CLINICAL NEEDS/VALUES OF IMAGING BIOMARKERS

OR

WHAT THE HECK IS AN IMAGING BIOMARKER ANYWAY

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My Top Words

Most fuzzy and overused
– Correlative study
– Targeted therapy
– Biomarker
– Response
– Surrogate

Least fuzzy and underused
– Variability/Heterogeneity
– Control
– Qualification
– Predictive biomarker
– Prognostic biomarker
– Pharmacodynamic biomarker
Oncologic Therapeutics

• All drugs are “targeted”
  – If they weren’t they wouldn’t work

• Some of our best drugs are “dirty”
  – They hit multiple targets

• We don’t have “better targeted” drugs
  – We have more drugs and targets

• True drug mechanism often discovered after drug effectiveness is demonstrated
  – Putative mechanism may be wrong

Why Biomarkers?

• Individualized therapy
  – Most likely to benefit
  – Least likely to experience toxicity
  – Early identification of benefit
  – Early identification of resistance

• Understanding drug mechanism of action
• Understanding patient/disease heterogeneity
**Biomarker Definition**

A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention

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**Biomarkers**

- **Diagnostic marker**
  - Information on disease presence/absence
  - *e.g.*: 1cm spiculated nodule on chest CT

- **Prognostic marker**
  - Information on disease natural history, regardless of therapy
  - *e.g.*: ECOG performance status

- **Predictive marker**
  - Information on relative benefit from a specific therapy
  - *e.g.*: ER status and benefit from tamoxifen

- **Pharmacodynamic marker**
  - Information on therapy effect on host or tumor
  - *e.g.*: neutropenia following paclitaxel therapy

- **Treatment resistance marker**
  - Information regarding progression/resistance to ongoing therapy
  - *e.g.*: Secondary EGFR mutations
Biomarker Qualification

- **Known valid biomarker:**
  - A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, or clinical significance of the results.

- **Probable valid biomarker:**
  - A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, or clinical significance of the results.

- **Exploratory biomarker:**
  - A biomarker that does not meet the criteria for probable or known valid biomarker


Surrogate Endpoints

- **Subset of pharmacodynamic biomarkers intended to serve as a substitute for a clinically meaningful endpoint**
  - Relapse free survival in adjuvant breast cancer
  - Cytogenetic complete response in CML
  - Few if any “perfect” surrogate endpoints in oncology (Prentice criteria)
    - How good is “good enough”
The Two-Variable Problem

• Cannot test an unknown/exploratory biomarker and an unknown drug in the same trial

DCE-MRI As an Antiangiogenic Biomarker

• Utilizes standard 1.5T MRI with gadolinium contrast
• Kinetics of contrast uptake and washout reflect tumor “vascul arity”
• Changes detectable soon (1-30 days) following therapy with antiangiogenic agent
• Preliminary studies suggested that changes correlate with drug benefit and outcome
DCE-MRI $K_{trans}$ as Pharmacodynamic Biomarker

Baseline $K_{trans}$ is Prognostic For Time to Progression
BP Is a Pharmacodynamic Marker

Conclusions – Quantitative Imaging

- Numbers derived from cool technology and pretty pictures still require testing
  - Assay validity
  - Biomarker qualification
- The hypothesized utility of a biomarker must be specified a priori
  - Diagnostic, pharmacodynamic, predictive, etc
- A change with therapy may or may not be “good”