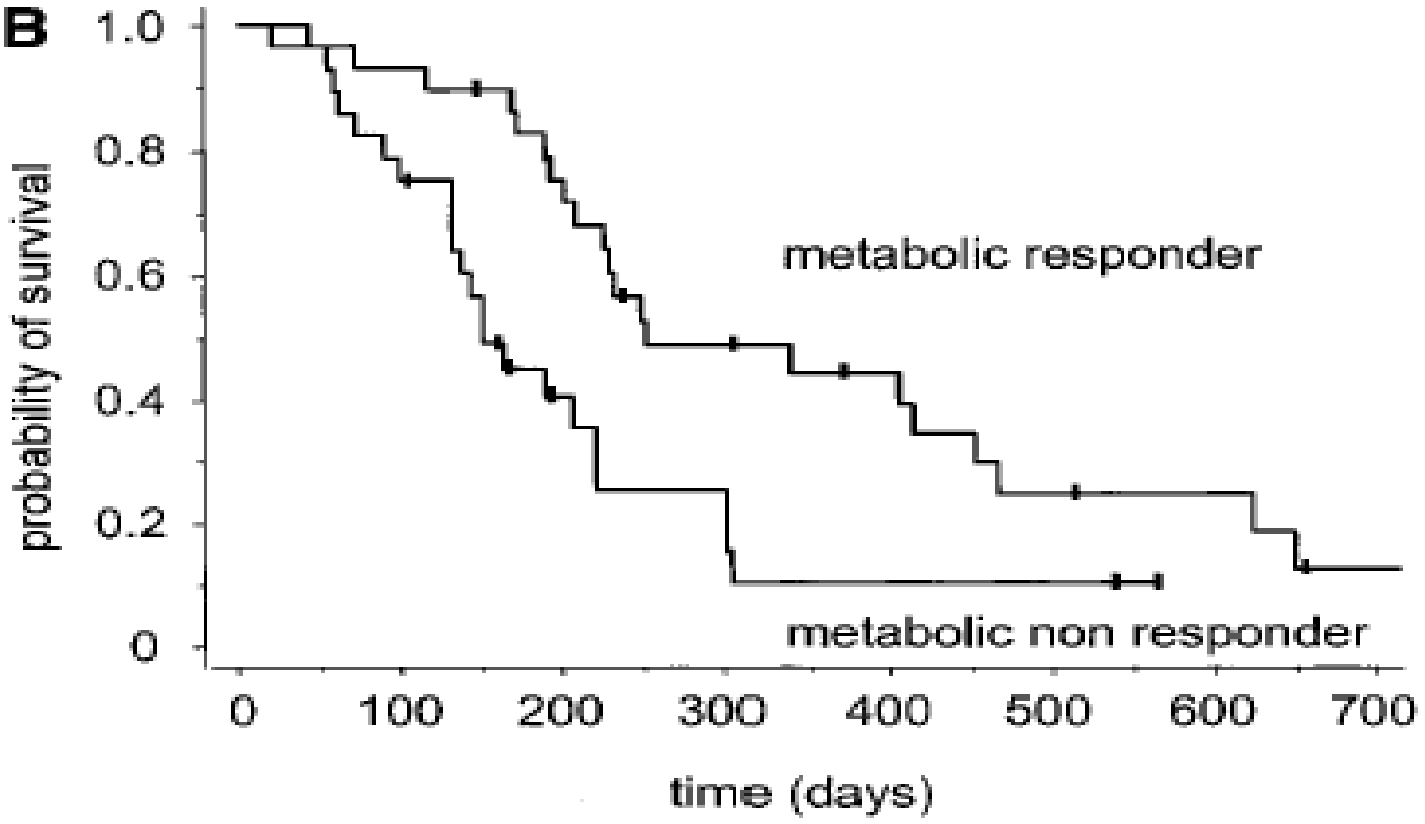
Courtesy of Drs. Binsheng Zhao and Lawrence H Schwartz

2. NCI Contract: caBIG: Virtual Imaging Workspace RIDER-NIST Bio-change



caBIG AVT: Algorithm Validation Tools: Clinical Performance

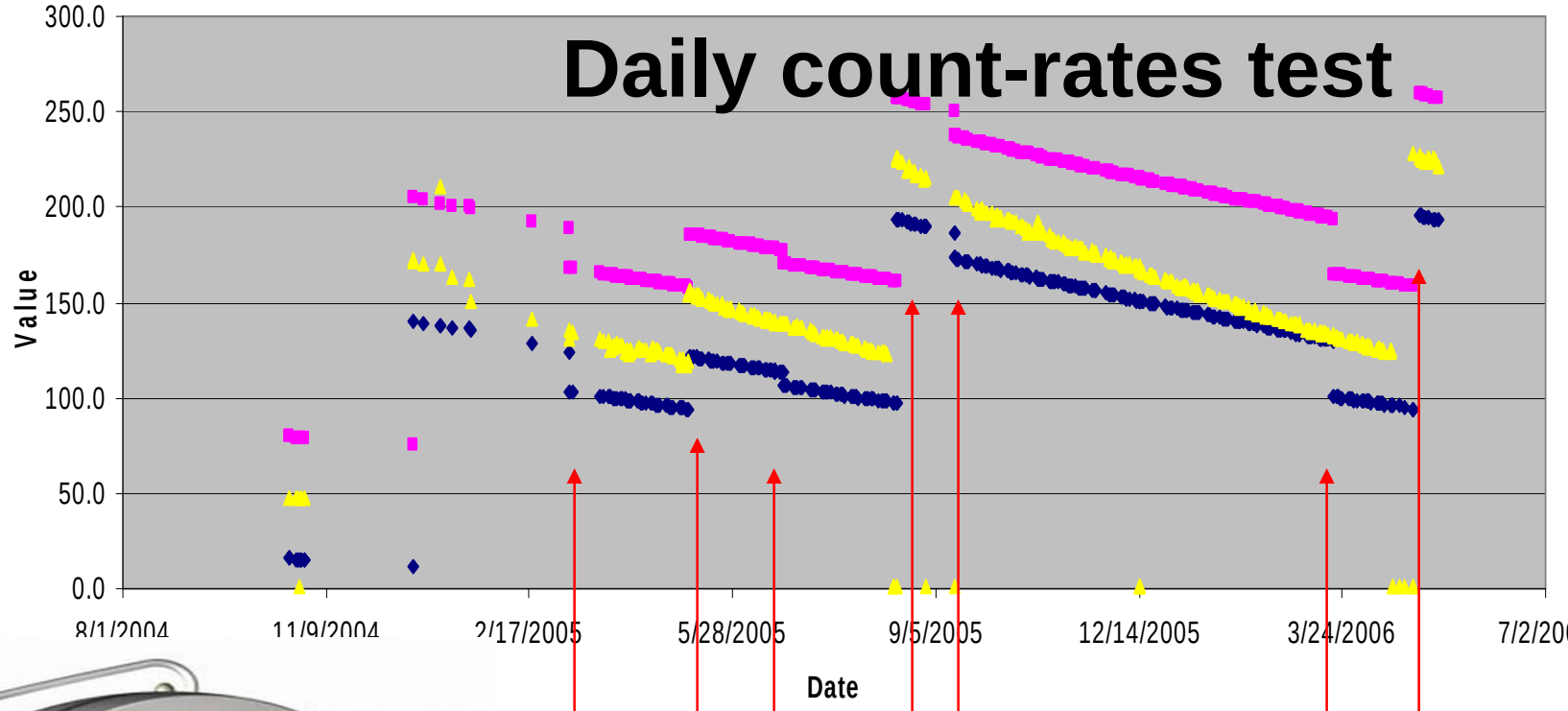
2. Example: Prediction of overall survival after chemo in patients with NSCLC by FDG-PET



Weber WA et al. J Clin Oncol 2003.

2. PET CT: Systems Changes Over Time
Sources of Bias/Variance:

Osama Malawi, PhD
MD Anderson CC



ew Baseline

Source Changed

Source Changed

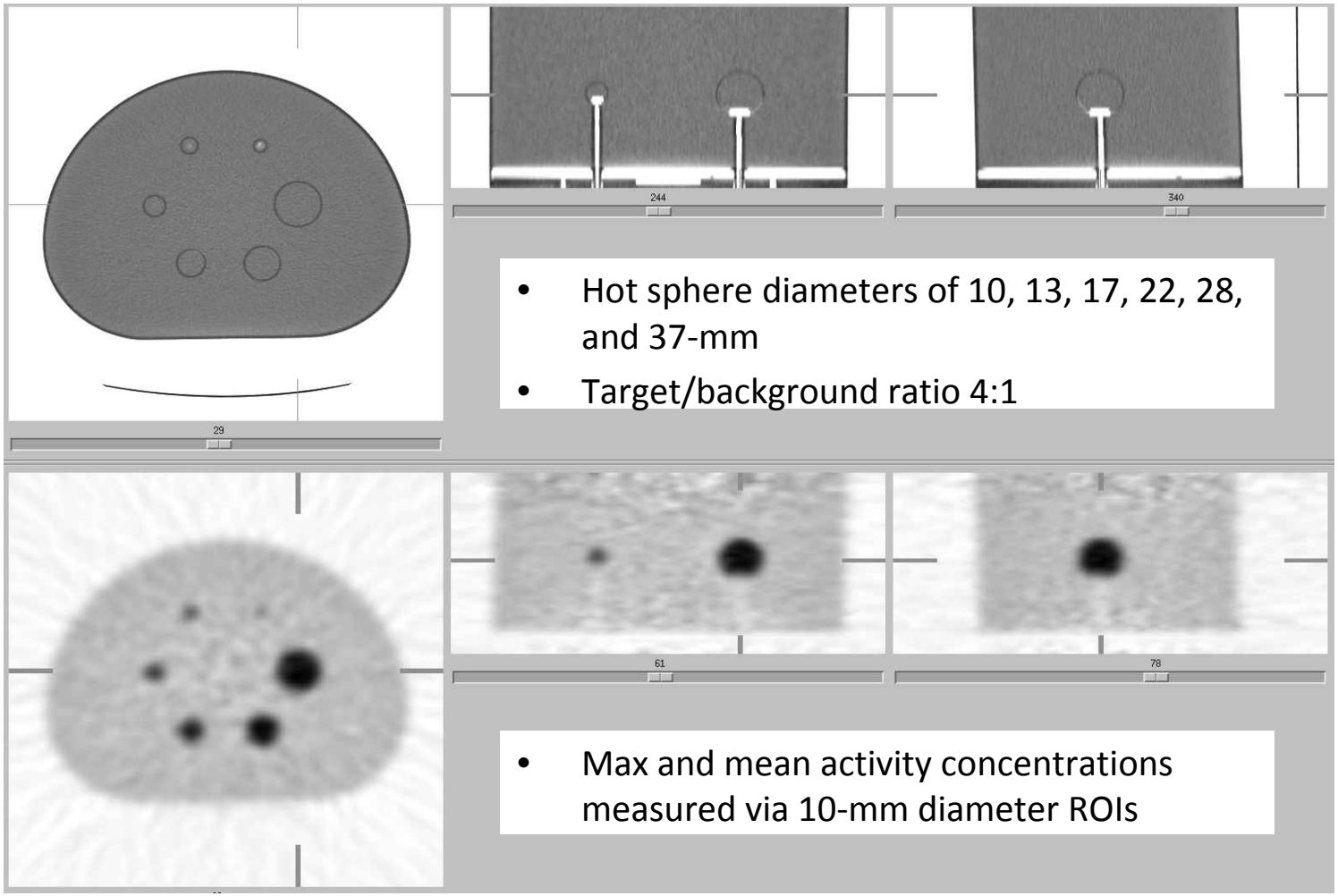
Software upgrade

CEM Board Exchange

New Baseline

2. NCI Contract: PET: System Drift over Time

Paul Kinahan Uni. Of Washington: SUV Sphere Measurements



- Hot sphere diameters of 10, 13, 17, 22, 28, and 37-mm
- Target/background ratio 4:1

- Max and mean activity concentrations measured via 10-mm diameter ROIs

Joint Collaboration: [NCI, FDA , NIST] and [SNM, AAPM, RSNA]

3. NCI PAR:07 214: R01 Traditional Funding Mechanism Academic-Industry Partnerships: $500K/year.

Translational Research Goals: Early cancer detection, diagnosis, IGI, and therapy response, including imaging as a biomarker

Research emphasis:

- **Imaging Platforms: Human and Pre Clinical**
- **Validation of multi-modality imaging platforms**
- **Quantitative Imaging methods as a biomarker**
- **Development of public resource for Q/C, phantoms, software tools assessment**
- **Travel –Collaboration: FDA and NIST scientists**
- **Multiple PI's: Option International PI's.**
- **caBIG Compliant: Open source architecture and software**
- **CSR Review: Special Emphasis Panel.**
- **Link to NCI funded U01's and U54's [Described later]**

3.PAR 08 225: Quantitative Imaging Network (QIN) Evaluation of Responses to Cancer Therapies

Mission

- **Quantitative Imaging:** Develop methods for data collection and analysis that permit the implementation of quantitative clinical decision tools to measure response to therapy.
- **Implementation Model:** Clinical trials in cancer centers or other oncology trial groups -

Commercial Platform Example: PET CT

Goals

- **Multi PI U01 Grants:** Support multi-disciplinary and multi-site teams, including industry
- **Budget:** Total direct costs not to exceed $500k
- **Research Component:** Imaging scientists with expertise in quantitative imaging and informatics
- **Clinical Component:** Cancer Centers, SPORES, other groups experienced in early phase clinical trials
- **U01 Mechanism. International investigators can apply.**

3. PAR 08 225: Quantitative Imaging Network (QIN) Evaluation of Responses to Cancer Therapies

Proposed Strategy

- **10-15 U01 centers**
  - Array of Therapy Trials
  - Array of Imaging Platforms
  - Array of Software Tools
- **Consensus Deliverables**
  - Imaging Protocols
  - Imaging Q/C Methods
  - Image Database Resources
  - Clinical Outcomes
  - Optimization-Validation Studies for Therapy and Drug Trials
- **Associate Members (AM's)**
  - Expand the number of sites Cancer centers and Overseas

Web Assessable Resources

3. Network For Translational Research (NTR)

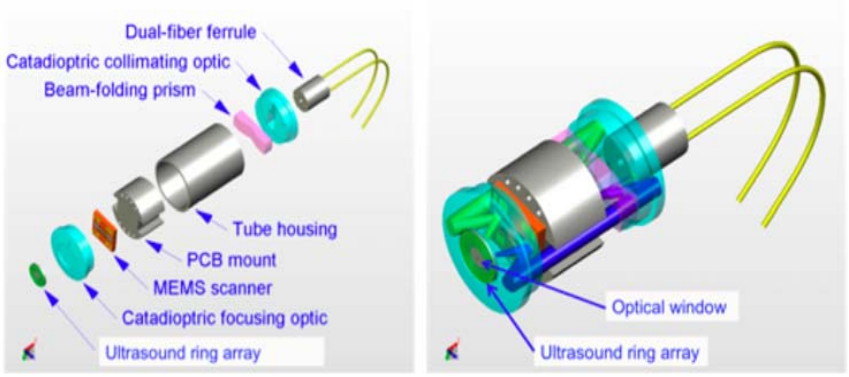
Mission

- To develop, optimize, and validate multi-modal molecular imaging platforms and methods so that they can enter single or multi-site clinical trials and incorporated into clinical trials/practice within 5 years.

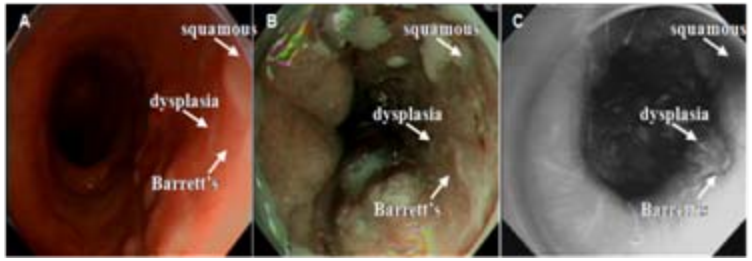
Goals

- Develop integrated platforms for an array of imaging modalities across different resolution scales from the tissue -organ level.
- Drive consensus on methods to validate performance of these multi-modal platforms with a goal of broader dissemination and FDA approval.

3MM MEMS Optical/US System Detection/Characterization/Treatment



GI: Cather Based Molecular Imaging



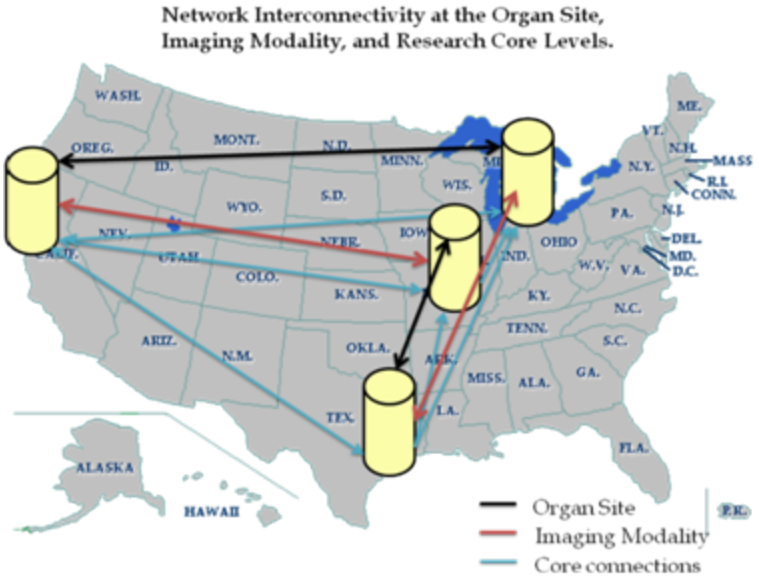
Normal illumination **Fluorescence** **Filtered White light**

3. Network for Translational Research (NTR): Optical Imaging in Multimodal Platforms

- Four Multi Site centers
  - Two studying cancers of GI tract.
  - Two studying breast sentinel lymph node staging.

- Five network-wide cores
  - Standards & Compliance
  - Chemistry Probes & Guided Therapy
  - Information Technology
  - Instrumentation & Industrial Relations
  - Validation & Clinical Studies

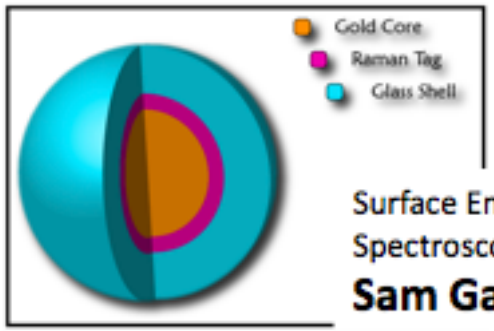
- Associate Members (AM's)
  - **International investigators can apply**
  - **Leveraged funding sources**



Stanford University
University of Michigan
Washington University
University of Texas Health Science

3. Validation Challenges: Multi Modality Molecular Imaging Platforms

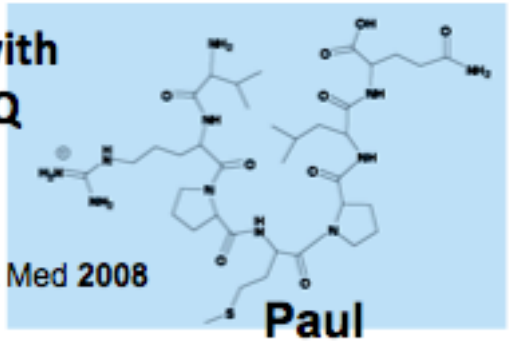
Multiplexed Probes



Surface Enhanced Raman Spectroscopy (SERS) Nanoparticle

Sam Gambhir

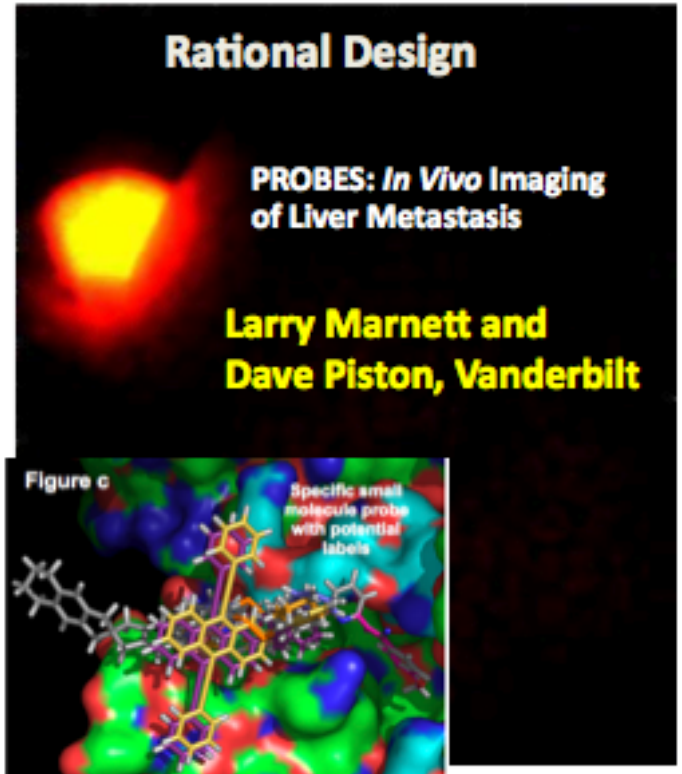
Directed therapy with Peptides: VRPMPLQ



Hsiung *et al.* Nat Med **2008**

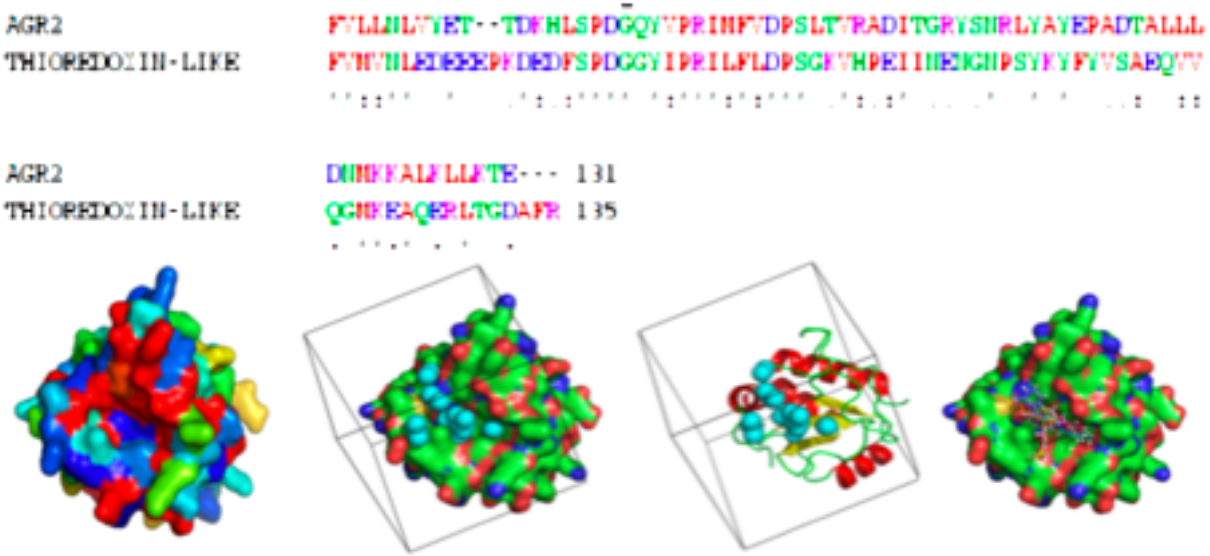
Paul Wender

Rational Design



Larry Marnett and Dave Piston, Vanderbilt

Molecular Modeling

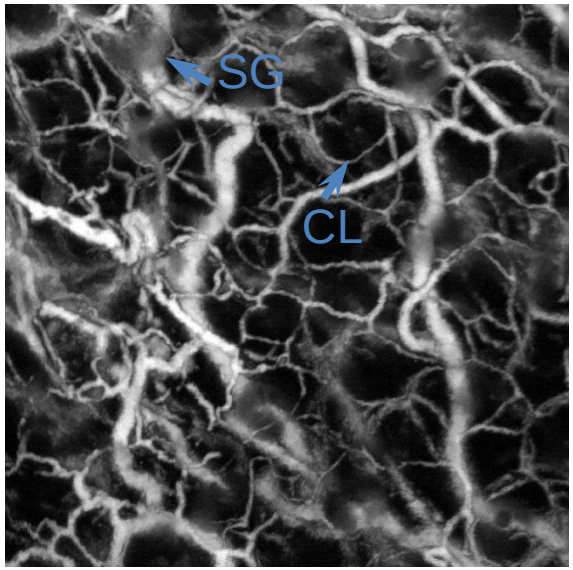


Therapeutics: AGR2 control of esophageal cancer

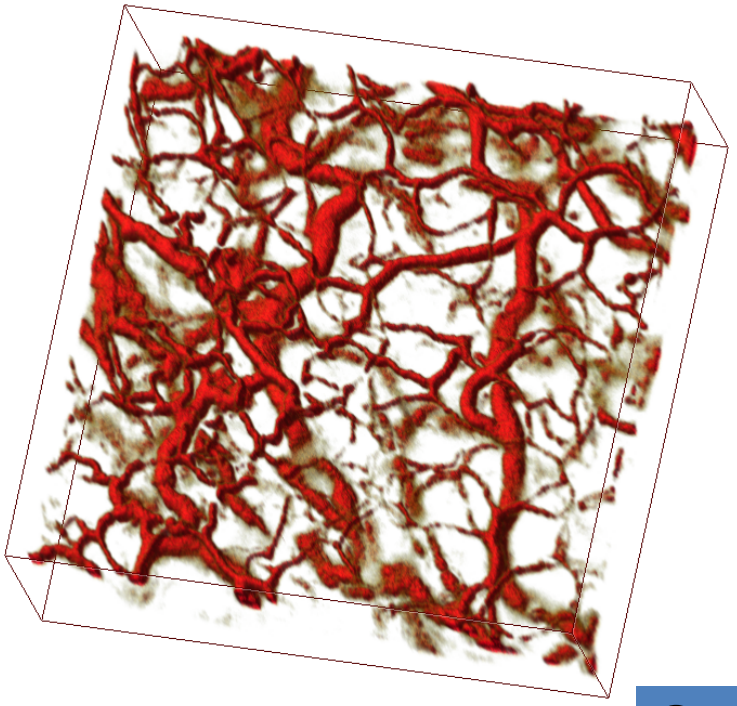
David Ostrov, University of Florida

3. Validation Challenge: High Resolution Platforms
Photo-acoustic Microscopic Imaging
Nude Mouse In Vivo: 5 Micron Resolution

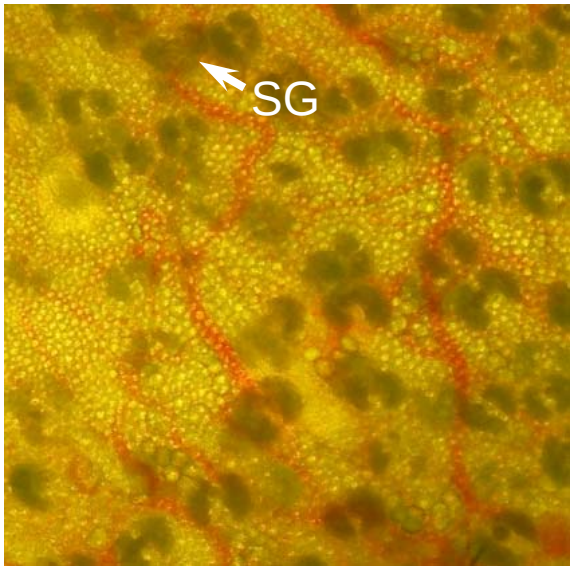
Photoacoustic image: Projection



Photoacoustic image: 3D



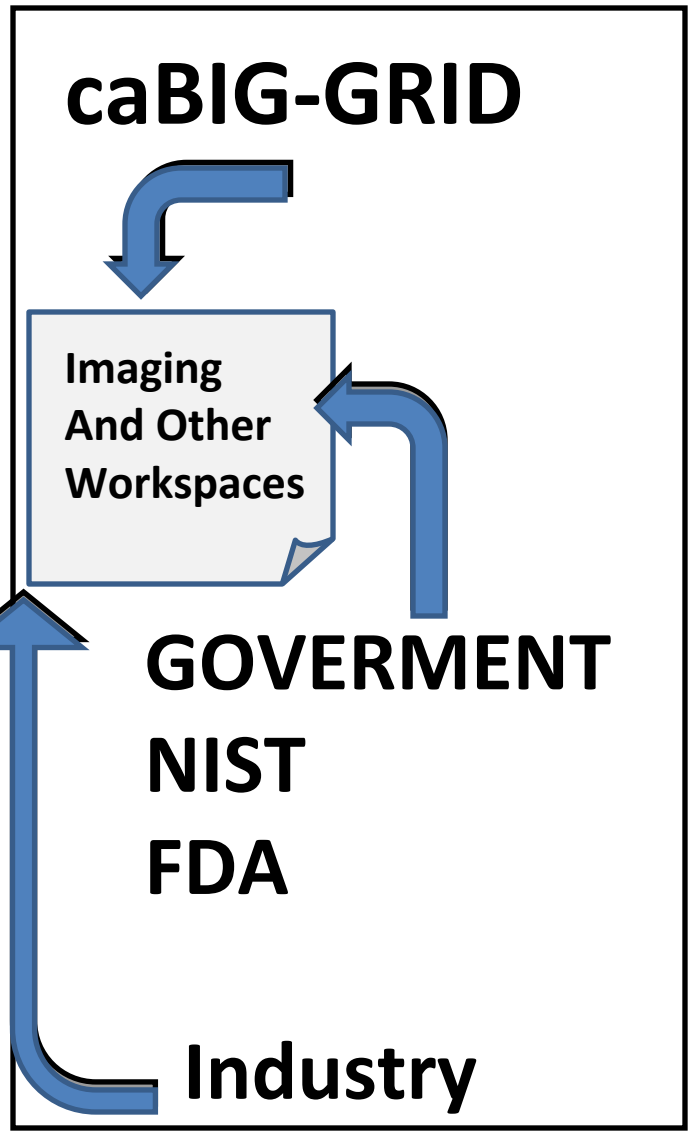
Optical microscopic image



SG: sebaceous glands
CL: capillary (diameter of ~5 μm)

Optics Letters 33, 929 (2008).

4. NCI is exploring an integrated approach for creating reference standards for both data and software tool interoperability and clinical decision software tools.

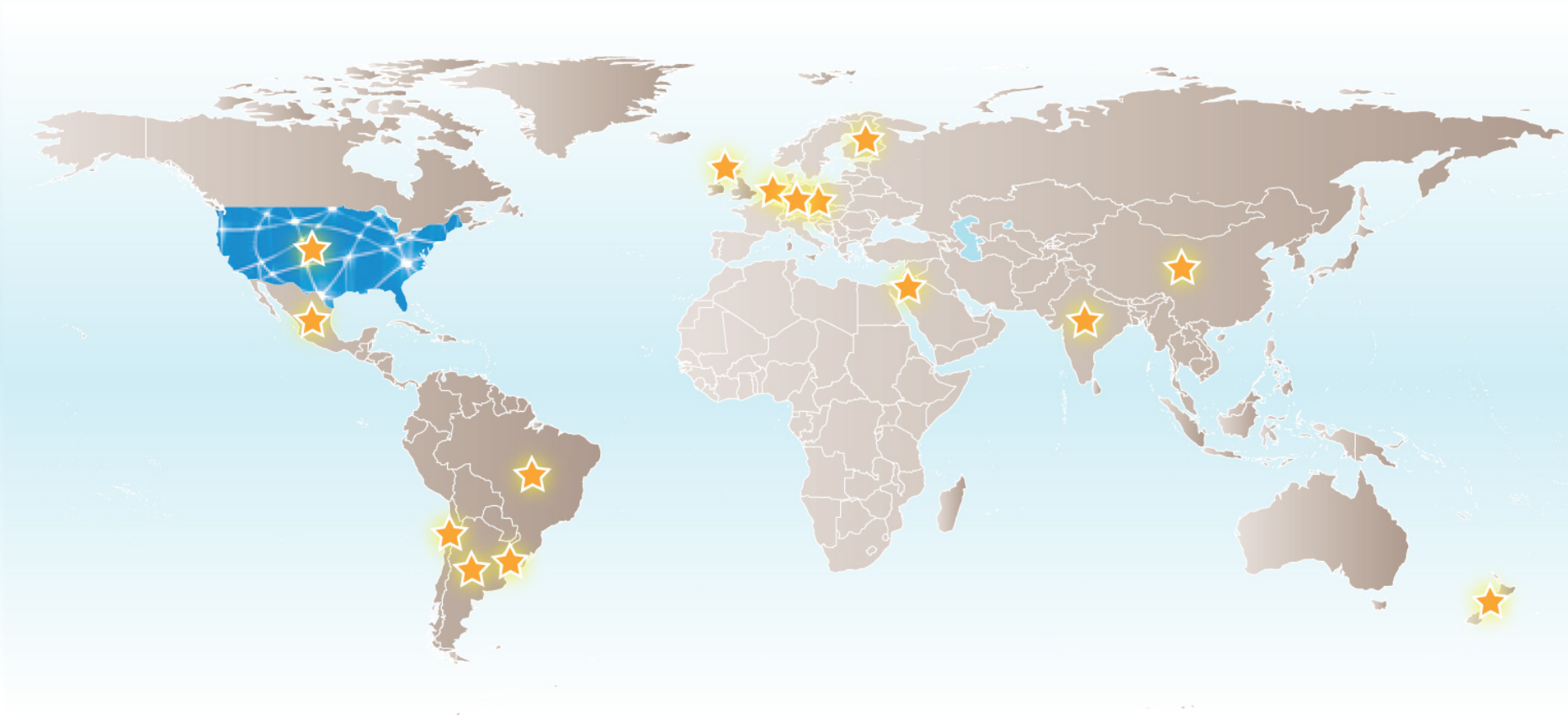


Research Networks
Academia-Industry

R01 Funding
Academia-Industry

USA: Cancer and other Research Centers –
Consensus: Measurement Uncertainty
Consensus: Data Integration-Standards
Critical Need……..
National and International Outreach!

4. Explore Pilot Project: Extend caBIG to include Global Research Networks



caBIG®, the world's largest biomedical research "highway", connecting a growing number of people and organizations across the globe

Pilot Project: Potential Avenues

NCI Imaging Networks

❑ Membership Roles

- Steering Committee
- External Advisory Committee
- Selected Research Cores

❑ Functional Role

- Participate PAR 07 214 (R01)
- Link R01's with Networks
- Workshop Reports
- Consensus based Publications-
  - Validation Methods
- Public Private Partnerships Foundation NIH or FDA

Potential Impact

❑ Technology Dissemination

- Reduce scientific barriers for approval of combined technologies
- Development of resources to promote standards for validation of imaging platforms
- Promote GLP and GMP in earlier in development of technology
- Participate in comparative effectiveness early in the validation of technologies

URL's for reference

- **NCI CIP Program: http://imaging.cancer.gov/**
- **caBIG™ Website: https://cabig.nci.nih.gov**
- **FDA Critical pathways report: Drug Response:**
- **http://www.fda.gov/oc/initiatives/criticalpath/**
- **FNIH Biomarkers Consortium**
  http://www.biomarkersconsortium.org
- **Network for Translational Research (NTR):**
  http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-08-002.html
- **Quantitative Imaging Network (QIN)**
  http://grants.nih.gov/grants/guide/pa-files/PAR-08-225.html
- **RSNA QIBA RSNA QIBA**
  http://www.rsna.org/Research/qiba.cfm
- **NIST: Interagency Workshop on Biomarkers 2006: (NCI, NIH, FDA, NIST)**
  http://usms.nist.gov/workshops/bioimaging.htm

3. Network: Expansion and Opportunities

Associate Members

- **Associate Member Organizations.**
  - Strengthen Research Teams
  - Strengthen Research Cores
  - Increase consensus-building base.
  - Bring data & methods to the research community on a timely basis.
  - Develop web bases resources
- **Leverage funding**
  - Associate members will have grant funding in cancer imaging.

International Members

In progress

- **Cancer Research UK?**
  - Imperial College London
  - The Institute of Cancer Research (ICR)
  - King's College London (KCL) & University College London (UCL)
  - University of Oxford
- **EU Funded Centers?**
- **Australia/other**

Network Governance

Steering Committee

❑ **Membership**

- The PI and one other investigator from each center (1 vote cumulative)
- 3 NCI program staff (1 vote cumulative)
- Other Research staff (FDA, NIST etc.); no voting rights

❑ **Functional Role**

- Provides guidance on governance issues of NTR including cores

External Advisory Committee

❑ **Membership**

- **Scientific Societies:** RSNA (QIBA), SNM, AAPM, ISMRM.
- **FDA, NIST**
- **Imaging Industry and Pharma:** Leverage interest in common validation approaches for FDA guidance documents etc
- **International:** Cancer Research UK, EU, others?

Network: Validation Challenges

Key Requirements

- Large Scale: Inter-operable validation and statistical tools
- Multi-Modal Image Registration
- Pathology Correlation-Registration across different resolution scales
- Sharing devices, tools and probes
- Animal Cancer Models
- GLP and GMP across sites

Common Research Cores

- Information Technology
- Chemistry Probes & Guided Therapy
- Instrumentation & Industrial Relations
- Validation & Clinical Studies
- Standards & Compliance

NCI Research Resources

NCI (SAIC Contracts)

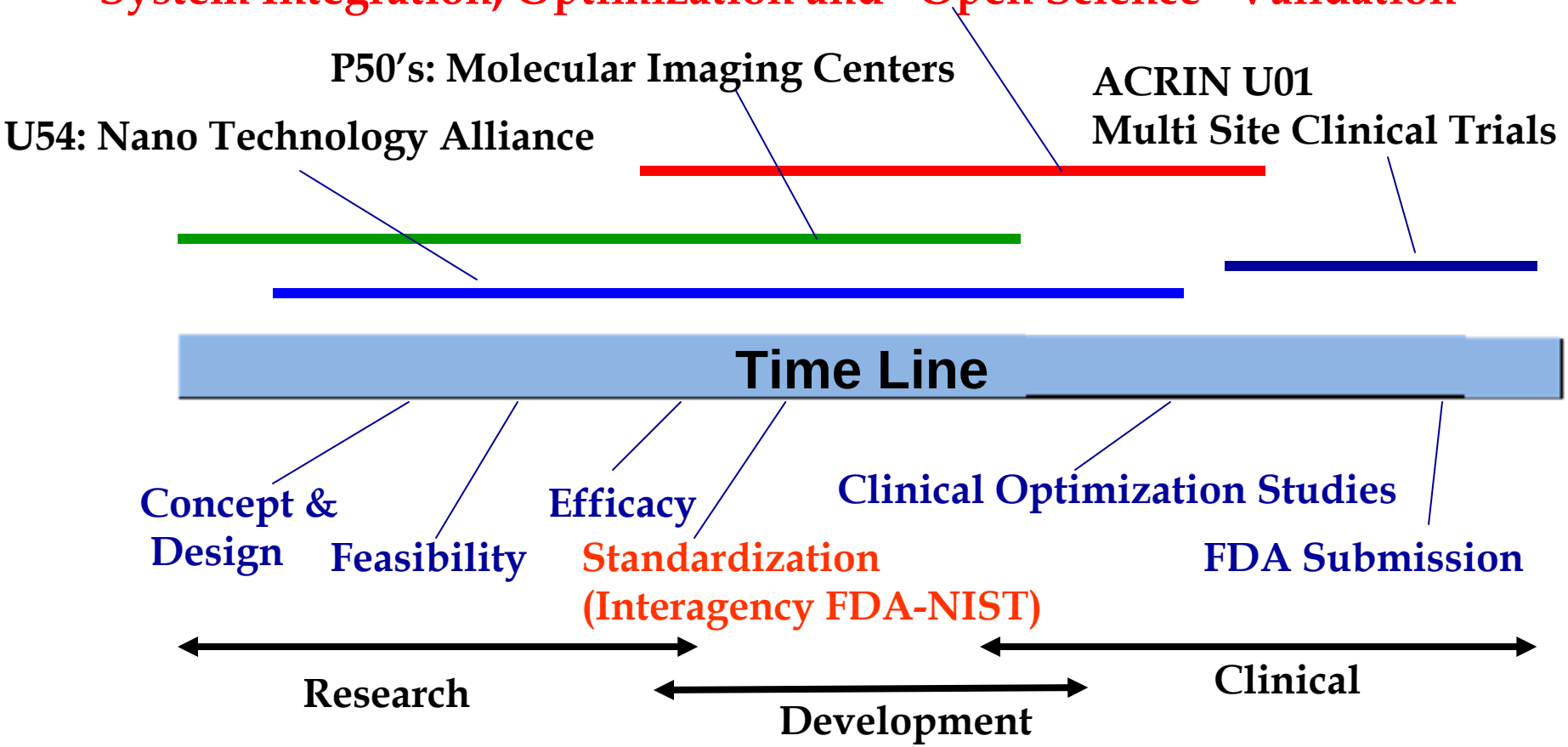
- Ca-GRID and Federated Databases
- NCI caBIG Imaging Workspace
- NCI Biomedical Imaging Archive
- Reference Image Database to Evaluate Response (RIDER)
- RIDER: Quality Control Phantoms

Goals

- Data Integration and Clinical Decision Tools
- Computer Platform for Interoperable Tools
- Storage Clinical Trial Data
- Targeted Data Sets for Benchmarking Tools
- Q/C for Drug Trials

Optimization of Imaging Platforms for Next Generation of Clinical Trials (5 years)

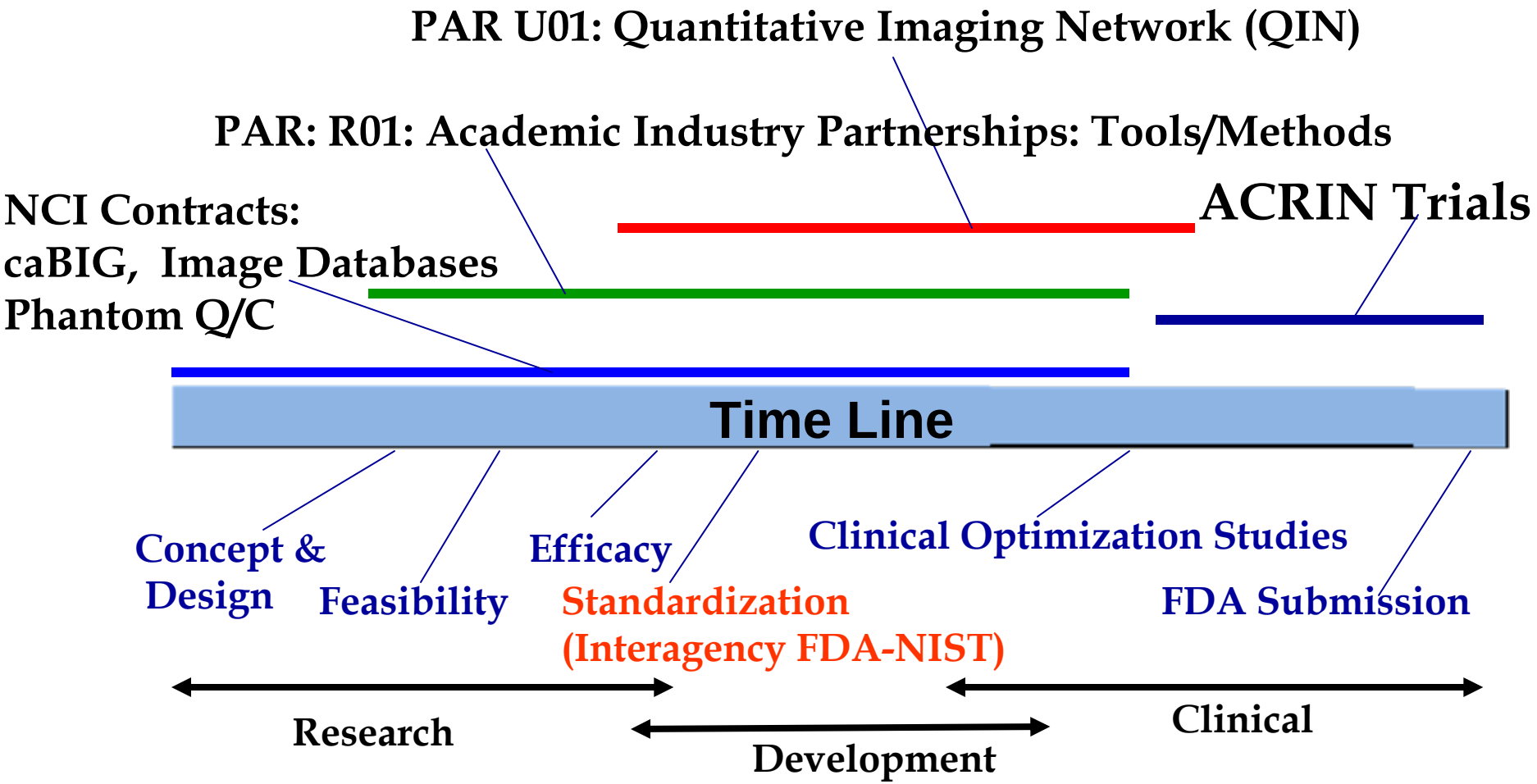
U54: (NTR): Network of Networks: Highly Leveraged System Integration, Optimization and "Open Science" Validation



http://imaging.cancer.gov
lclarke@mail.nih.gov

I SPY Trial Web Portal
Academic Software Tools

NCI Strategy: Current Generation of Imaging Platforms For Clinical Trials



http://imaging.cancer.gov
lclarke@mail.nih.gov

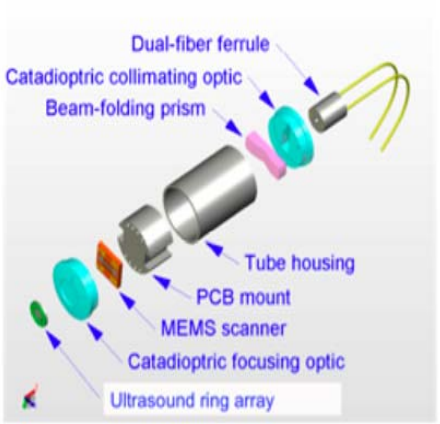
Mission: Imaging Technology Branch:

- **Development and validation of current and next-generation of imaging platforms, methods and web accessible resources, as required for their broad dissemination, and FDA approval**

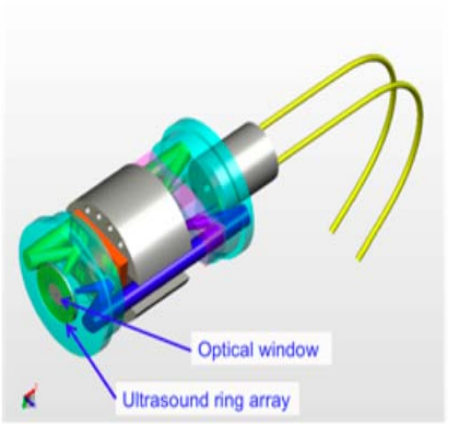
- **Goal: Provide imaging methods for cancer research and clinical trials that are validated in a standardized manner**

Current Generation: PET CT

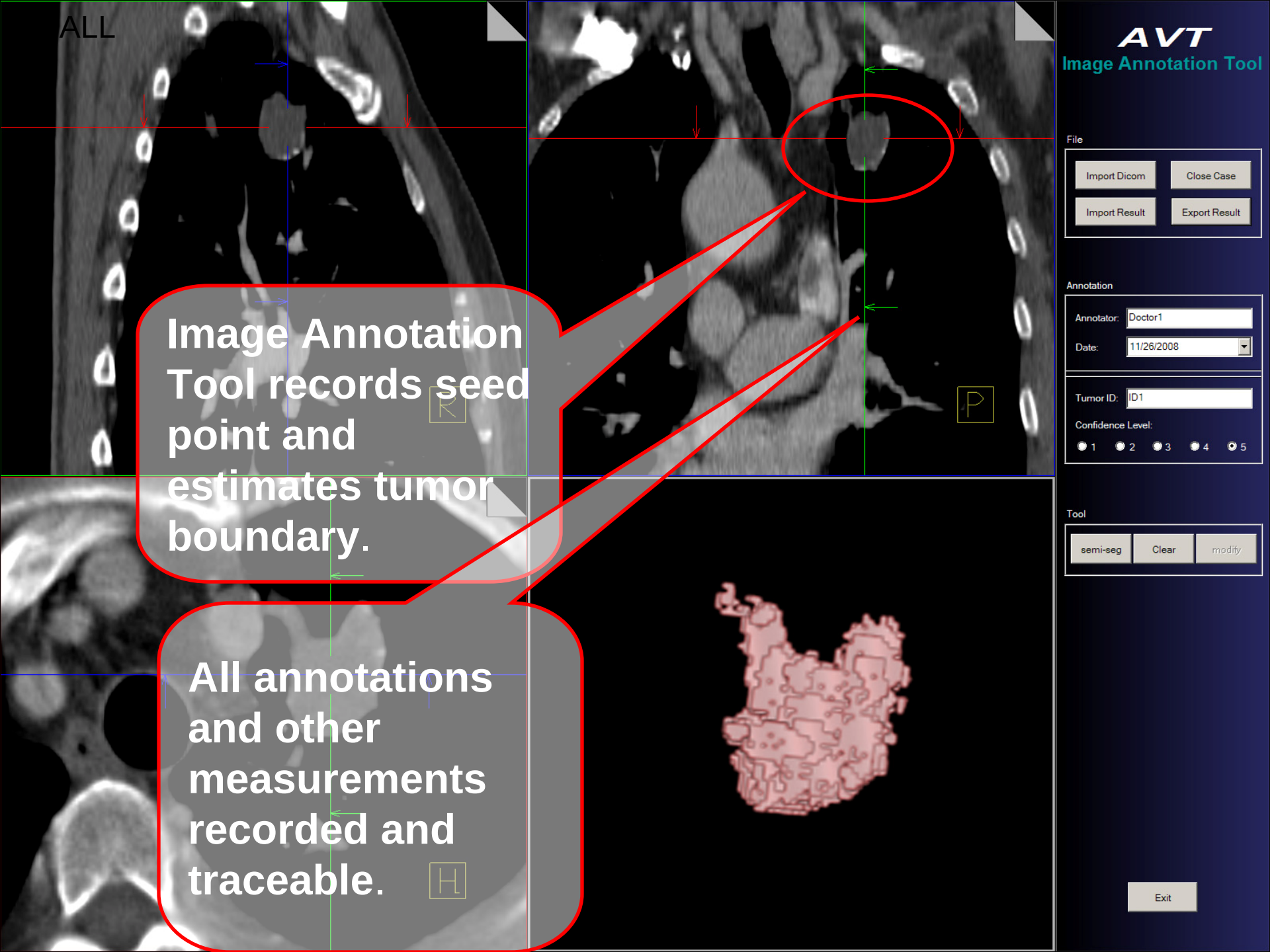
Next Generation: Optical-US 3 mm



(a)



(b)


ALL
AVT
Image Annotation Tool
File
Import Dicom
Close Case
Import Result
Export Result
Annotation
Annotator:
Doctor1
Date:
11/26/2008
Tumor ID:
ID1
Confidence Level:
1
2
3
4
5
Tool
semi-seg
Clear
modify
Exit
Image Annotation Tool records seed point and estimates tumor boundary.
All annotations and other measurements recorded and traceable.

CaBig Data Integration Problem
I SPY Neoadjuvant Breast Trial

Mine data to bring better science insight to bear on decisions to change therapy and guide the introduction of new therapeutic agents

NCI Cancer Bioinformatics Grid

Modalities	Participating Sites
Genomic & Expression Markers	UCSF, UNC, NKI, MSK
Serum Markers, MRI Imaging & Marker Correlation	UCSF
Clinical Study Design & Patient Accrual	MD And + Wyeth-Ayerst
Cyclin Assays & MRI Pathology Coordination	U Penn
Tissue Processing & Marker Core Facility	UCSF & UNC

Pharma/Biotech

Amgen
Genomic Health
Genentech
Novartis
eVelos
Agendia
Wyeth-Ayerst

Participating Sites

Univ. of Chicago
Dartmouth
Univ. of Alabama
UT Southwestern
Univ. of Washington
U of Minnesotra
Emory