Liquid Biopsies for Genotyping and Monitoring Breast Cancer: Ready for Prime Time?

Pro:

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Disclosures

- Circulating MUC1
  - Was involved in early studies that established CA15-3, but received no royalties (although I did get academic promotion)
- Circulating Tumor Cells
  - Have received financial support for laboratory and clinical research from Immunicon/Veridex/Janssen Diagnostics (serial manufacturers of CellSearch®
  - Have patent for CTC-Endocrine Therapy Index
  - Have patent pending for novel mechanisms of capturing and evaluating CTC

Are Liquid Biopsies Ready for Prime Time?

- What is a liquid biopsy?
- What is Prime Time?
- What is Ready?

What is a Liquid Biopsy?

- **Ideally, one would like to do serial biopsy of all metastases**
  - **Pro**
    - **Permits Body-wide analysis of tumor heterogeneity**
    - **Permits monitoring of emerging genetic and phenotypic differences**
  - **Con**
    - **Invasive, associated with risk**
    - **Impractical (not all metastastic sites are accessible)**
    - **Expensive**
- **Blood tests: May get around all of these**

- **"Liquid Biopsy": Term first coined by Klaus Pantel and colleagues to refer to phenotypic analysis of circulating tumor cells (CTC)**
  - ***Alix-Panabieres, et al., Curr Opin Oncol 19:558-63, 2007***

“Liquid Biopsies”

Pro

- Increasing standardization
  - Pre-Analytical
  - Analytical
- Permits interrogation of the liquid phase of the tumor
  - Biologically determined
  - Not just bulk/tumor burden
  - Some of what we are capturing is biologically not important, some is
    - We need to better understand how it relates to tissue phase

What is a Liquid Biopsy?

- CTC enumeration
- CTC genotype and phenotype
- ? Circulating free tumor DNA
- ? Circulating free miRNA
- ? Circulating soluble protein
- ? Circulating exosomes

Are Liquid Biopsies Ready for Prime Time?

- **What is Prime Time?**
  - **First coined in USA to describe a time of the evening when most Americans would be watching TV: 7-10PM**
  - **Made famous by the "Not – Ready – for – Prime Time Actors" in Saturday Night live**

Are Liquid Biopsies Ready for Prime Time?

- **What is Prime Time?**
- **For a Tumor Biomarker:**
  - **Application for a specific use in clinical care**
    - **Risk, Screening, Diagnosis, Prognosis, Prediction, Monitoring**
  - **Application in a clinical trial**
    - **Correlative**
    - **Direct Care within the Trial**

When is a Tumor Biomarker Ready for Prime Time?

- When the Analytical aspects of the assay for the biomarker are reliable
- When Clinical Utility has been demonstrated

Tumor Biomarker Publications and Use: Definitions

- **Analytical Validity**
  - **Does the assay accurately and reproducibly measure what you say?**
- **Clinical (or "Biologic") Validity**
  - **Does the assay actually identify a biologic difference ("pos" vs. "neg") that may or may not be clinically useful?**
- **Clinical Utility**
  - **Do results of the assay lead to a clinical decision that has been shown with high level of evidence to improve outcomes?**

Teutsch S.M., et al. Genet Med. 11:3-14, 2009

Overview

Gilbert S. Omenn, MD, PhD

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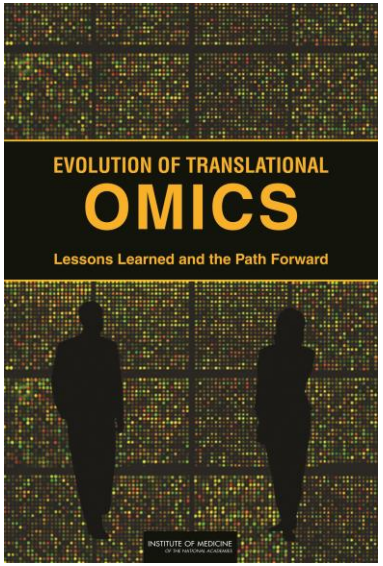
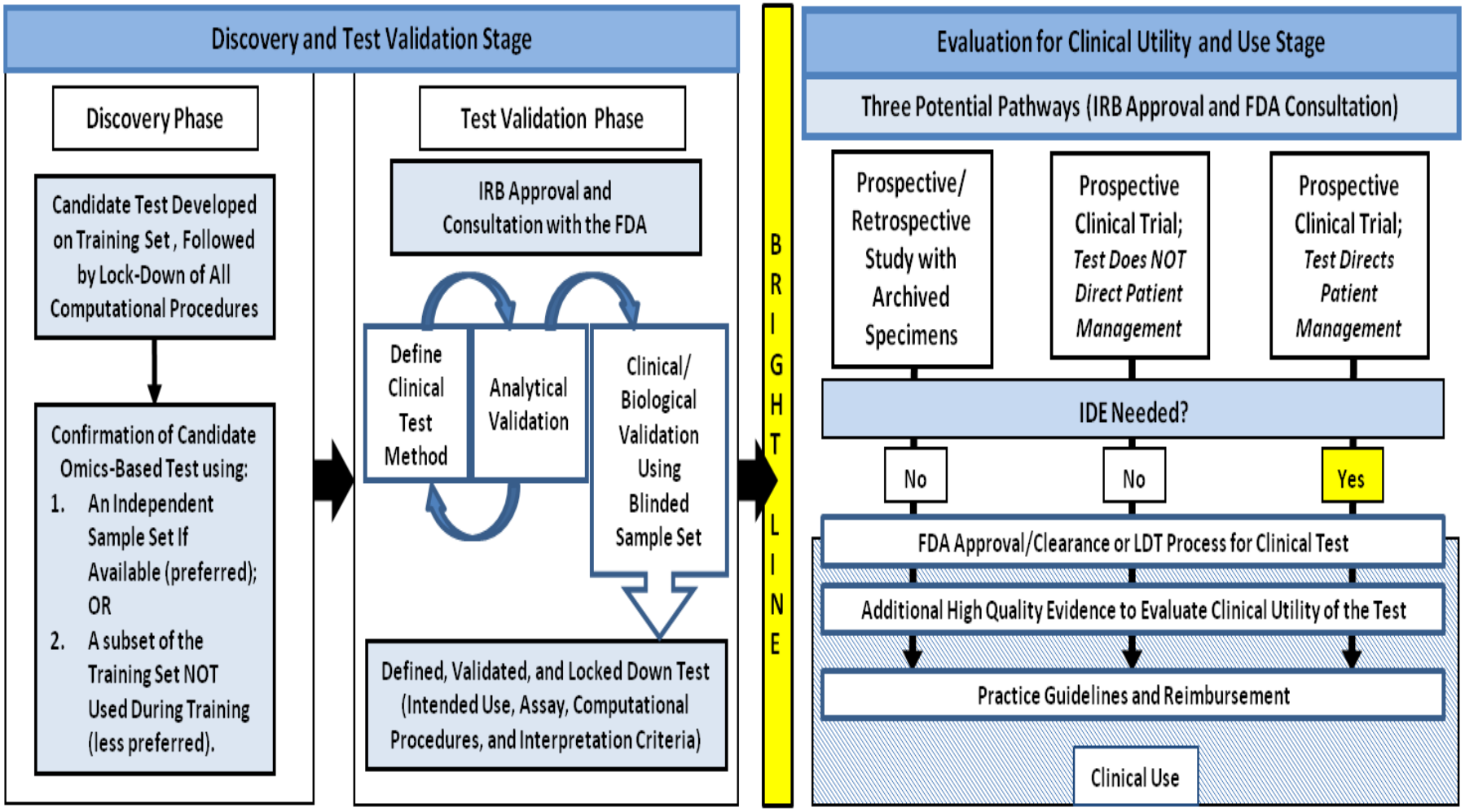


Evaluation for Clinical Utility and Use



When is a Marker Clinically Useful?

- It is either prognostic or predictive
- The magnitude of effect is sufficiently large that clinical decisions based on the data result in outcomes that are acceptable
  - *Greater chance for benefit*
  - *Smaller toxicity risk*
- The estimate of magnitude of effect is reliable
  - *Assay is reproducible*
  - *Clinical trial/marker study design is appropriate*
  - *Results are validated in subsequent well-designed studies*

Henry N.L., Hayes D.F. Oncologist. 11:541-52, 2006

Are Any Circulating Biomarkers Ready for Prime Time:
Standard Care?

- **YES**
  - Circulating MUC-1 (CA15-3, CA37.29) and CEA
    - Monitoring patients with metastatic disease
- **NO**
  - Circulating nucleic acids for any use
  - Circulating proteomics for any use
  - Any for Prognosis in Early Stage Disease

Are Any Circulating Biomarkers Ready for Prime Time: Standard Care?

- **MAYBE?**
  - Enumeration of CTC in metastatic disease
    - Prognosis
      - Baseline: Probably not
      - After one cycle of first-line chemotherapy for metastases; S0500
    - Decrease radiographic and scintigraphic staging
      - If history, physical, circulating MUC1 and CEA, and CTC are NOT rising – odds of progression are nearly 0.
      - After one cycle of first-line chemotherapy for metastases: SWOG S0500

Are Any Circulating Biomarkers Ready for Prime Time: Clinical Trials?

- **YES: CTC with genotype or phenotype; circ cftumorDNA; ? Circ miRNA**
  - **Correlate with outcomes to see if the circulating marker is a good surrogate of outcome (Response, PFS or OS)**
    - ***Example: PSA in prostate cancer***
  - **Use to direct patient care or stratify on different arms**
    - ***Example: ER, HER2***
  - **As pharmacodynamic monitoring tool**
    - ***Example: reduction of ER after fulvestrant***
  - **Direct patient onto innovative genomics trials**

Are Any Circulating Biomarkers Ready for Prime Time

- **Conclusions**
  - **Standard Care**
    - **CA15-3, CEA** — **YES**
    - **Others** — **NO or MAYBE**
  - **Clinical Trials**
    - **CTC** — **Yes**
    - **Circ cell free DNA** — **MAYBE**
    - **Proteomics** — **MAYBE**

But He Is a Good Grandfather!!