FDA Perspectives on Biomarkers

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Importance of Biomarkers

- Earlier diagnosis
- Focusing expensive & invasive therapies on the right populations
- Monitoring disease progression & therapeutic benefits
- Facilitating drug development & discovery
  - Many more roles than surrogate endpoints

Biomarkers

- Recombivax HB Source & Structural Changes
  - Antibody to HBsAg correlates with protection
  - Large trial for antibody titer; Smaller trial showing prevention in maternal-fetal transmission
- Flu Vaccine & Antibody titers
- Cellular immunity biomarkers very challenging

- BUN/Creatinine
- Hemoglobin
- HbA1C
- Cholesterol
- Blood pressure
- ANC

Valid Biomarker Definition

- The FDA pharmacogenomics guidance defines a valid biomarker as
  - " a biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic,or clinical significance of the test results. "

Context ***Evidence***

Context in Labels

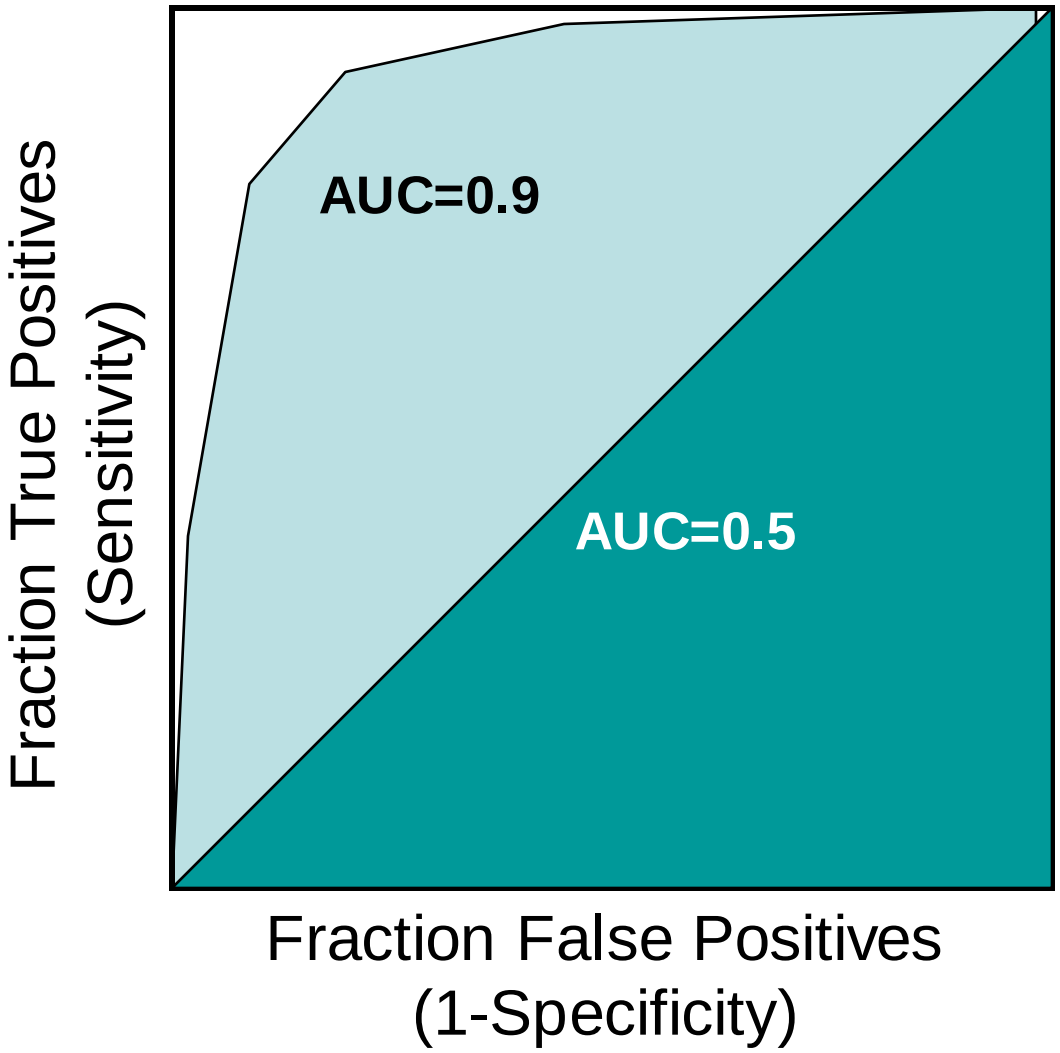
http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm

Her2/neu Over-expression ***Trastuzumab***	**Overexpresion of Her2/neu necessary for selection of patients appropriate for drug therapy** **"**Detection of HER2 protein overexpression is necessary for selection of patients appropriate for HERCEPTIN therapy (see INDICATIONS)." "HERCEPTIN should be used in patients whose tumors have been evaluated with an assay validated to predict HER2 protein overexpression (see PRECAUTIONS: HER2 Testing and CLINICAL STUDIES: HER2 Detection)."

EGFR expression ***Colorectal Cancer*** ***Cetuximab***	**Epidermal Growth Factor Receptor presence or absence**- "Patients enrolled in the clinical studies were required to have immuno-histochemical evidence of positive EGFR expression using the DakoCytomation EGFR pharmDx™ test kit."

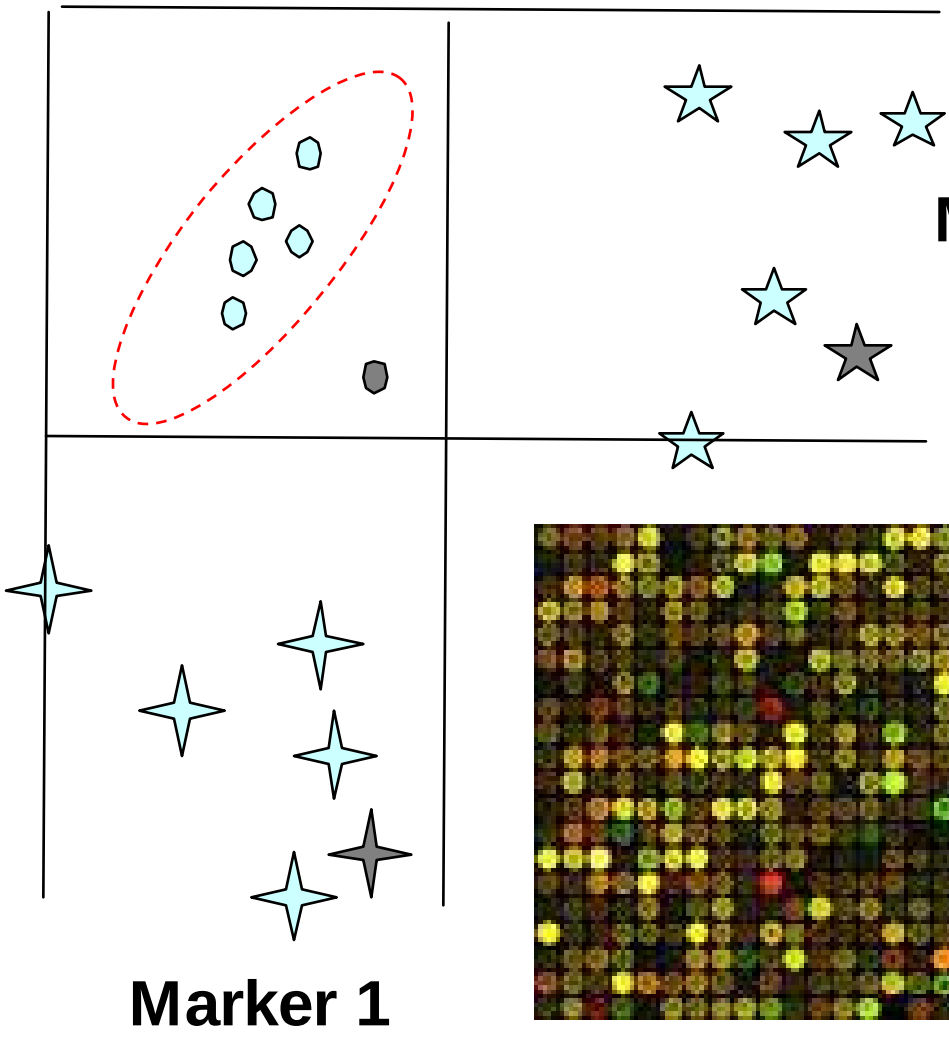
Comparisons

- Clinical endpoints
- Other biomarkers
  - Performance & Context may not be clear
- ROC
  - Receiver Operating Curves



Multiplicity

- **Looking at more than one marker can improve performance**
- **In biology variables are often inter-dependent**
- **A multivariate analysis uncovers relationships**
- **The correct statistical tools are important**



Adapted from T. Kourti

Approaches

- Study Design
- Sample Collection & Storage
- Technology Platforms
- Analytical Algorithms
- Biological Pathway Interpretation
- Data Submission Formats

What is the process for biomarker qualification at the FDA?

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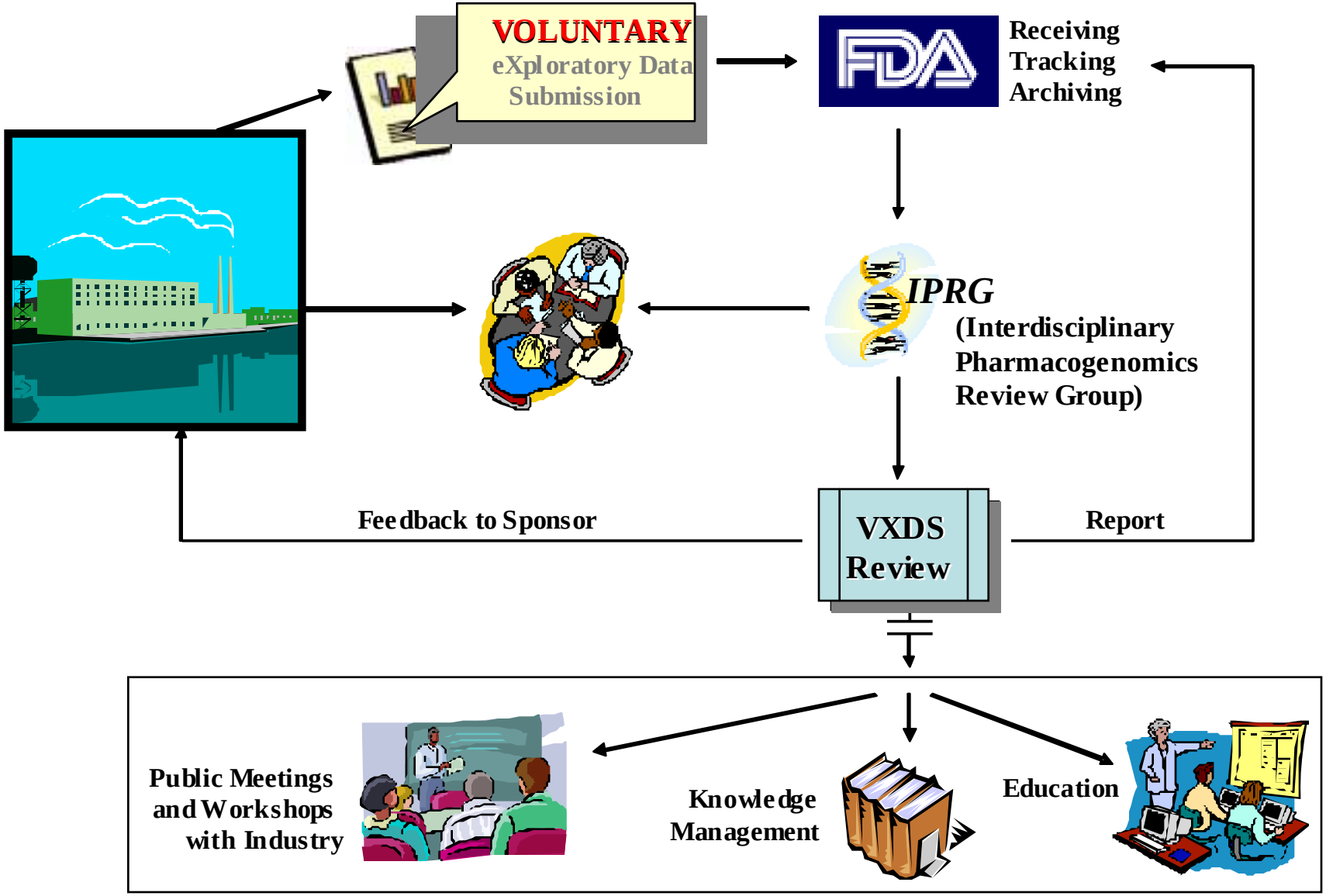
Introduction of Exploratory Biomarkers to the FDA: *Voluntary eXploratory Data Submissions*



Exploratory Biomarkers

(VXDS Meetings)

Qualified Biomarkers

(Biomarker Qualification Process)

Regulatory Decision Making

Why do we need to do it?

- To develop an efficient process for the qualification of biomarkers.
- To capture consensus on the value of biomarkers.
- To encourage the development of new biomarkers.

How do we qualify biomarkers today at the FDA?

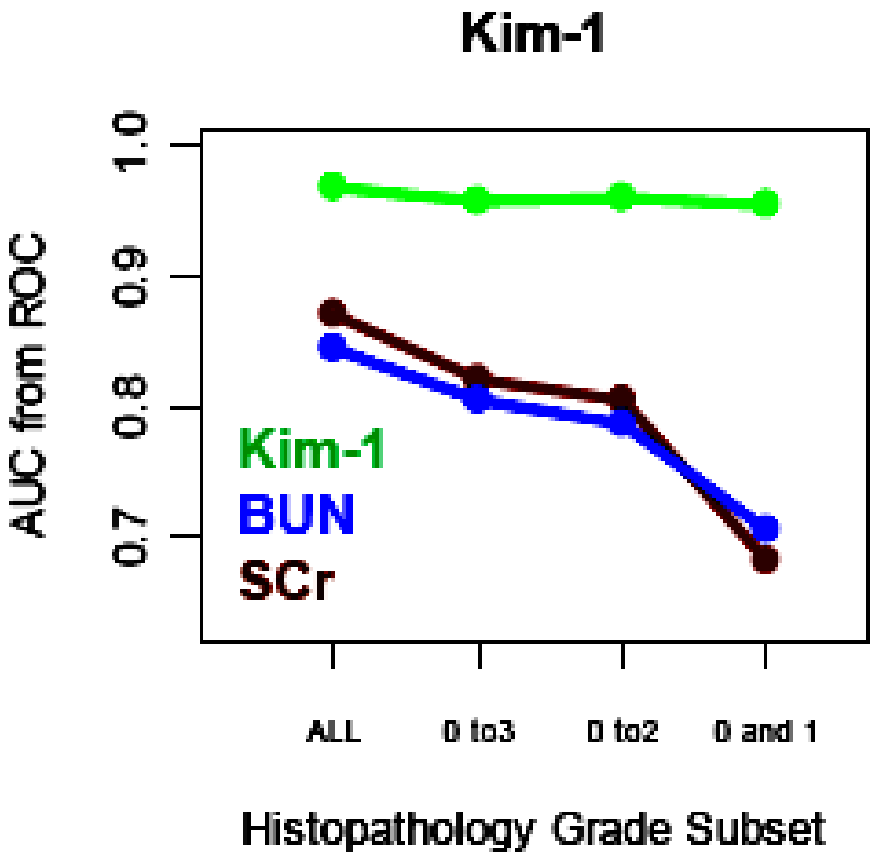
- Case-by-case. Context of use *always* drug-dependent.
- Codevelopment of drug and test.
- Labeling Updates
- Biomarker Qualification Process

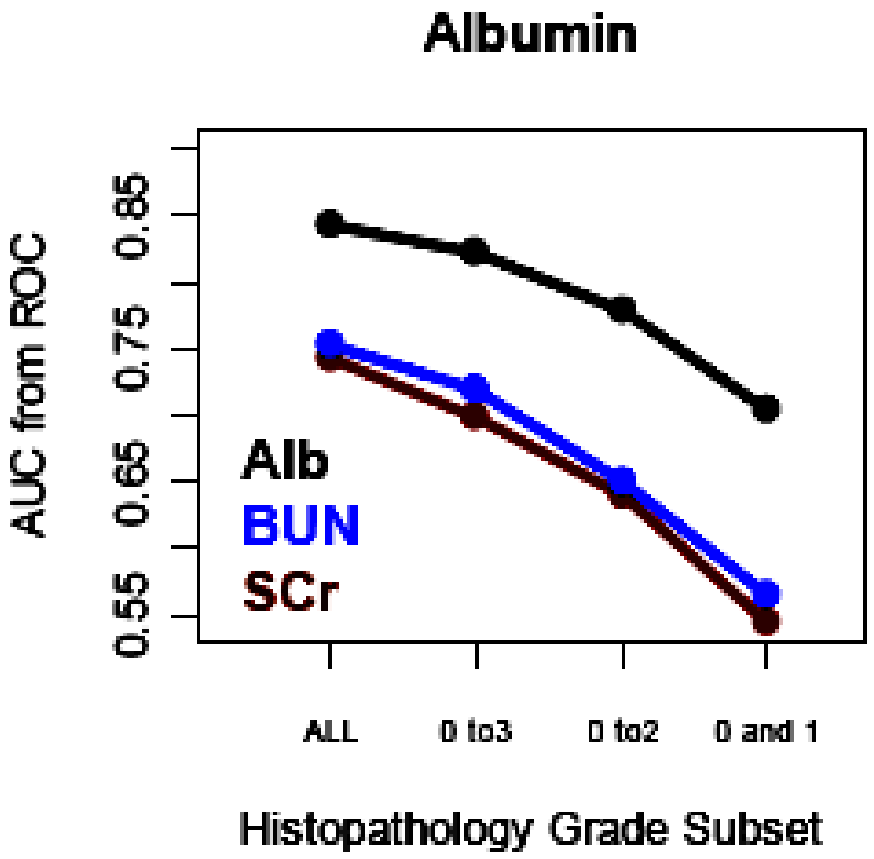
Context of Use

- Comprehensive statement which fully and clearly describes the manner and purpose of use for the biomarker, which may include:
  - range of clinical disorders
  - range of drug classes
  - range of species (for a preclinical biomarker)
  - circumstances of obtaining the biomarker samples (or measurements)
  - purpose for which biomarker measurements are obtained
  - how the measured biomarker results can be interpreted
- The qualified context of use
  - does not imply that the biomarker is necessarily invalid outside that context
  - only that use outside the qualified context will require careful consideration by the relevant CDER review group prior to acceptance.

What is a good candidate for biomarker qualification?

Performance of PSTC Rat Biomarkers of Nephrotoxicity





Biomarker Qualification Process

EVALUATION PROCESS
1) Informal discussion of a potential biomarker sponsor with the Biomarker Qualification Coordinator (BQC).
2) Biomarker Sponsor submits to BQC a written request for qualification of an exploratory biomarker.
3) BQC evaluates qualification request.
4) Biomarker Qualification Management Team (BQMT) accepts or declines the sponsor's request to proceed with qualification process.
5) Biomarker Qualification Review Team (BQRT) requests briefing document from biomarker sponsor.
6) BQ Project Manger schedules face-to-face meeting between the sponsor and the BQRT.
7) BQRT evaluates the briefing document and prepares for the Biomarker Qualification face-to-face meeting.
8) BQRT and Sponsor BQDS Meeting.
9) BQRT identifies and requests additional data from sponsor.

Biomarker Qualification Process

REVIEW PROCESS
10) BQRT receives full data package and review period begins
11) BQRT writes draft biomarker qualification review.
12) BQC routes the draft biomarker qualification reviews to all Offices
13) BQ Project Manager schedules the BQ review for presentation at a CDER Regulatory Briefing.
14) CDER Regulatory Briefing presentation and discussion is held.
15) CDER Office Directors make decisions to accept or reject the BQRT recommendations.
16) BQC drafts letter for sign-off by the Director of CDER communicating to the sponsor the results of the biomarker qualification..

Cancer Biomarkers

From CEA to SELDI-TOF MS Patterns

- Screening
- Staging
- Selecting & Monitoring Therapies

Better Diagnostic & Treatment Decisions