Scientific Evaluation of the Clinical Validity and Utility of Genetic and Genomic Risk Factor Information

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Duke Institute for Genome Sciences & Policy

Personal Genomics
December 17-18, 2008

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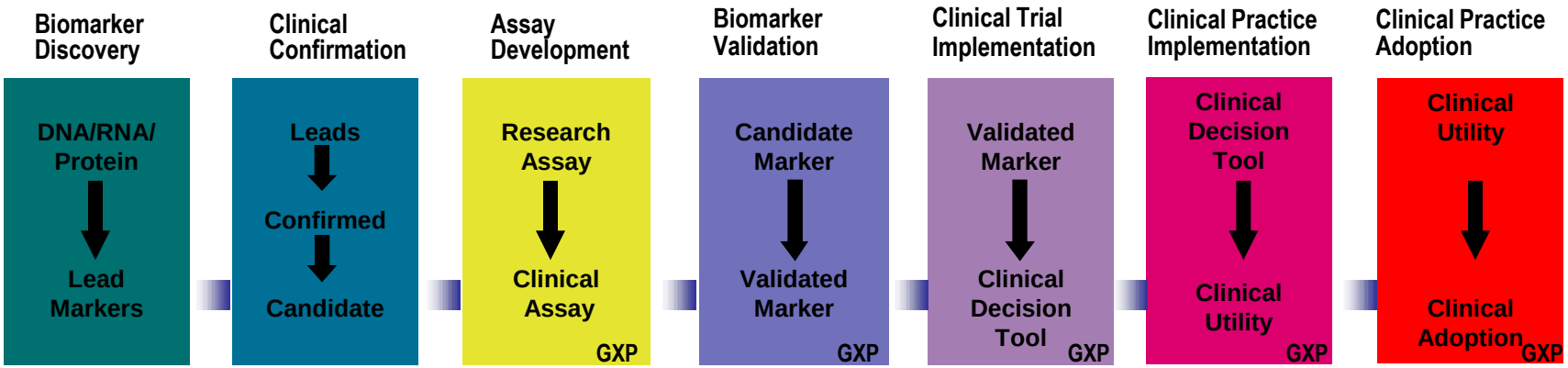
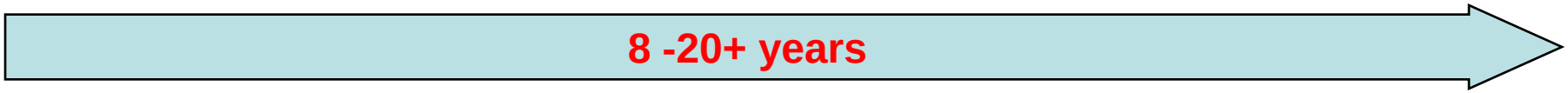
The 'Translational Continuum' for Biomarkers





Ginsburg, 2001

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Building the Infrastructure to Make this Work

- Biobanking
  - Coordinated efforts
  - Operational and informatics support
  - Standards
- Genomic Technologies
  - Core laboratories
  - Economies of scale
- Informatics
  - Reliable, interoperable EHRs
  - Integration of research, clinical, molecular data
- Biostatistics
  - Critical shortage must be addressed
  - Physician training in quanitative skills
- Decision Making
  - Understanding of human decision making
  - Biological, psychological and social factors
  - Education of health care professionals

Califf and Ginsburg, JAMA, 2008

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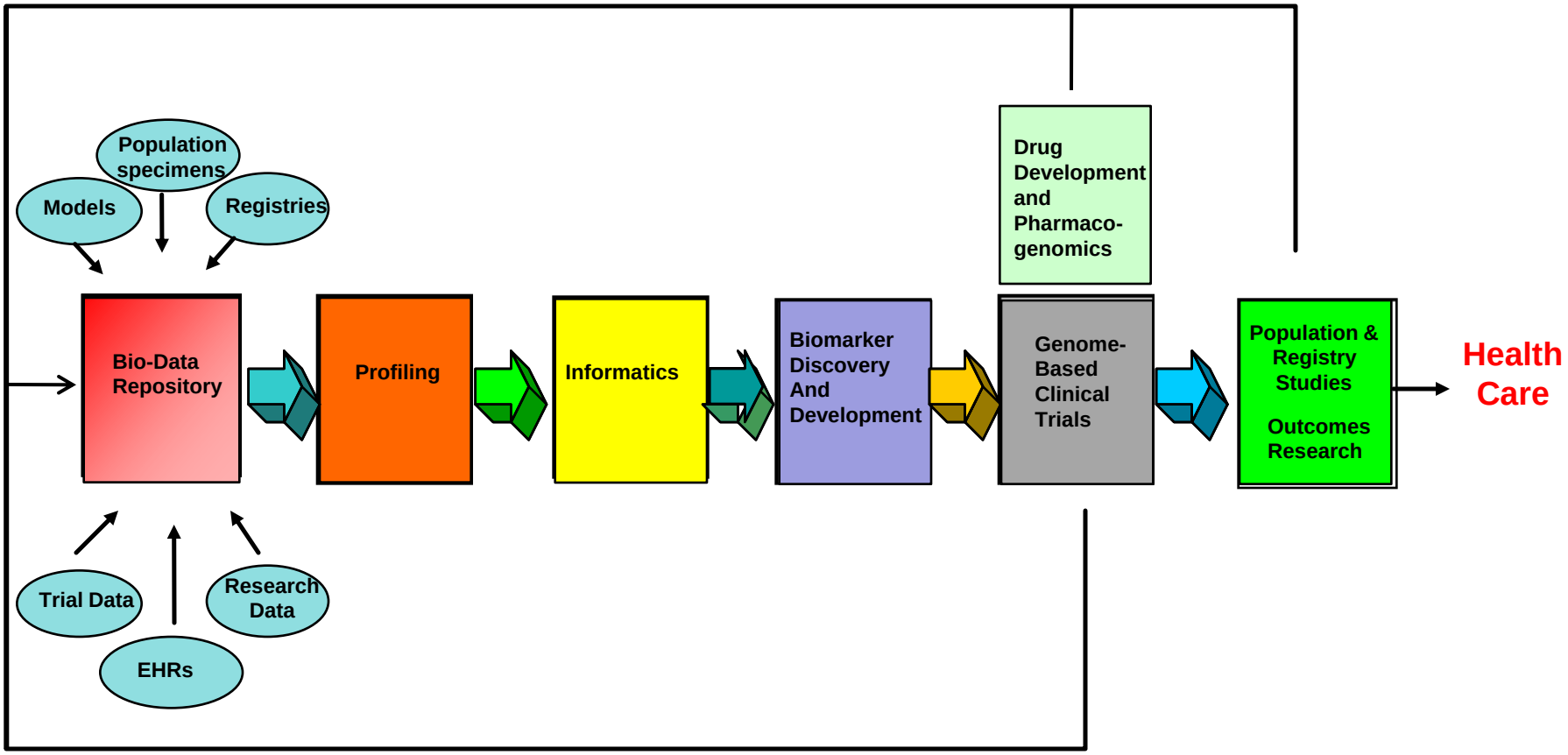
Enabling Genomics From Discovery to Health Applications



Ginsburg, *Genomic and Personalized Medicine*, 2008

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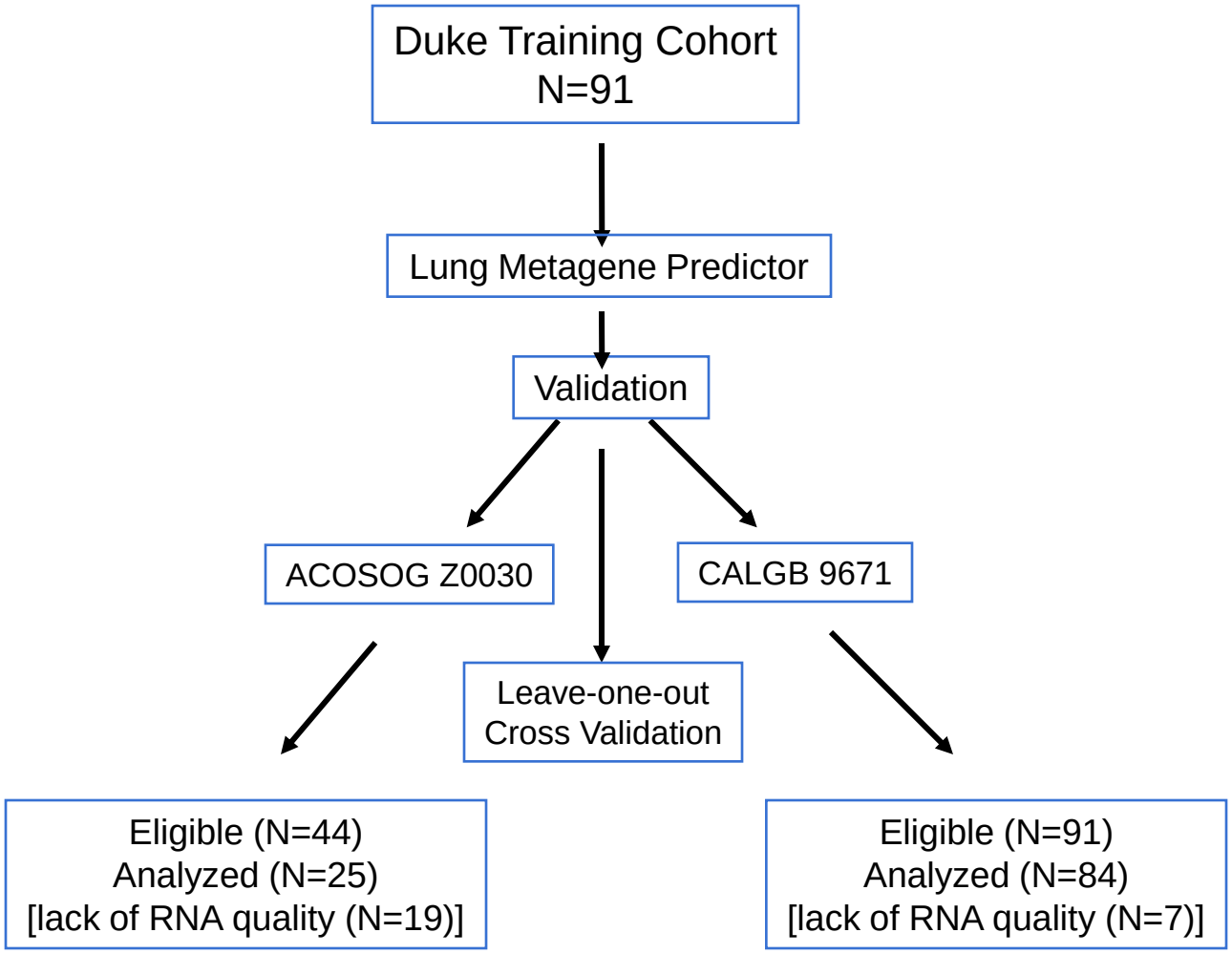
Lung Cancer *Prognosis* Genomic Signatures: The General Approach



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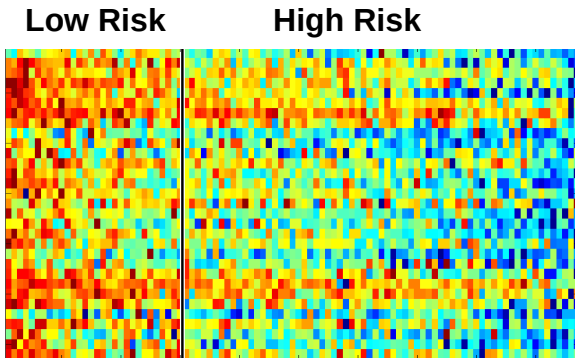
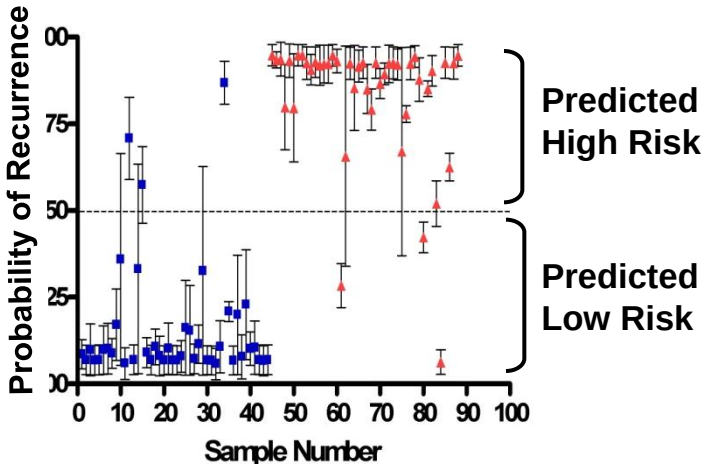
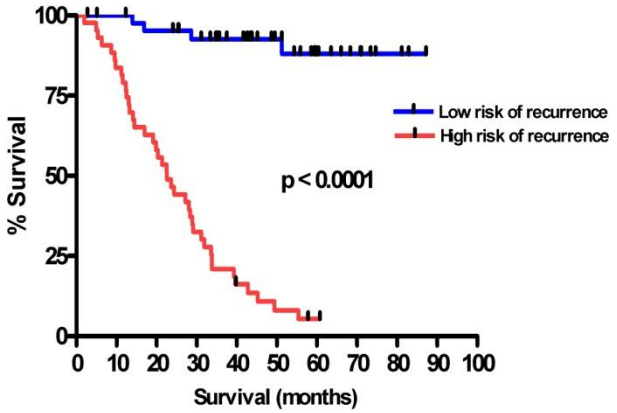
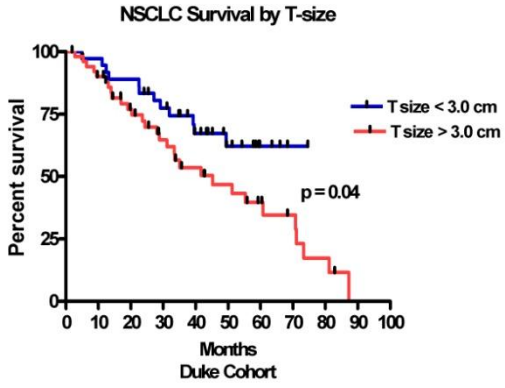
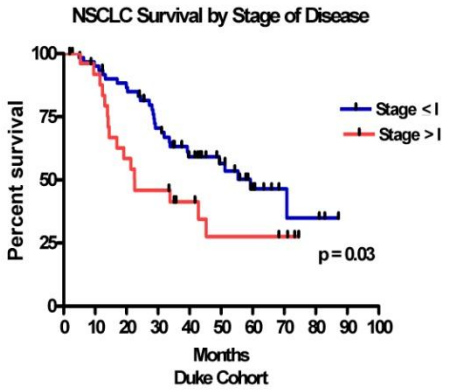
A Metagene Predictor of Recurrence











Potti, NEJM, 2006

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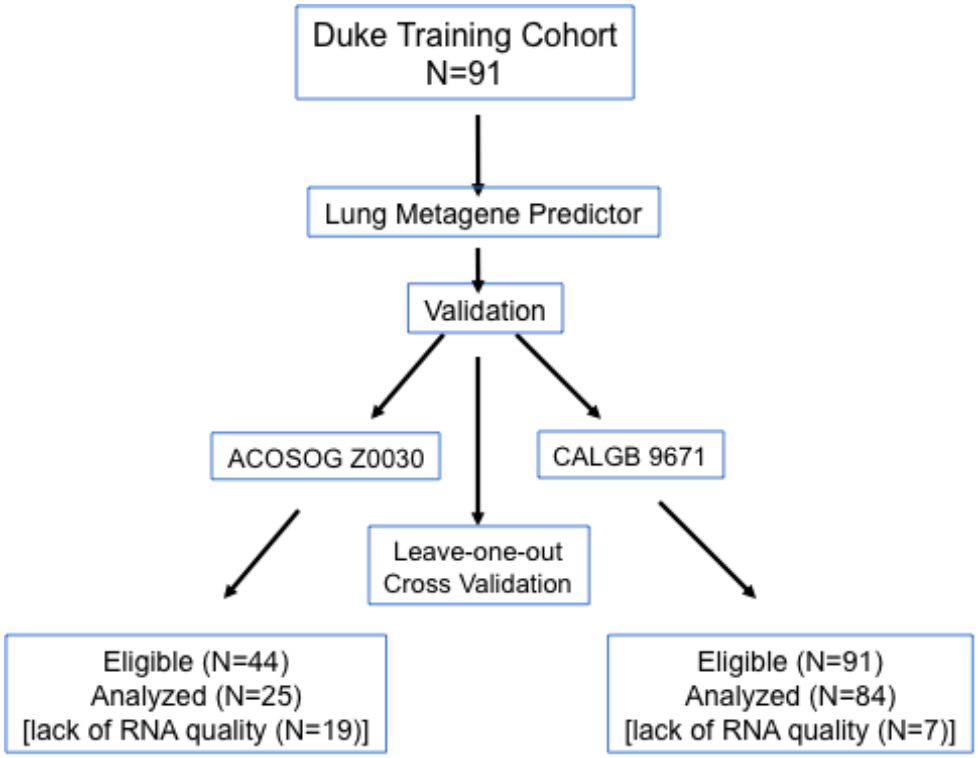
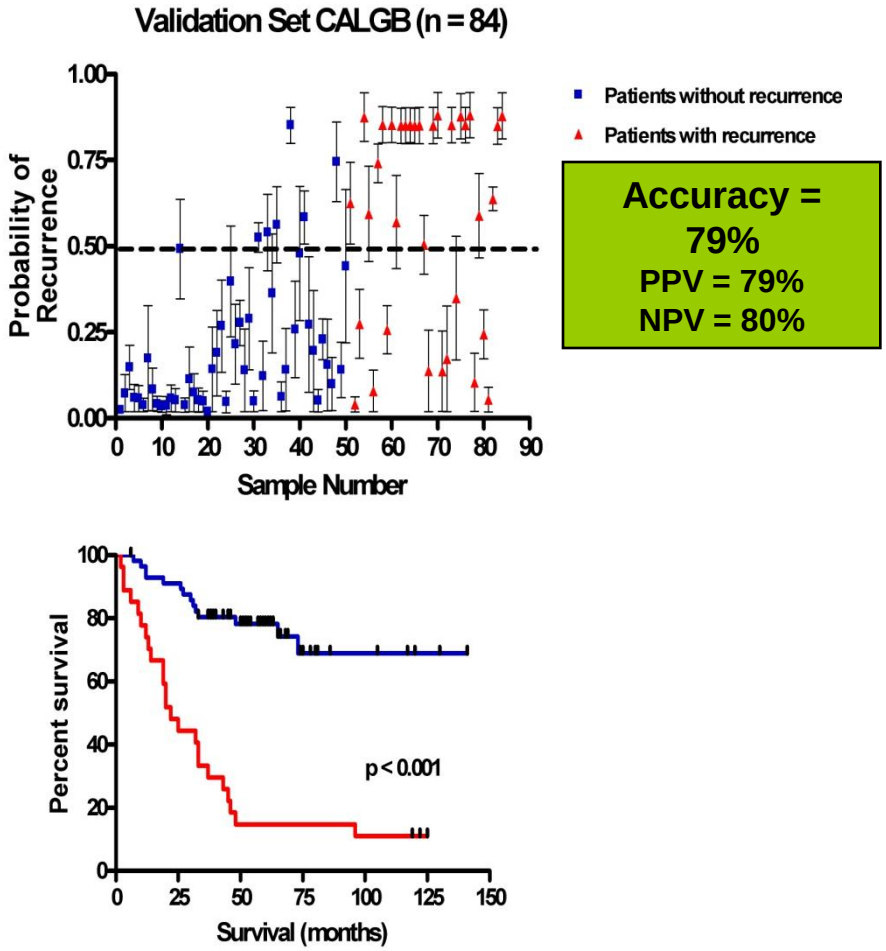
Independent Validation





Potti, NEJM, 2006

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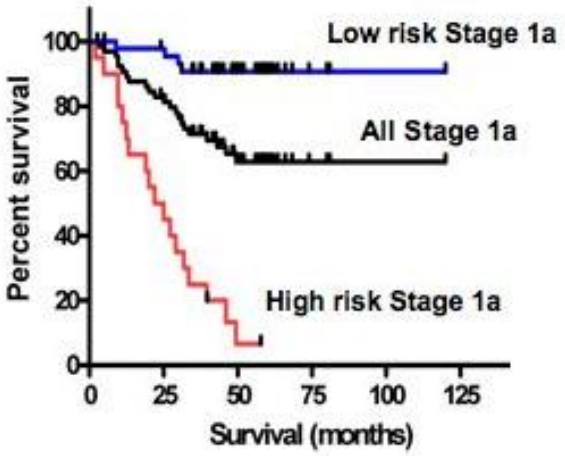
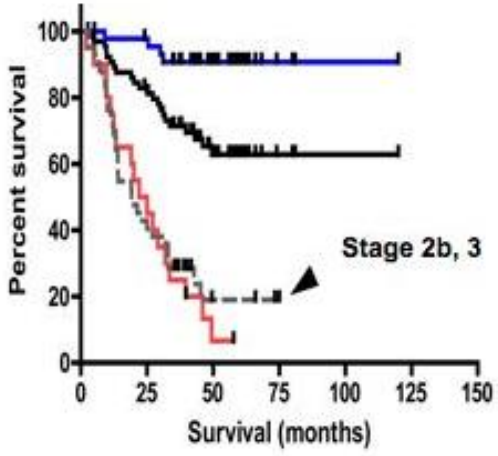
An Opportunity to Improve Prognosis in Lung Cancer

Stage Ia: Observation

Stage Ib-III: Adjuvant Therapy





Potti, NEJM, 2006

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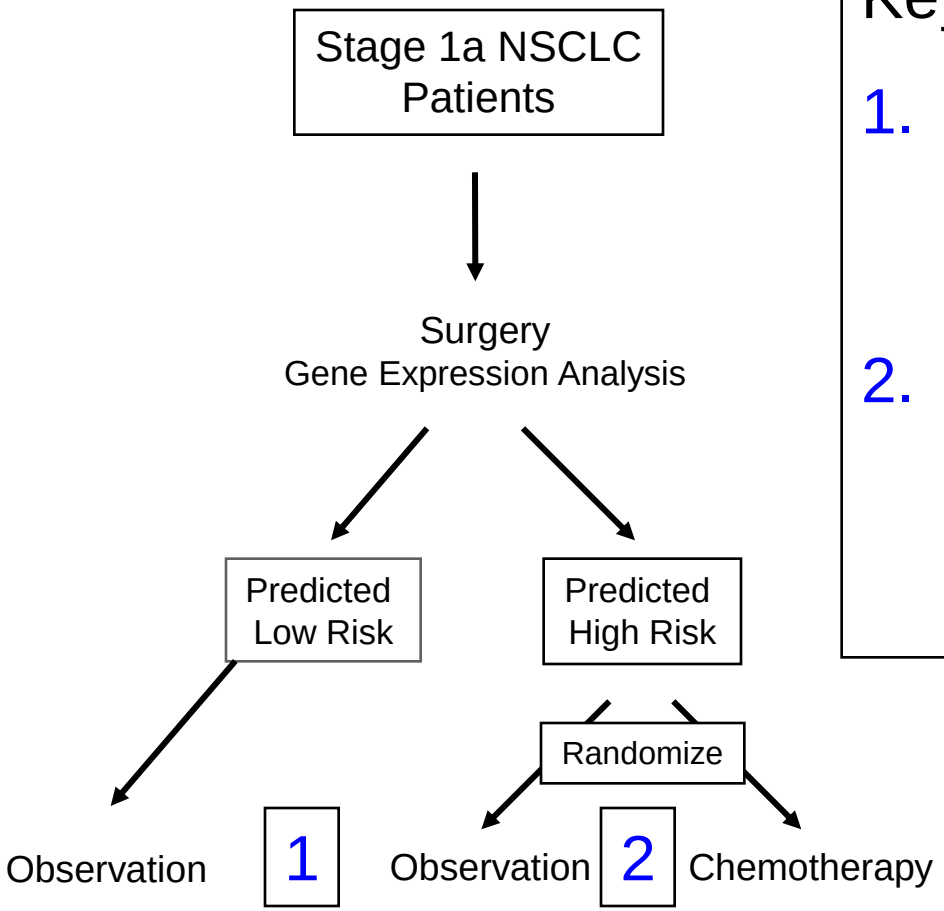
CALGB 30506 - A Phase III Trial to Evaluate Genomic Prognosis



Key Points:

1. Does the genomic assay accurately predict low vs high risk?
2. Do patients predicted to be at high risk for recurrence benefit from chemotherapy?

Approved by NIH/NCI/CTEP

Initiates in early 2009

Potti, NEJM, 2006

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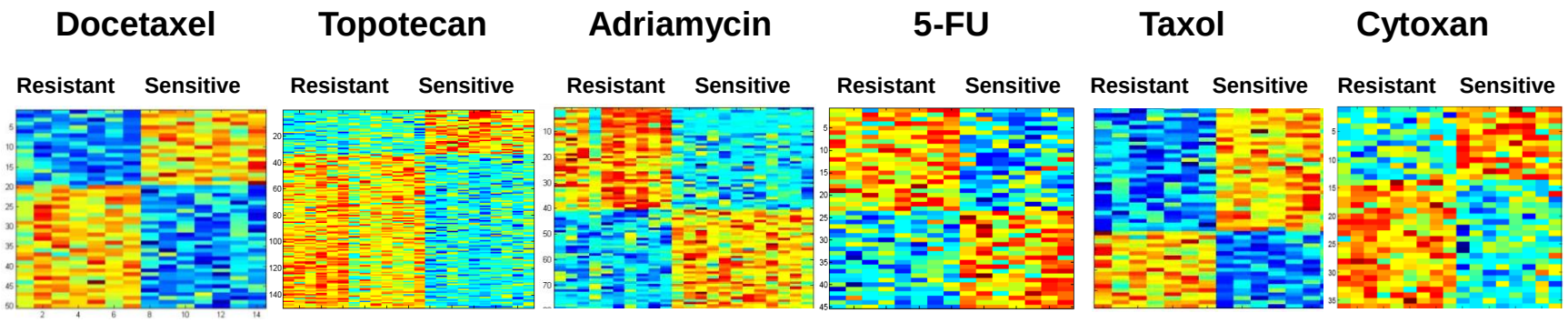
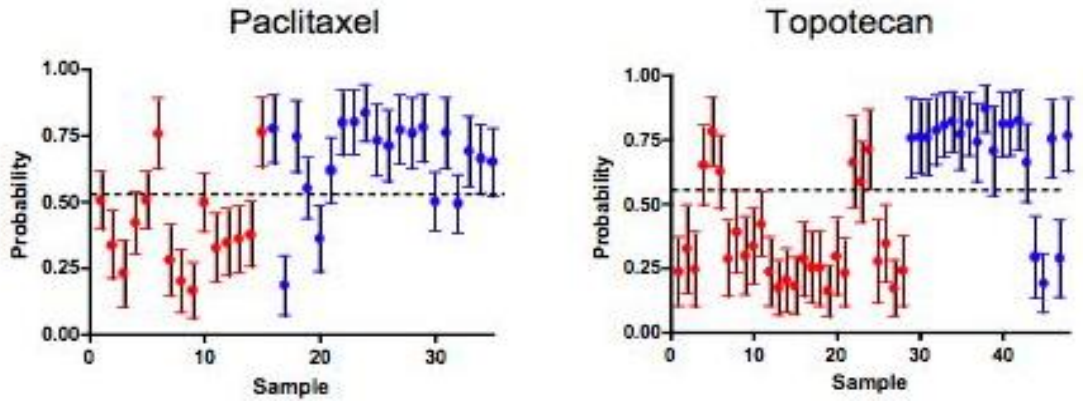
A Panel of Signatures to Guide the Use of Cytotoxic Chemotherapies





> 600 In vivo validations were performed for adriamycin, paclitaxel, gemcitabine, cyclophosphamide and topotecan

(Nature Medicine, 2006)

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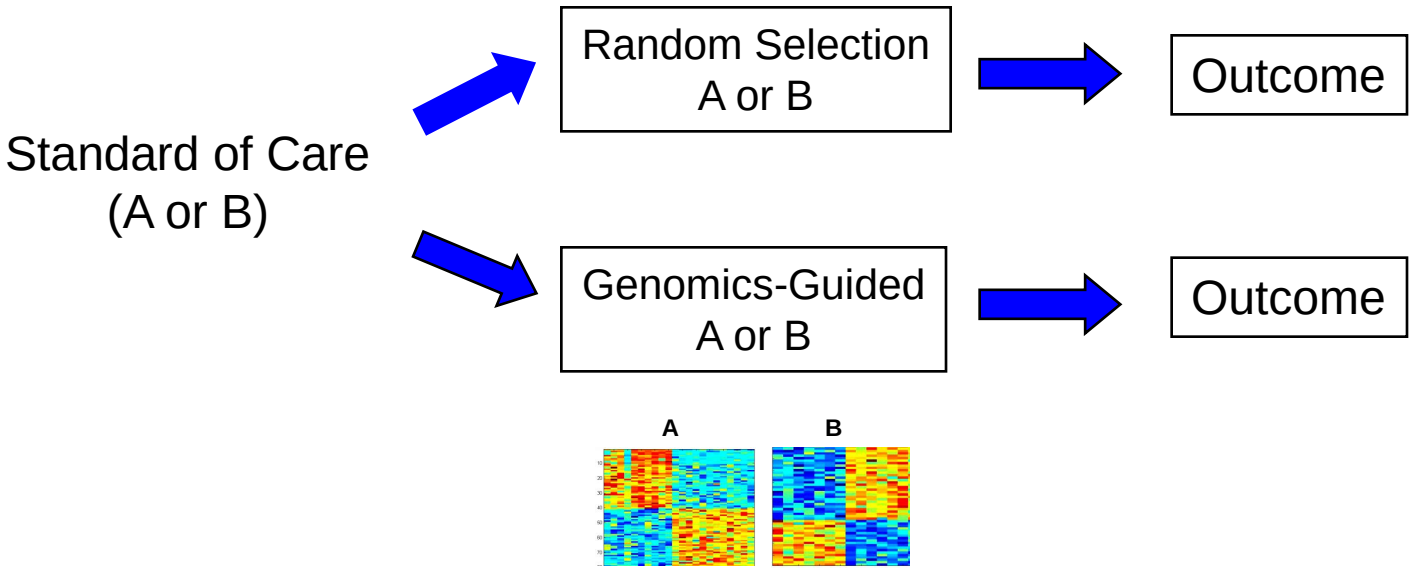
A Prototype for Clinical Utility Studies: Guiding *Standard of Care* Therapies



Health and Economic Outcomes

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A Breast Cancer Neoadjuvant Trial

Breast Cancer Patient
>T1c, Her2-

Biopsy

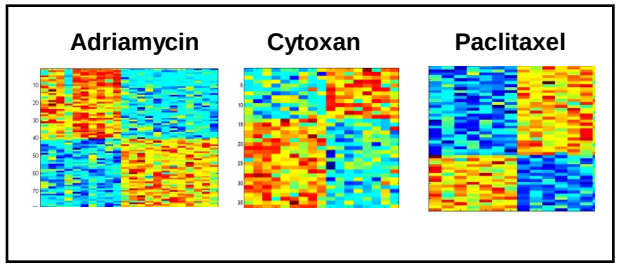
Randomize

Random Selection
AC or TC

Outcome
(pCR)

Genomics-Guided
AC or TC

Outcome
(pCR)



DOD funded

Initiated in June, 2008

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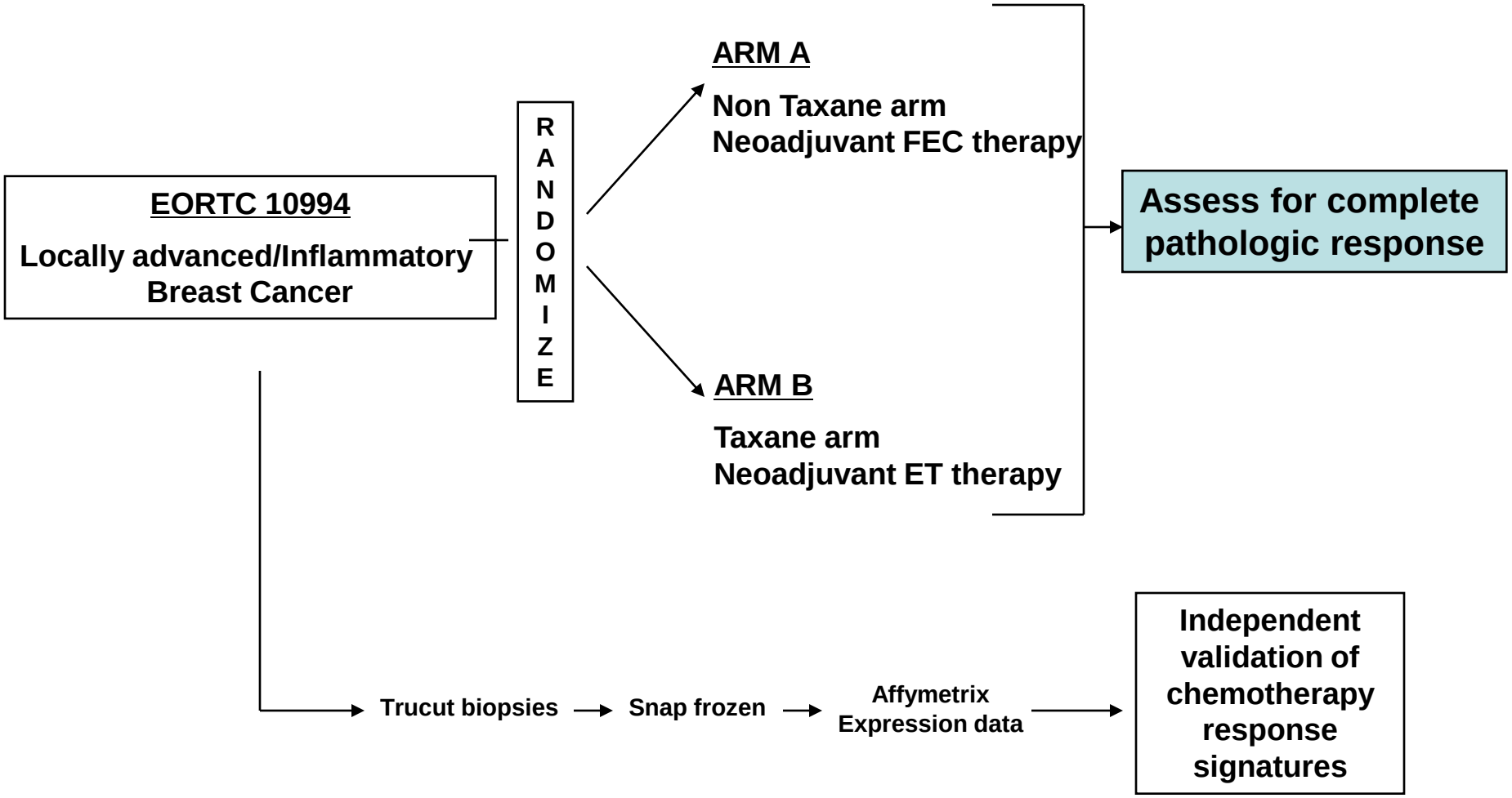
EORTC10994 Multicenter Prospective Neoadjuvant Phase III Breast Cancer Trial
BLINDED VALIDATION (n = 162)



Bonnefoi, Lancet Oncology 2007

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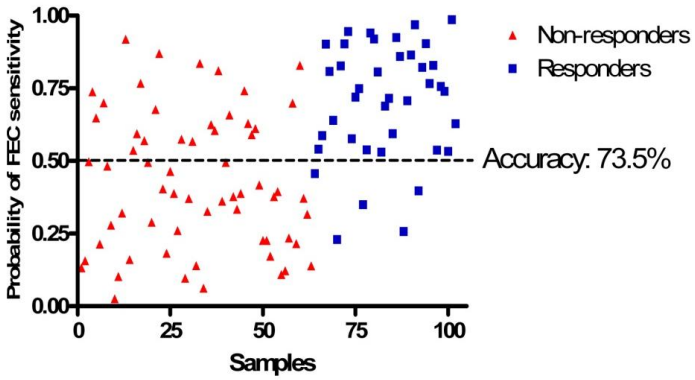
EORTC10994 Multicenter Prospective Neoadjuvant Phase III Breast Cancer Trial
BLINDED VALIDATION (n = 162)

ARM A

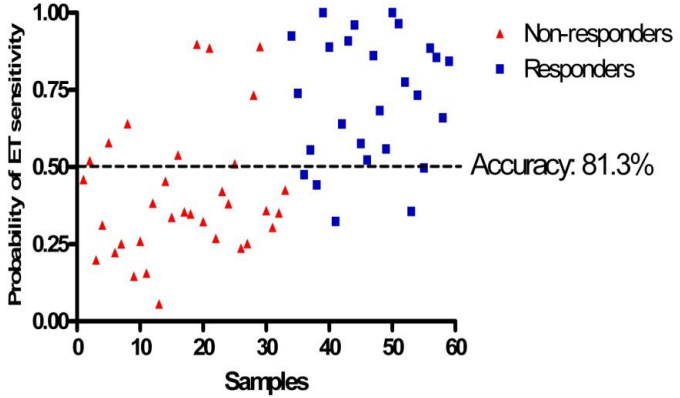
Neoadjuvant FEC



FEC predictor

ARM B

Neoadjuvant ET



ET predictor

Bonnefoi, Lancet Oncology 2007

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A Primary Care Based RCT for Clinical Utility of TCF7L2 in Diabetes

- Primary objective: to assess the ability of a genetic test for Type 2 diabetes risk to alter behavior and health measures in a general clinic population
  - HOmeostasis Model Assessment of Insulin Resistance (HOMA-IR)
  - waist circumference
  - weight loss
  - serum glucose
  - diet and energy expenditure

- Secondary goals :
  - to measure whether changes in perceived risk, and beliefs about genetics correlate with behavior change following genetic testing for Type 2 diabetes risk
  - To determine whether a genetic-guided clinical trial will change primary care MDs' beliefs and understanding of genetics and its role in their practice

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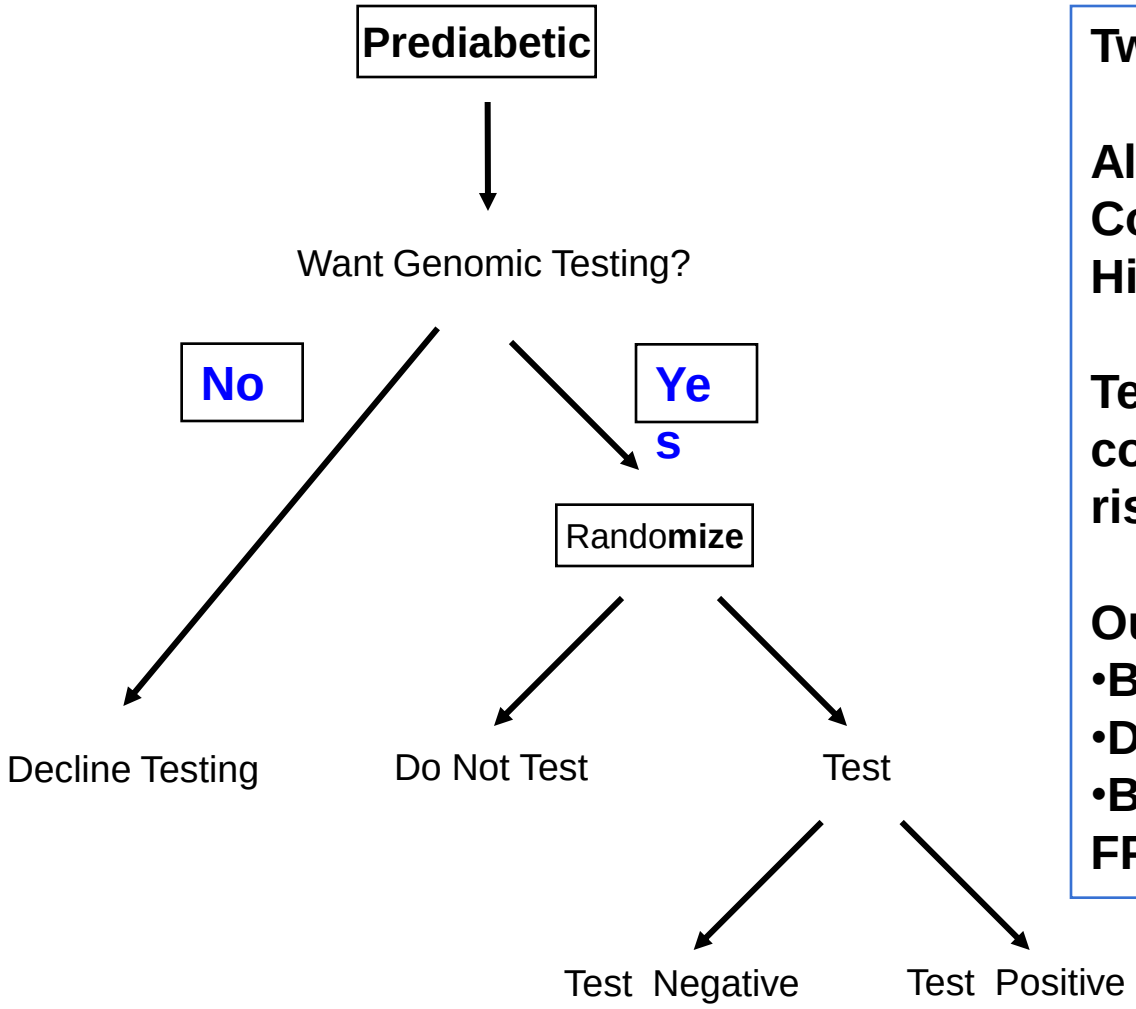
A Primary Care Based RCT for Clinical Utility of TCF7L2 in Diabetes



Two Primary Care Practices

All Participants Receive Counseling based on Family History, BMI, FPG results

Test group also receives counsel based on genomic risk factors

Outcomes at 3 and 12 mos:
- **Behaviors**
- **Diet/Exercise**
- **BMI, Waist circumference, FPG, HOMA IR**

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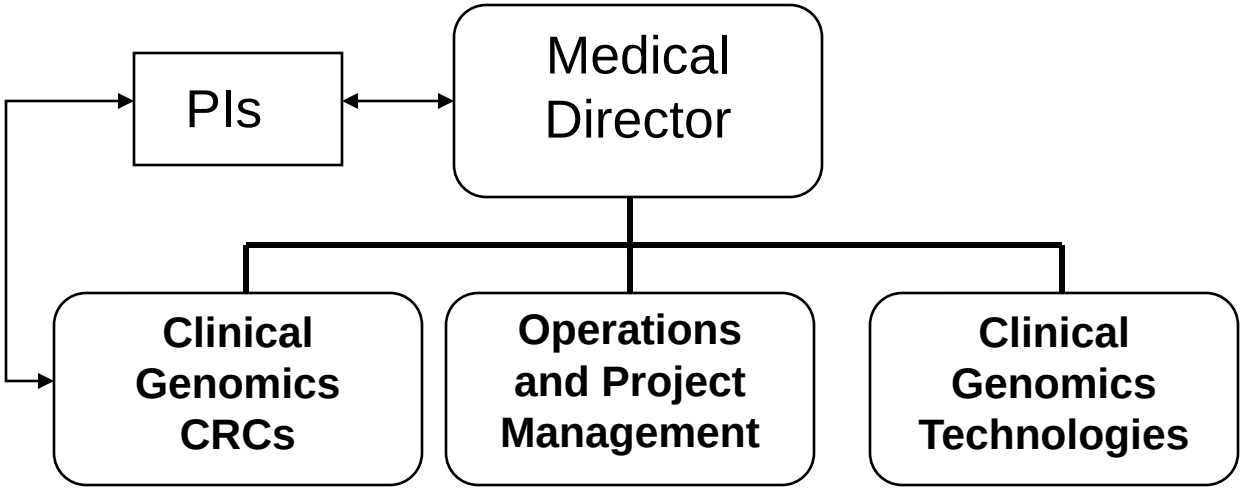
An Interdisciplinary Unit Driving Translational Genomics



- Genomic Protocols
- Informed Consent
- Patient Education
- MD Education
- Tissue navigation
- Risk communication

- Trial Operations
- Project Management
- Finance Analysis
- Regulatory
- Protocol writing
- Data management

- Assay standardization
- CLIA environment
- Bioinformatics
- Algorithms
- Genomic data repository
- Biorepository

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Opportunities to Enable Scientific and Clinical Evaluation of Genomic Markers

- Patient registries (common and rare diseases)
  - Longitudinal follow up
  - Robust phenotypes
- Population studies linked to EHRs
- Prospective clinical trials
  - “Genomics Trials Cooperative Group”
- Industry
  - Public-private partnerships
  - Sample collection in phase II-IV trials
- A national virtual sample biorepository linked to research and clinical data

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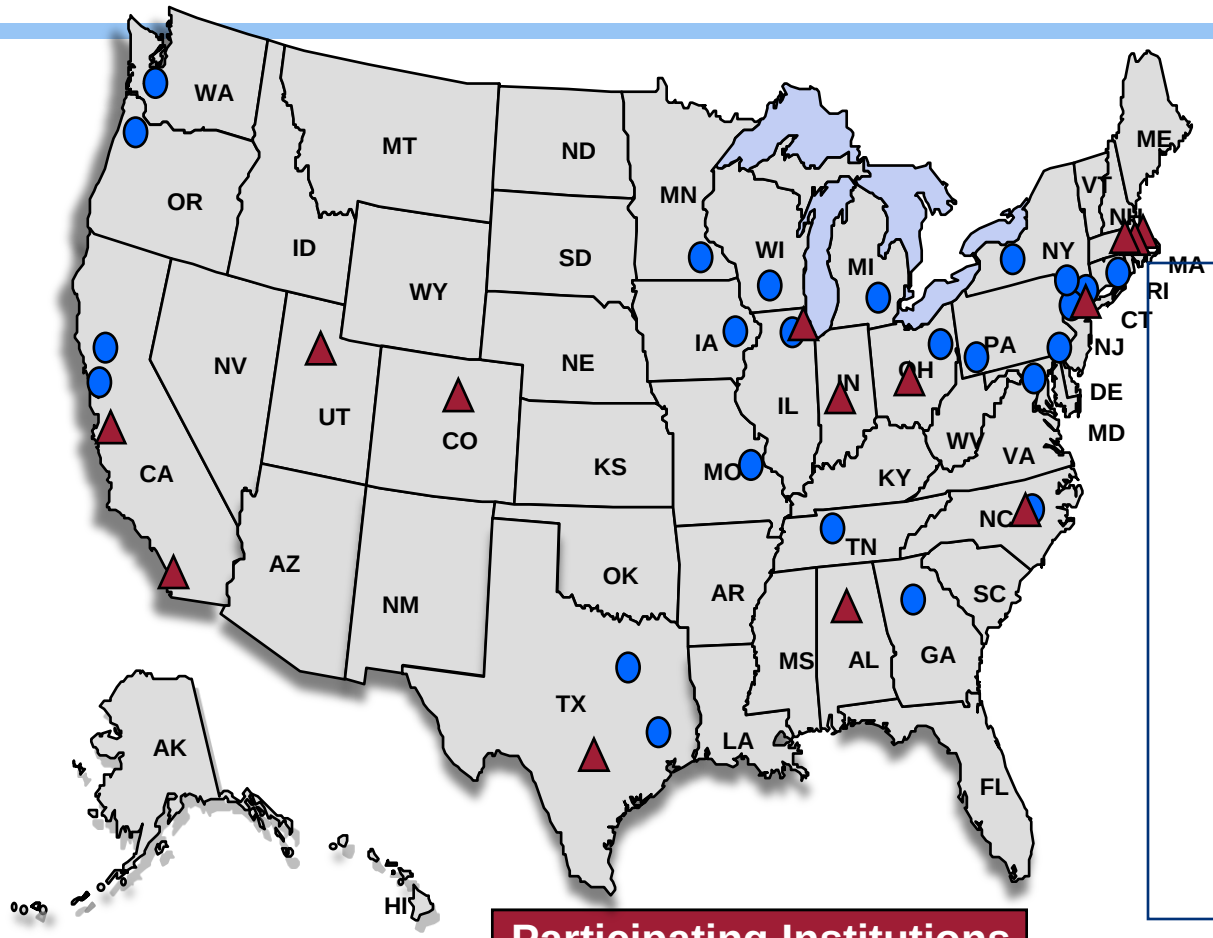
Building a National CTSA Consortium



Participating Institutions

- New members 2008
- Members 2006 & 2007

Enhancing national clinical and translational research capability

- clinical research management
- research infrastructure
- phenotyping - human and preclinical models
- Data sharing
- Community engagement

CTSA Clinical & Translational Science Awards

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