Perspective From the U.S. FDA on Biomarkers

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Biomarkers in Oncology

- Define patients likely to respond
- Define patients likely to have S/E
- Predict dose

- Early prediction of outcome
  - Response
  - Progression
  - Recurrence
Biomarker Development

• Many candidate biomarkers published—350,000 peer reviewed articles
Biomarker Development

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Very few ever reach clinical use
Biomarker Development

• Biomarker discovery is fast….. the understanding of clinical meaning develops very slowly
Biomarker Development

• Process for developing biomarkers for various uses is “broken”
  – Lack of understanding of scientific and pathway to qualification for use
  – Lack of understanding of regulatory pathway
  – Lack of viable business model
PSA

• Approved 1986 for monitoring and 1994 for early detection
  – Results varied between labs (different IR of AB, lack of external standard)
  – Practice standards discrepancy: FDA cut of decision making 4 mg/dl
  – Decision making combine PSA with other tests not accepted as standard f/c PSA, PSA velocity etc.
PSA

• Analytical comparison.. immunoassays is challenging

• Clinical utility of tumor marker assays may remain undetermined... biological nuances of disease, clinical decision making, and changes in the concomitant use of other diagnostic and therapeutic tools.

• Without controlled, systematic collection of data on test results and ultimate clinical outcome many questions about test performance will remain unanswered.
Drug Metabolizing Assays

• CYP-450: Strattera; UGT1A1: Irinotecan; CYP2C9 & VKORC1: Warfarin
Pharmacogenetic FDA Label Changes

- UGTA1*28 applicable to white populations
- UGTA1*6 polymorphism more important in Asian populations
- Need studies to determine appropriate starting dose for such patients.
Drug Metabolizing Assays

- CYP-450: Strattera; UGT1A1: Irinotecan; CYP2C9 & VKORC1: Warfarin
  - Clear instruction of how tests was lacking, e.g. dosing decision
  - Drug/allele general association, no specific advice
  - Negative reimbursement decision
Drug Metabolizing Assays

- No clear evidentiary standards on making labeling changes

- Use of pharmacogenomic information may be limited by what is known about clinical impact of its use and by the difficulty incorporating this information into established decision making.

- Health care providers are hesitant to use, and payors are hesitant to pay for, pharmacogenomic information without a sound empiric or evidence base on which to ground correct use.
Challenges for Biomarker Development

- Laboratory method to form a viable assay for wider use
- Analytical validation
- Clinical qualification
- Uptake in clinical labs; acceptance in clinical practice; reimbursement
Regulatory requirement

• Exploratory---minimum

• Demonstration/Characterization---more elaborate
Background

- Federal Food, Drug, and Cosmetic Act of 1938 (The Act)
- Medical Device Amendments of May 28, 1976
- Safe Medical Devices Act of 1990
- FDA Modernization Act (FDAMA) of 1997
- Medical Device User Fee and Modernization Act of 2002
The Current Regulatory System does not properly address

- Qualifying new biomarkers
- Approval pathways for diagnostics
- Linking targeted drug and diagnostic during development
- Clinical trial designs and development programs when targeting subsets of traditional patient groupings
- Evaluating combinations of investigational therapies
Qualifying New Biomarkers

• No real understanding of evidence needed for qualification
• Amount of evidence depends on use
  – Modify dose
  – Select/non-select trial participants
  – Stratify risk
• Conceptual framework strongly needed
• Current thinking overly dominated by “surrogate endpoint” issue
The Current Regulatory System is Not Designed Around Personalized Approaches

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• Approval pathways for diagnostics
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Approval Pathways for Diagnostics

• Currently diagnostics marketed as diagnostic service (“home brew”); analyte specific reagents (ASR); or FDA-approved diagnostic test

• Not clear how the new targeting markers will reach the market
Draft Guidance: “In Vitro Diagnostic Multivariate Index Assays”

• Pertains to assays that report out an “index”, “Score” etc. based on an algorithm developed for the assay

• FDA believes that most IVDMIAs will be classified as class II or III devices
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Linking Investigational Drug and Diagnostic Development

- Prior examples problematic

- Requires close collaboration among drug and dx manufacturer and FDA CDER and CDRH review staffs

- FDA “concept paper”; draft guidance under development
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Clinical Trial Designs to Target Subsets of Traditional Groups

- Ability of biomarker to distinguish subgroups must first be demonstrated (often using retrospective samples with “training” and validation datasets)
Clinical Trial Designs to Target Subsets of Traditional Groups

• Depending on quality of evidence, clinical trial may—
  
  – Include evaluation of biomarker predictive value (i.e., test biomarker negative subsets) ?

  – Enroll only biomarker + subjects ?

  – Have a sequential design or stepwise outcome measure that is statistically valid ?
The Current Regulatory System is Not Designed Around Personalized Approaches

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The Critical Path Initiative

Innovation

Stagnation

Critical Path Opportunities List

Critical Path Opportunities Report

U.S. Department of Health and Human Services
Food and Drug Administration
March 2006
Critical Path: Six Areas of Focus

• Improving clinical trial design
• Biomarker development
• Bioinformatics
• Product manufacturing
• Products for Public Health needs
• Product for special populations
Partnerships to Advance Molecular Diagnostics

- Oncology Biomarkers Qualification Initiative (OBQI): FDA-NCI-CMS
- NIH Biomarker Consortium
- Interagency Oncology Task Force: NCI-FDA
- AACR/FDA/NCI Cancer Biomarker Collaborative
- ASCO-FDA Clinical Trial Alternative Design
Oncology Biomarker Qualification Initiative (OBQI)

- Outgrowth of FDA/NCI Interagency Oncology Task Force
- OBQI: agreement between FDA-CMS-NCI to foster biomarker development
- Implement public-private partnerships to share resources and conduct studies using “neutral ground”
How are OBQI projects implemented/funded?

OBQI Federal Alliance: FDA/NCI/CMS

- Cancer Imaging
  - FDG-PET in NHL, FDG-PET in NSCLC
  - Foundation for NIH 501(c)3
    - The Biomarker Consortium
      - solicits for private funds
      - routes funds to NIH via Conditional Gift Fund authority
      - may issue/manage contract for projects
      - provides no scientific input
      - coordinates Exec. Comm and Working Gps
      - provides reports, coordinates communication with partners
      - Projects implemented

- Molecular Assays/Targeted Therapies
  - EGFR (Tarceva)
  - Critical Path Inst. 501(c)3
    - The “MATT” Consortium
      - solicits for private funds
      - no direct link to NCI to supplement appropriations
      - will issue/manage contract for projects
      - will lead scientific activities e.g. work with Cooperative Gps
      - coordinates with FDA/NCI/CMS and Working Gps
      - provides reports, coordinates communication with partners
      - Projects implemented
AACR/FDA/NCI CBC
Cancer Biomarker Collaborative

4 Subcommittees:

– Sample Standardization
– Assay Validation
– Information Sharing
– Bioinformatics
Biospecimen Standardization

- Establish process for specimen Validity
- Establish process for specimen handling to insure reliable evaluation of assays
- Establish standardized reporting systems for specimen handling
- Develop guidelines for IRBs to allow data sharing and data collection beyond response data
Assay Validation

• Develop a pathway for biomarkers assay validations
• Recommendation on Guidance
• Recommendation on policy changes
• Develop coherent integrated educational plan
• Develop unified terminology
• Develop universal physical standards that promote cross referencing
Bioinformatics

• standardization of reporting

• Standardization of platforms for data incorporation and sharing
Information Sharing

- Develop models pre-competitive consortium

- Develop incentives including regulatory, laws, financial

- Divorce drug response data from other clinical data during industry trials to allow development and evaluation of markers through data sharing.
FDA-ASCO Alternative Clinical Trial Design

• Include evaluation of biomarker predictive value (i.e., test biomarker negative subsets)?

• Enroll only biomarker + subjects?

• Have a sequential design or stepwise outcome measure that is statistically valid?