Are Genomics and proteomics biomarkers ready for prime time?
Outline

1. Use of “omics” in patient diagnosis or stratification in cancer: examples in breast, and lymphoma
2. Use of “omics in the management of lung cancer
   • Non-invasive diagnosis of lung cancer
   • Prediction of response to therapy
3. Clinical trial designs
4. Conclusions
Publications and FDA approved Cancer Biomarkers

20 plasma cancer biomarkers, in 10 cancers, none in aero-digestive tract cancers

Ludwig and Weinstein

Vanderbilt-Ingram Cancer Center

Nature Reviews Cancer 5, 845-856, 2005
### ER and Her2 in Breast Cancer

<table>
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<tr>
<th>ER (IHC)</th>
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Genomic signature in Breast Cancer

- **Oncotype DX™ from Genomic health in ER+ BC**
  - likelihood of disease recurrence
  - magnitude of chemotherapy response NN BC
  - Based on RT-PCR on 21 genes in FFPE tissue

- **MammaPrint® from Agendia**
  - 70 genes signature to predict survival
Prediction of Recurrence of Tamoxifen-Treated NN BC

RT-PCR 21 genes

Paik, NEJM 351, 2004
Prediction of survival in Burkitt’s Lymphoma

Gene signature distinguishes BL vs DLCL and best Rx for BL.

Affy
Top 100 genes
Outline

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   • 1. Non-invasive diagnosis of lung cancer
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Criteria for Diagnostic Biomarkers

1. Robust and reproducible
2. Of proven clinical value
   And trigger a clinical decision
3. Clinical community adopts its use and takes advantages of benefits it affords
4. Competitive in terms of cost and insurance reimbursement.
# Lung cancer diagnostic biomarkers

<table>
<thead>
<tr>
<th>Candidates</th>
<th>Phase 1</th>
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Management of lung cancer

Risk Assessment

Symptoms  Screening  Chemoprevention

Non invasive Diagnosis

FNA  Bronchoscopy  Surgical bx

Staging

CT chest/abn  PETscan  Mediastinoscopy

Treatment

Surgery  Chemo  Radiation

Response  Recurrence  Prognosis

SNPs

Serum proteomics
Autoantibodies

Genomic/
Proteomic sig

ERCC1
Gene signature

Serum proteomics
FISH
Gene signature
Non-invasive diagnosis

**Surgical**

- Clinical data
- Exhaled breath
- Sputum, **Serum**, Urine
- Chest CT
- Bronchoscopic specimen
- Transthoracic specimen
- Surgical specimen
Serum proteomic profiling

288 serum samples
142 cases and 146 controls

Training set
N=182
92 cases 90 controls

Matched Test set
N=106
50 cases 56 controls

Signature
7 features

Sensitivity 58.0%
Specificity 85.7%

Yildiz et al. JTO 2007
Genetic profiling predictive of lung cancer

- Expression profile from large airway epithelial cells may predict tumor development
- Tissue accessible (Br. Brush or buccal swab)
- Quantitative assay (RT-PCR)
- Association with cancer
- Assessment of drug related function
  - Response to therapy
  - Needs validation

Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer


a. n=52
b. n=35

Affy HG-U133A

Accuracy of classification
a: 83%
b: 80%
Prediction of response to Rx

Non-surgical

95-100% risk of progression

Non-surgical

Chemo

Predict response?
Overview

Training cohort
Italian A (70)
Japanese (69)

Algorithm Generation
(8 peaks -> good vs poor outcome)

Application of the algorithm

Test cohort
Italian B (67)
good / poor
TTP
OS

Control Test cohort: (61)
good / poor
TTP
OS

Test cohort
ECOG-Erlotinib (96)
good / poor
TTP
OS

Assessment of the prediction
Training cohort

Test cohort

Taguchi/Solomon et al, 2007 JNCI
**ECOG 1594 cohort:**

Advanced NSCLC, first line erlotinib

n = 58, stage IIIB and IV

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**Control test cohort**

Advanced NSCLC received Chemotherapy excluding EGFR TKIs

(n = 61, stage IIIB or IV)

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*Taguchi/Solomon et al, 2007 JNCI*
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Clinical utility of predictive marker
Study Design -1

Marker assessment $\rightarrow$ Screen or Intervene “Marker +” only

Single arm validation study
Comparison to historical controls
Clinical utility of predictive marker
Study Design - 2

Randomization based on assessment of marker.

Proves that the predictive test improves pts outcome when compared with unselected use of same management.
Clinical utility of predictive marker

Study Design-2

ECOG 1507

IIIIB-IV NSCLC
First line

MALDI profile

Serum MALDI Good

Random

Erlotinib

Treat SOC

Serum MALDI Poor

Treat SOC
Clinical utility of predictive marker
Study Design -3

Randomization based on assessment of marker.
Proves that intervention A is better than intervention B in both Marker + and - groups.
1.1 cm suspicious nodule

Surgical candidate

Tissue diagnosis

PET CT scan

Surgery

Observation

Avoid futile thoracotomies

Avoid missed cures
### Lung Cancer Biomarkers Group
**NCI/SPORE/EDRN**

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Conclusions

• The complexity of the biology challenges our ability to measure the effectiveness of diagnostic strategies.

• Signatures as opposed to single biomarkers are likely to provide better biomarkers.

• Utility of diagnostic biomarkers need to be tested in the appropriate clinical context.

• MALDI-TOF MS is able to predict OS and TTP in 2 blinded test sets, treated with both gefitinib and erlotinib. Serum proteomic assay may assist in the pre-treatment selection of NSCLC patients who will show improved survival after treatment with EGFR TKIs.

• Large number of candidates needs to be evaluated across institutions and platforms and validated in existing serum/plasma repositories.
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