Genomic Guided Clinical Trials to Evaluate the Clinical Utility of Cancer Pharmacogenomics

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A Paradigm for Discovery and Development of Cancer PGx Biomarkers

- **Discovery**
  - Genomic Signatures Unit
  - New signature development
  - Signature database

- **Translation**
  - Clinical Genomics Studies Unit
  - Genomic Phase II clinical trials

- **Implementation**
  - Commercial Partner
  - Phase III clinical trials
  - Rx/Dx combinations
  - Rx/Dx partnerships
Concept of a Genomic Signature

Biological State A  Biological State B

Genome-scale gene expression data

State A  State B

Prognosis  Drug sensitivity  Cancer biology
Lung Cancer Prognosis Genomic Signatures: The General Approach

Duke Training Cohort
N=91

Lung Metagene Predictor

Validation

ACOSOG Z0030
Eligible (N=44)
Analyzed (N=25)
[lack of RNA quality (N=19)]

CALGB 9671
Eligible (N=91)
Analyzed (N=84)
[lack of RNA quality (N=7)]

Leave-one-out Cross Validation
A Metagene Predictor of Recurrence

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Independent Validation

Accuracy = 79%
PPV = 79%
NPV = 80%

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Stage Ia: Observation

Stage Ib-III: Adjuvant Therapy
CALGB 30506 - A Phase III Trial to Evaluate Genomic Prognosis

Stage 1a NSCLC Patients

Surgery
Gene Expression Analysis

Predicted Low Risk
Randomize
Observation
Chemotherapy

Predicted High Risk
Randomize
Observation
Chemotherapy

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
Initiated in May 2009

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How Best to Treat? Many Choices But No Guidance

Regimens developed for groups of cancer patients, not individuals.
Signatures of Drug Sensitivity

Drug Resistant  Drug Sensitive

Resistant  Sensitive

Docetaxel  Topotecan  Adriamycin  5-FU  Taxol  Cytoxan

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

Standard of Care (A or B)

Random Selection
A or B

Genomics-Guided
A or B

Outcome

Outcome

Health and Economic Outcomes
A Breast Cancer Neoadjuvant Trial

Breast Cancer Patient
>T1c, Her2-

Random Selection
AC or TC

Outcome (pCR)

Genomics-Guided
AC or TC

Outcome (pCR)

Random Selection
AC or TC

Adriamycin          Cytoxan              Paclitaxel

DOD funded
Initiated in June, 2008
EORTC10994 Multicenter Prospective Neoadjuvant Phase III Breast Cancer Trial
BLINDED VALIDATION (n = 162)

Randomize

ARM A
Non Taxane arm
Neoadjuvant FEC therapy

Assess for complete pathologic response

ARM B
Taxane arm
Neoadjuvant ET therapy

Trucut biopsies \(\rightarrow\) Snap frozen \(\rightarrow\) Affymetrix Expression data

Independent validation of chemotherapy response signatures

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

ARM A
Neoadjuvant FEC

ARM B
Neoadjuvant ET

FEC predictor

ET predictor

Novel Paradigms for Drug Development

Cytotoxic Predictor: Moving Therapies to 1st Line

Stage IV NSCLC
n = 100

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

High p(Platinum)
Cisplatin + Gemcitabine

Low p(Platinum)
Pemetrexed + Gemcitabine
Surrogate Signatures for Pathway Activation Underlying the Oncogenic Phenotype
Linking Pathways Underlying the Oncogenic Phenotype with Therapeutics

- Dasatinib
- FTI
- FTTS
- Roscovitine
- LY-294002
- RAD001
- Iressa
- DNA Damage
- Hormones (Estrogen)
- Growth Signals (EGF, PDGF)
- Wnt
- Frizzled
- p53
Pathway Signature = Drug Sensitivity Signature

Predict pathways in cell lines

Compare with drug sensitivity

Two-phase design: treat all comers with Dasatinib, measure SRC activity
If non-responders are SRC- and responders are SRC+, then stratify in phase II
A Multi-Step Strategy for Personalized Cancer Therapy

Current:
- Cancer Patient
  - Standard-of-Care
    - A, B, or C

Genomics-guided:
- Cancer Patient
  - Biopsy/Tumor Sample
    - Recurrence Prediction
      - Chemotherapy Response Prediction
        - Drug A
        - Drug B
        - Drug C
        - Resistant
          - Pathway Prediction
            - Drug D or Targeted Drug

Who to treat
How to treat
The Duke Clinical Genomics Studies Unit:
Driving Genomics Guided Trials

- PIs
- Medical Director

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

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

Clinical Genomics Technologies
- Assay standardization
- CLIA environment
- Bioinformatics
- Algorithms
- Genomic data repository
- Biorepository
The Duke Clinical Genomics Studies Unit

Principle Investigator

Eligible Patient

Trial/Treatment Assignment

Consent

Surgery/Biopsy

Tissue/Blood Sample

Data Analysis and Report

Extraction and Analysis in CLIA Facility

Biorepository

Future Research

Trial/Treatment Assignment
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 quantitative skills
• Decision Making
  – Understanding of human decision making
  – Biological, psychological and social factors
  – Education of health care professionals

Califf and Ginsburg, JAMA, 2008
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