Responding to the Challenges of Personalized Medicine: Back to Basics - Again

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The Challenges

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Drug/Diagnostic Development Today

Advancing Personalized Medicine

Potential of PM

Faster and cheaper clinical trials
Larger effect sizes = smaller sample sizes = faster recruitment and completion
Increase probability of regulatory approval and reimbursement
Decreased uncertainty – risk and costs
Address unmet needs even in established therapeutic areas

Pitfalls of PM

Finding the right biomarkers with enough time to develop a CoDx to co-launch with the drug
Finding sufficient patients to enroll for biomarkers with a low prevalence
Evolving regulatory landscape
Relative lack of precedence
Finding the best test method, platform and partner
Ensuring HCPs understand the use and consequences of a diagnostic

Research Challenges

Regulatory Uncertainty: Which FDA Path to Follow?

Oncology Indication

Drugs

Diagnostic Test Predicts Label

Cetuximab (Erbitux)

EGFR

Efficacy

Required

Imatinib (Gleevec)

C-KIT

Efficacy

Informational Part of Diagnosis

Trastuzumab (Herceptin)

HER2 over-expression

Efficacy

Required

CV Indication

Drugs

Diagnostic Test Predicts Label

Clopidogrel (Plavix)

CYP2C19

Effectiveness

Unknown

Warfarin (Coumadin)

CYP2C9

Adverse Events

Recomended

HIV Indication

Drugs

Diagnostic Test Predicts Label

Abacavir (Ziagen)

HLA-B*5701

Adverse Event

Informational

Maraviroc (Selzentry)

CCR5 Tropism

Efficacy

Part of Diagosis

Labeling Information: Drug and Diagnostic
WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of Plavix is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see Warnings and Precautions (5.1)]. Plavix at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with Plavix at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see Clinical Pharmacology (12.5)]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see Dosage and Administration (2.3)].

Reimbursement Uncertainty: Key Components of the US System

Coding
- The US public and private health care systems use CPT codes (Current Procedural Terminology codes) to file claims for tests
- In the absence of a compliant code, a new service, procedure or technology must pursue a new code or use an unlisted/rare-specific code

Coverage
- US public and private payers may cover services, procedures, or technologies deemed medically necessary
- New technologies may still face noncoverage if they are viewed as investigational/experimental
- Routine tests (e.g., blood chemistry tests) are not described in coverage policy but some complex or costly/specialized tests (e.g., genetic or molecular tests) are increasingly subject to explicit coverage policy

Payment
- Outpatient test payment is usually benchmarked from the Medicare Clinical Laboratory Fee Schedule (includes both public payers such as Medicare/Medicaid and private/commercial payers)
- Payment is set based on existing tests or on the test activities performed

Reimbursement Uncertainty: Value Chain

Analytic Validity
- A test's ability to measure the biomarker of interest accurately and reliably
- Analytic sensitivity, analytic specificity, precision, robustness

Clinical Validity
- A test's ability to detect and predict the outcome associated with the biomarker
- Clinical sensitivity, clinical specificity, positive predictive value, negative predictive value

Clinical Utility
- Clinical effectiveness – value of the information in informing actionable clinical decisions
- Intermediate outcomes or measures, morbidity, mortality, HRQoL, AEs

ECONOMIC VALUE
- Budget Impact of test to provider or healthcare system
- CEA, CUA, CBA

Drug/Diagnostic Development Today

The Ideal Diagnostic Test
- Globally available and part of HCP work-flow
- Sensitivity and specificity demonstrated versus "gold standard"
- Rapid turn around of results where necessary
  - Point of Care Offerings
- Broadly reimbursed – at launch of therapy
- Widely accepted and adopted by medical community
- Results well-correlated with clinical outcomes
Goal: Bring companion diagnostics from concept to clinic use

**Discovery and Characterization of Biomarkers**
- TPP
- Tx Value Creation
- Competitive Assessment
- Investment

**Clinical Diagnostics**
- Lab Developed Test (LDT)
- In-Vitro Diagnostic (IVD)

**Launch Readiness**
- Ubiquitous Access - Channels
- Payer Acceptance
- Physician and Patient Adoption
- Investment Trade Offs

**Companion Dx CoE**
- Established Framework for informed and effective decisions

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**Ideal Development Scenario**

“Align drug-diagnostic co-development to enable timely and cost-effective access to companion Dx at launch”

**Pre-Clinical**
- Feasibility
- Discovery
- Analytical Validation

**Clinical Phase I**
- Clinical Trials
- Regulatory
- Clinical Validation

**Clinical Phase II**
- Clinical Trials
- Regulatory
- Clinical Validation

**Clinical Phase III**
- Clinical Trials
- Regulatory
- Clinical Validation

**FDA Filing / Approval**
- High and regulatory
- Payer
- physician
- patient
- commercial

**Launch**
- Marketing
- Sales
- Sales

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**Biobanks**
- High-quality, clinically annotated biospecimens
  - VA Million Genome Program
  - Pre-competitive consortia

**Regulatory/Reimbursement Reform**
- Parallel review for CoDxRx
- Clinical utility demonstration programs
- Value-based payment – flexible and transparent
- Predictable incentives

**“Revival” Incentives**