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CONFERENCE SERIES III

Futurescape of Pathology



Quantifying Biomarkers: A Present and Future Disruptive Dilemma

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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

Why?

- 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

No Gold Standard

- 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.

Biomarker Quantification vs. Clinical Significance



- 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.

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