Quantifying Biomarkers: A Present and Future Disruptive Dilemma

Bruce Horten, M.D.
Medical Director
Genzyme Genetics, New York
Goals of This Presentation

- To present current dilemmas which create challenges in quantifying biomarkers
- To stimulate members of the audience to develop disruptive technologies that will alleviate some or all of these challenges
Use of Biomarkers

- Diagnostic
- Prognostic
- Predictive
Quantifying Biomarkers

- Increasingly important as one moves from

- Diagnostic to Prognostic to Predictive
A predictive marker - frequently in isolation - will determine to an often significant extent the choice of a specific therapeutic drug.

In general, a predictive marker is reported as a quantified score (the result) which then leads to an interpretation.
Technology has expanded in an attempt to meet the needs of Quantifying Biomarkers.
Technologies for Detecting Biomarkers

- Immunohistochemistry - Proteins
  Flow Cytometry

- Karyotyping - Chromosomes

- ISH / FISH - Chromosomal Fragments, Genes and Gene Clusters

- Molecular Pathology
  - PCR - DNA
  - RT·PCR - RNA (m-, i-, etc.)
  - Gene sequencing
  - Allele specific gene analysis
Quantifying Biomarker Technology

**IHC**
- Tissue Intact
- Variations of an H Score
  - % of tumor cells reactive
  - Intensity of reaction
- Technologies for Measuring Biomarkers
  - Visual
  - Image Analysis

**ISH FISH**
- Tissue Intact but Visualization a Challenge with FISH
- Dot Enumeration
- Technologies for Measuring Biomarkers
  - Visual
  - Image Analysis
Quantifying Biomarker Technology

Karyotyping
- Tissue Disaggregated
- From 1 to 20 Cells Analyzed
- Chromosomal Enumeration
- Technology for Evaluating Chromosomes
  - Image Analysis

Molecular Pathology
- Tissue Disaggregated
- Technology for Measuring
  - Basically as in clinical chemistry (e.g. graphs, light intensity, etc.)
Disruptive Dilemmas - Present & Future - in Quantifying Biomarkers

- No Gold Standard
  - Exception: Molecular Techniques
- Qualitative vs. Quantitative
- Intact vs. Disaggregated Tissue
- Tumor Heterogeneity
- Increasing Sensitivity of Technologies vs. Clinical Significance of Biomarker Results
QA requires a comparison of one lab with another. A relative comparison.

Upshot: One innovative lab may not compare favorably with a host of regular labs.

The generally accepted approach prevails.

Unless guidelines are initiated.

But these are themselves a compromise.
Qualitative vs. Quantitative Tests

- IHC is far more effective as a qualitative than as a quantitative test. Fixation, tissue thickness, etc.

- Tests such as FISH/CISH with dots or points to count lend themselves better to quantitation.

- The lure of numbers over qualities.
Intact vs. Disaggregated Tissue

- An area for major errors in testing.
- Observed tissue allows for ensuring that only tumor is analyzed.
- Disaggregated tissue loses this important QA step.
Tumor Heterogeneity

- Only now being adequately addressed with some quantifying biomarker test.

- Even if tissue still remains after the test, the methods employed for analysis vary in the extreme when heterogeneity is encountered.

- Visual and imaging methods both suffer from this dilemma.
Perhaps the greatest challenge of biomarker analysis to date.

Witness the demise of EGFR (IHC) for selection of Erbitux in colorectal cancer, or the failure to pay for genetic tests governing coumadin dosage by some managed care organizations.

Vast numbers of biomarkers available for study versus the clinical value of the tests.
- Prognostic vs. predictive
- Clinical Studies
Possible Solutions (Disruptive Technologies) to Improve Biomarker Quantitation

- **Guidelines**
  - Encompassing tissue heterogeneity
  - See Archives of Pathology, April 2009, Genetic Heterogeneity in HER-2 Testing in Breast Cancer

- **Return to Tissues**
  - Micro dissection of tumor prior to analysis
  - FISH ➔ CISH
  - Genomics ➔ Proteomics

- **Other Sources**
  - Serum
  - Circulating tumor cells

- **Novel Technologies**
  - Incorporating molecular analysis of intact tissues. Avoiding disaggregation.
Goals of This Presentation

- To present current dilemmas which create challenges in quantifying biomarkers
- To stimulate members of the audience to develop disruptive technologies that will alleviate some or all of these challenges