Predictive Biomarkers

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Predictive Biomarkers

- Class 1: Patients with a positive assay result benefit from a new therapy relative to another available therapy, whereas patients with negative assay result do not benefit from the new therapy relative to other therapy (ideal class)
- Class 2: The assay result identifies patients for whom a given therapy has (or may have) activity
- Class 3: The assay result identifies patients who are, versus who are not, likely to benefit from a wide class of treatments (e.g., adjuvant chemotherapy)
- Class 4: Patients with a positive assay result benefit from the new therapy relative to standard therapy

Predictive Biomarkers

- CDRH/FDA Companion dx guidance about to be final: need to have a result in both marker + and marker – to be called *predictive*; if don't have result in marker neg; can call *selective*
- Need to define what we are talking about.
- Clarity on the intended use of the test is crucial.
- Define that upfront in order to go on to determine what evidence is necessary.
- Context is specific in this endeavor

Clinical Utility Endpoints
All context depended (tumor type)

- Improved overall survival
- Improved progression free survival
  - Surrogate for overall survival, related to QOL
- Better patient reported outcomes
  - Decreased toxicity, QOL
- Lower resource utilization
  - Cost
- Response not likely to be valuable

Clinical Utility Endpoints
Biomarker Specific Considerations

- Additional interventions
  - Biopsy, “downstream” procedures, imaging
- Worse Quality of life
  - Hospitalization, psychological effects
- Increased Cost
  - Biopsies, molecular test

Types of needed evidence

- Anecdotal or rare dramatic responses
  - Lowest level of evidence, lots of “noise”, hypotheses generating,
- large databases studies
  - Better level of evidence (less noise) but highly dependent on size and quality of data
- Retrospective studies
  - Would require multiple studies with careful quality control
- Prospective-retroespective studies
  - Reasonable level of evidence, certainly valuable, emphases the need to collect tumor on all patients
- Prospective clinical trials
  - Randomized trials—gold standard
  - Single arm trials possible if a large treatment effect

Assay Issues

- FDA guidelines appear sufficient
- However-need to address variability in assays after initial approval
- Need transparent process for the "local" assay performance (CLIA lab assessments should be available to the public)
- Should all assays be compared to the "gold standard" (companion diagnostic)?

Assay Issues

- FDA should require similar standards for biomarker development as for drug development. With some flexibility in regards to development timeline.
- FDA should find a way to correlate "local" assays with response to the agent in order to "validate" the assay

What can NCI do

- Record and characterize rare responders
- Create a national database of genomic data from patients treated at institutions across the country
- Create a system which would allow patients (who otherwise could not) with specific mutations to obtain a targeted agent as long as all of the clincial data was provided into a NCI run database
- Clearing house linking genomic data to relevant clinical trials to assist the MDs

What can NCI do

- Engage other agencies to determine variability in biomarker assays (at different institutions).
- Generate performance statistics for biomarkers assays for the intended use.
- Foster collaboration among industrial partners, insurance companies and cooperative groups to conduct trials.

What can NCI do

- Should focus on studies which are critical for biomarker development and will NOT be funded by industry.
- Education of general community (physicians, patients and researchers) about biomarker validation (in “patient” terms
  - In conjunction with ASCO/professional organization