Genome Guided Clinical Trials: Evaluation of the Clinical Validity and Utility of Genomic Biomarkers

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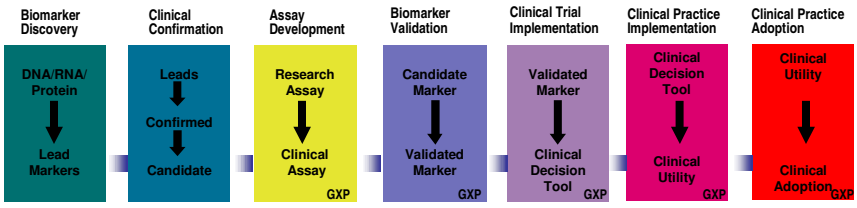
The 'Translational Continuum' for Biomarkers



8 - 80+ years

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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Key Questions for the Translational Continuum

- Genomic Guided Clinical Trials
  - *How do we build the evidence for adoption?*
- Genomics Testing Advisory Committee
  - *How do we implement in a health system?*

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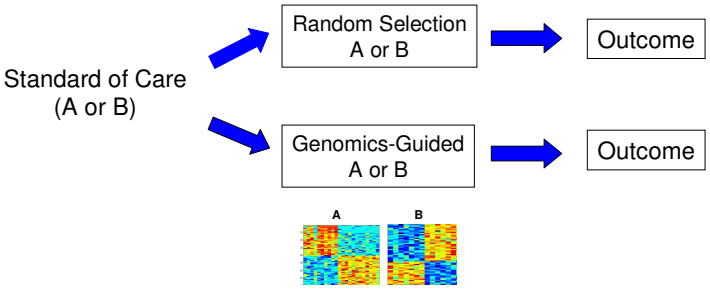
A Prototype for Clinical Utility Studies: Guiding *Standard of Care* Therapies



Health and Economic Outcomes

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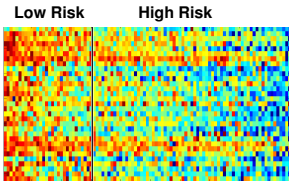
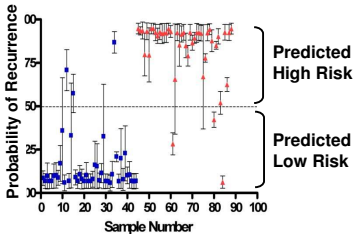
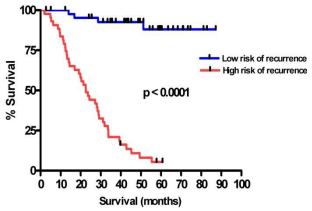
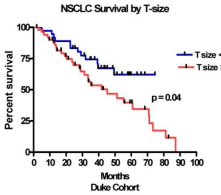
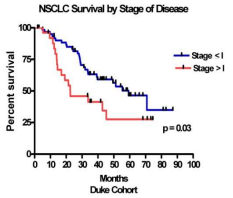
A Metagene Predictor of Lung Cancer Recurrence











Potti, NEJM, 2006

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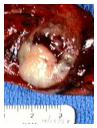
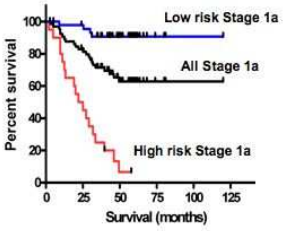
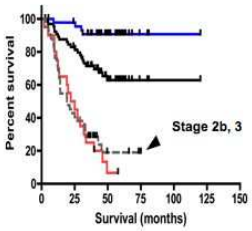
An Opportunity to Improve Prognosis in Lung Cancer



Stage Ia: Observation

Stage Ib-III: Adjuvant Therapy





Potti, NEJM, 2006

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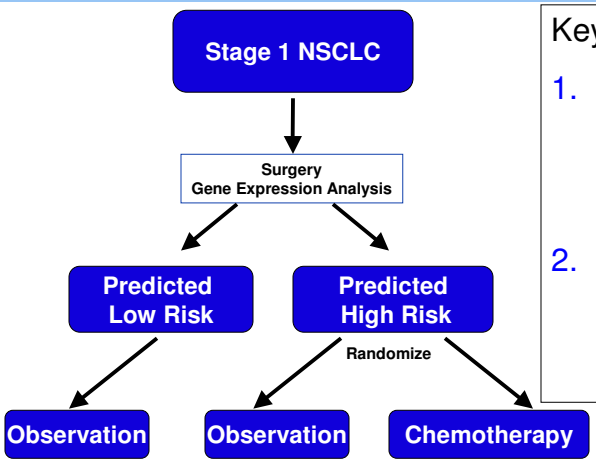
CALGB 30506 - A Phase III Trial to Evaluate Genomic Prognosis



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?

Parallel study by the Center for Clinical and Genetic Economics

Potti, NEJM, 2006

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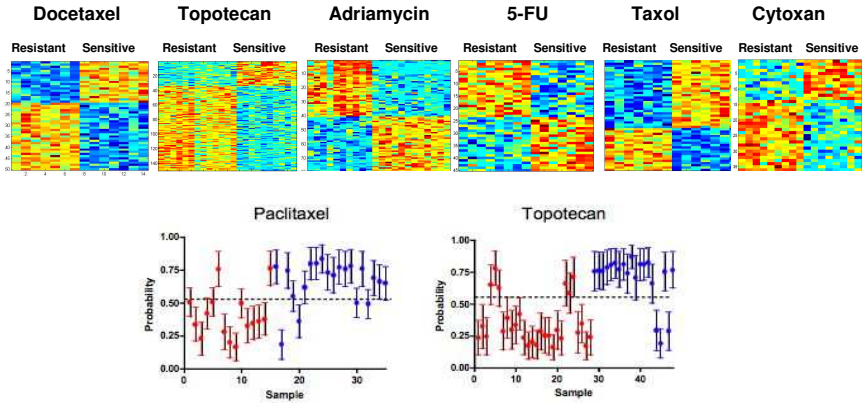
A Panel of Signatures to Guide the Use of Cytotoxic Chemotherapies



> 600 In vivo validations were performed for adriamycin, paclitaxel, gemcitabine, cyclophosphamide and topotecan
(Nature Medicine, 2006)

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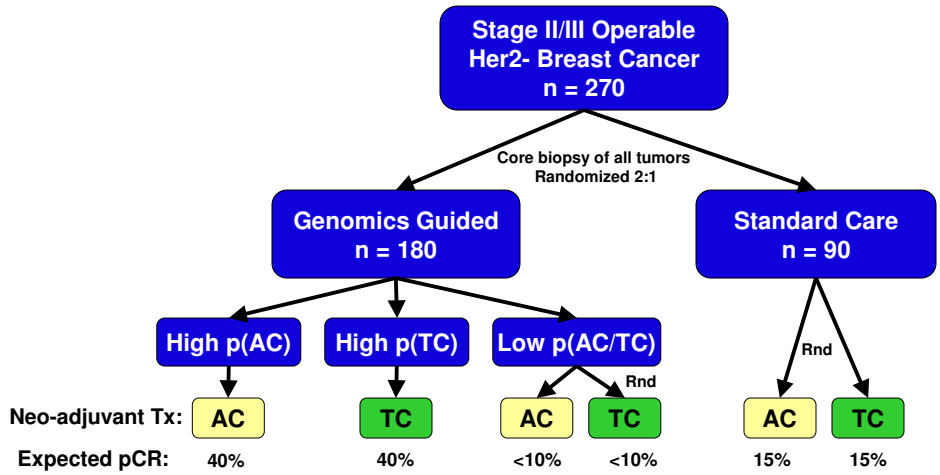
DOD-Funded Phase II Trial

Breast Cancer Neoadjuvant Tx



Parallel study by the Center for Clinical and Genetic Economics

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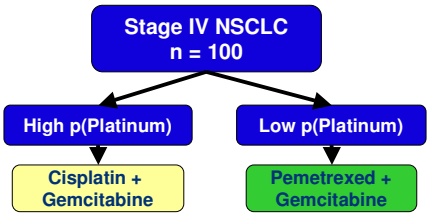
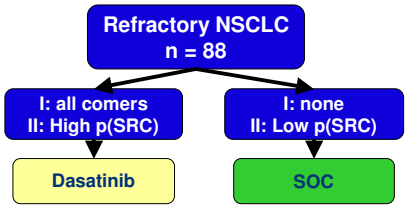
Novel Paradigms for Drug Development

Cytotoxic Predictor:
Moving Therapies to 1st Line



Identifies patients resistant to standard of care, initiate 2nd line Tx
Opportunity to move P+G to 1st line

Pathway Predictor:
Enrichment/Targeted Rx



Two-phase design: treat all comers with Dasatinib, measure SRC activity
If non-resp are SRC- and resp are SRC+, then stratify in phase II

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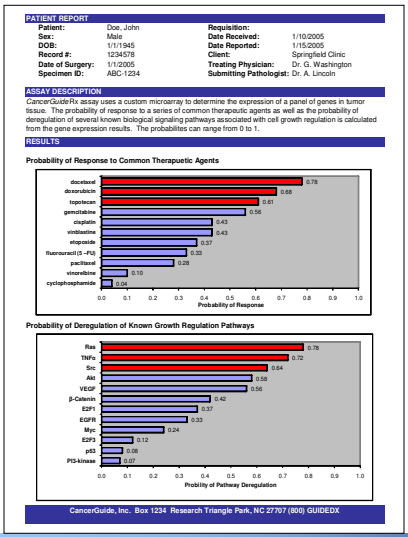
Clinical Decision Support: *Treatment Guide* Report


PATIENT REPORT

Patient:	Doe, John	Requisition:	
Sex:	Male	Date Received:	1/10/2005
DOB:	1/1/1945	Date Reported:	1/15/2005
Record #:	1234578	Client:	Springfield Clinic
Date of Surgery:	1/1/2005	Treating Physician:	Dr. G. Washington
Specimen ID:	ABC-1234	Submitting Pathologist:	Dr. A. Lincoln

ASSAY DESCRIPTION

*CancerGuide*Rx assay uses a custom microarray to determine the expression of a panel of genes in tumor tissue. The probability of response to a series of common therapeutic agents as well as the probability of deregulation of several known biological signaling pathways associated with cell growth regulation is calculated from the gene expression results. The probabilities can range from 0 to 1.

RESULTS

Probability of Response to Common Therapuetic Agents

docetaxel 0.78
doxorubicin 0.68
topotecan 0.61
gemcitabine 0.58
cisplatin 0.43
vinblastine 0.43
etoposide 0.37
fluorouracil (5 -FU) 0.33
paclitaxel 0.28
vinorelbine 0.10
cyclophosphamide 0.04

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Probability of Response

Probability of Deregulation of Known Growth Regulation Pathways

Ras 0.78
TNFα 0.72
Src 0.64
Akt 0.58
VEGF 0.56
β-Catenin 0.42
E2F1 0.37
EGFR 0.33
Myc 0.24
E2F3 0.12
p53 0.09
PI3-kinase 0.07

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
Probility of Pathway Deregulation

CancerGuide, Inc. Box 1234 Research Triangle Park, NC 27707 (800) GUIDEDX

Report derived from an analysis of a sample of a patient's tumor at CLIA-certified molecular dx facility

Provides accurate assessments of:

a) a patient's likelihood of response to 11 common cytotoxic agents
b) the degree of dysregulation of 12 oncogenic pathways

Use to rationally select optimal therapeutic regimen from within standard of care combos

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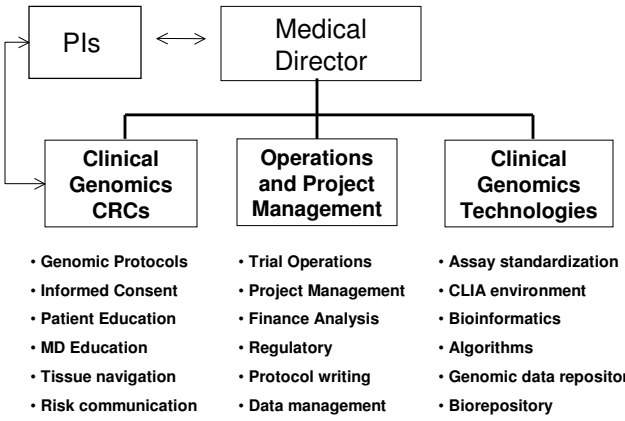
The Duke Clinical Genomics Studies Unit: Driving Genomics Guided Trials



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Opportunities to Enable 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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Genomic Testing Advisory Committee

GTAC Mission:

To promote appropriate evidence based utilization of tests related to genomic medicine that are available to clinicians to order both internally and externally for patients within the Duke University Health System.

Reporting to the Executive Committee, GTAC will serve as a resource to the Pharmacy and Therapeutics Committee, Clinical Laboratories Committee, Duke Prospective Health, and Duke Health System personnel.

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GTAC Process

- Test overview
  - Test name, methods
  - Indication
  - Clinical evidence
  - Risk to patients
  - Current utilization (if applicable)
  - Cost
- Briefing document
  - ACCE

- Actions
  - Advise that the test be utilized with or without restrictions
  - Advise that the test not be utilized
- Recommend educational goals and strategy
- Review clinical decision support tools

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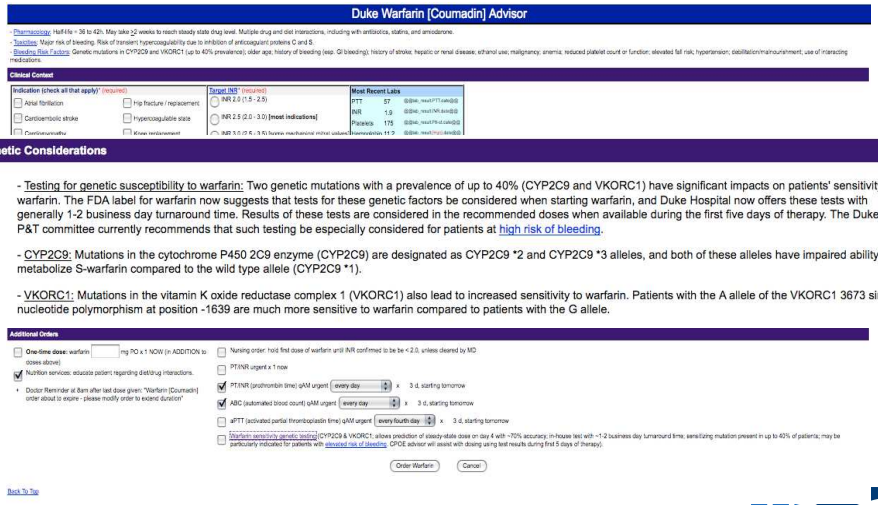
CPOE Decision Support for Warfarin



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An Integrated Strategy For Genomic Medicine from Bench to Bedside

Discovery → **Translation** → **Implementation**

- **Focus on clinical decisions**
- **Clinical equipoise/uncertainty**
- **Short time-to-outcome**
- **High clinical impact, or**
- **High economic impact**

- **Clinical studies to validate**
- **Clinical studies to establish utility**
- **Prospective design**
- **Registries**
- **Health and Economic outcomes**

- **Assay standardization**
- **Algorithm standardization**
- **Educational/Decision tools**
- **Policy development**
- **Public-Private Partnerships**

Enabling Infrastructure

Biorepository, 'Omics' Cores, Clinical Trials Unit (CGSU), Integrated Databases, Computational/Statistical Models, Team Approach, GTAC

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