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

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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

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. A reduced initial dose should be considered for patients known to be homozygous for the UGT1A1*28 allele (see DOSAGE AND ADMINISTRATION). Heterozygous patients (carriers of one variant allele and one wild-type allele which results in intermediate UGT1A1 activity) may be at increased risk for neutropenia; however, clinical results have been variable and such patients have been shown to tolerate normal starting doses.

- 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 from 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

- 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 ?

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The Critical Path Initiative

U.S. Department of Health and Human Services
Food and Drug Administration
March 2006

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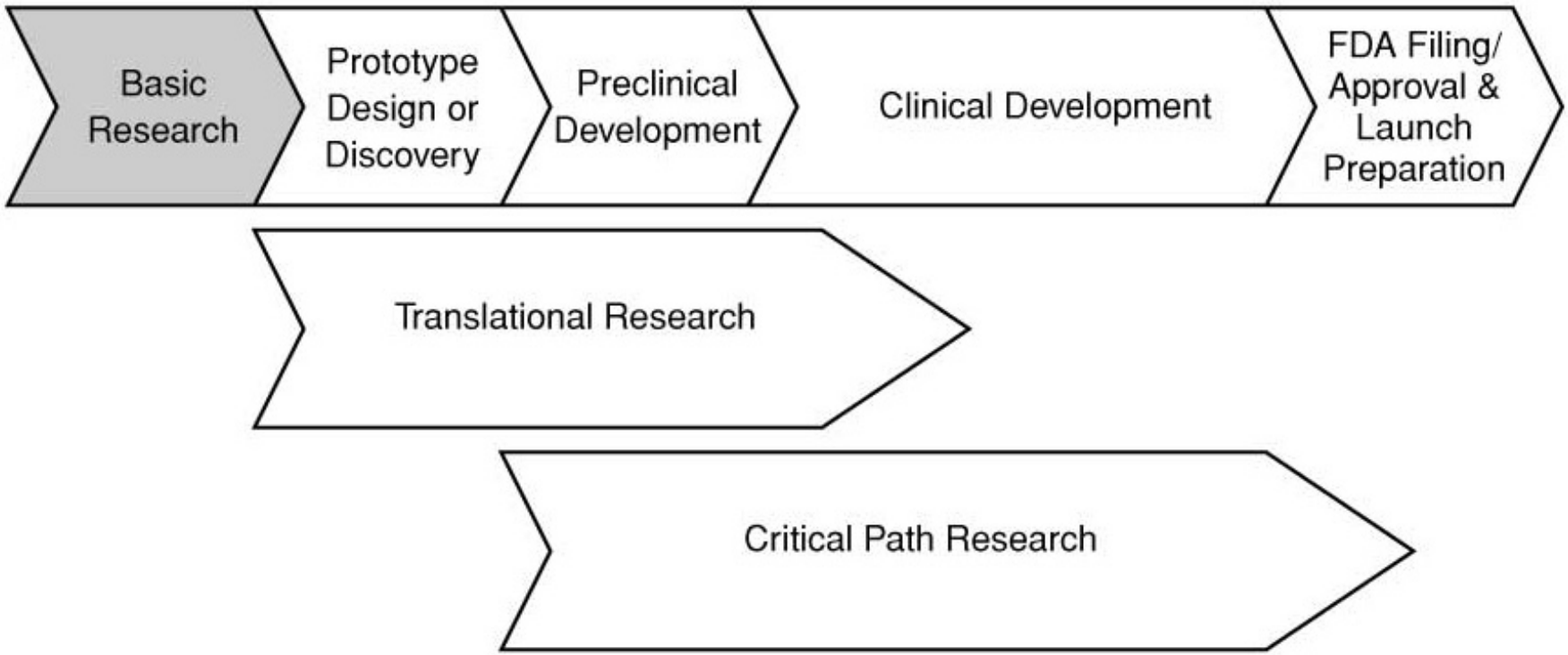
THE CRITICAL PATH



Critical Path: Six Areas of Focus

- Improving clinical trial design
- Biomarker development
- Bioinformatics
- Product manufacturing
- Products for Public Health needs
- Product for special populations

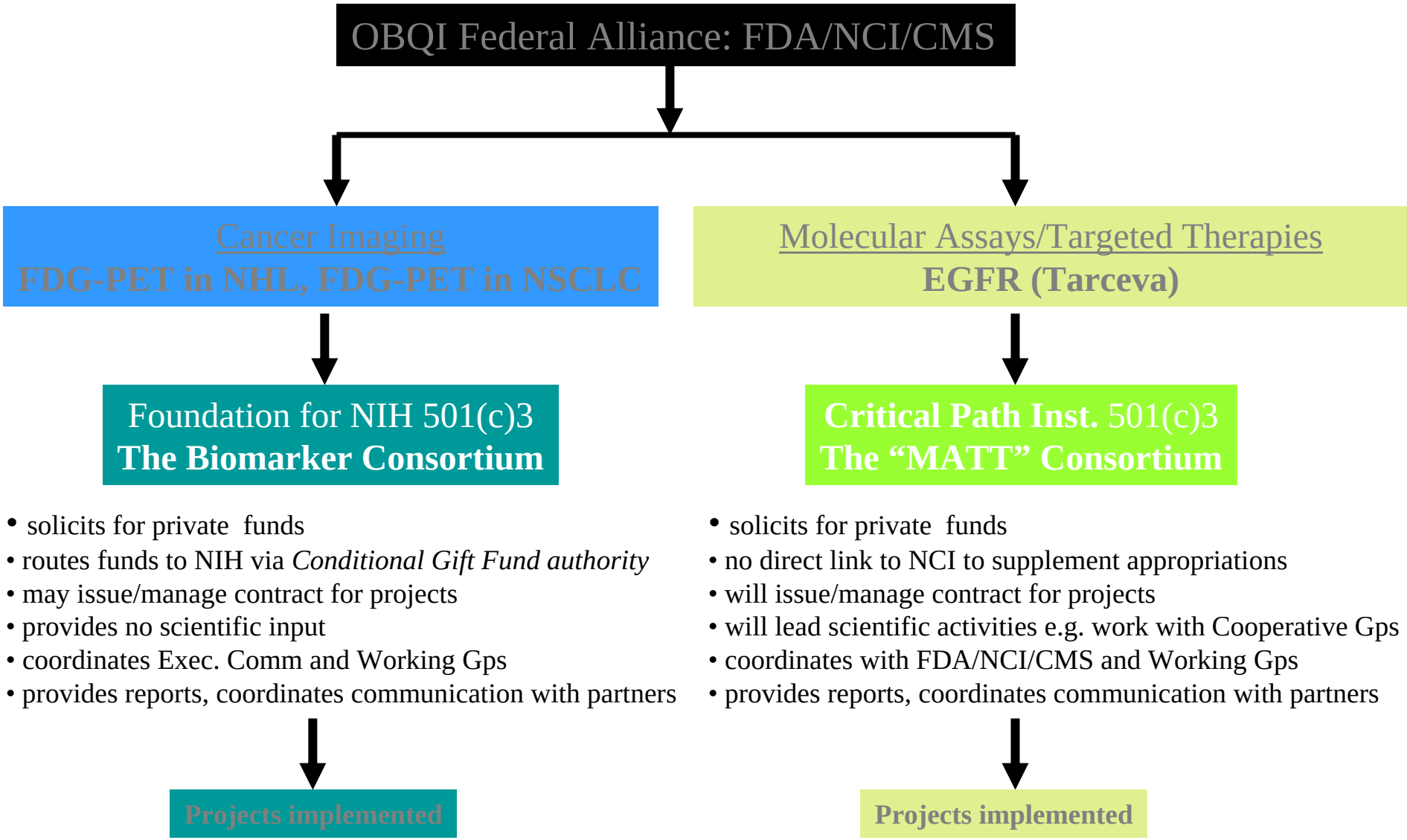
Partnerships to Advance Molecular Diagnostics

- 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?



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 ?