First Annual Biomarker Symposium
Quest Diagnostics Clinical Trials

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Key Considerations: Biomarker Development & Companion Diagnostics
Biomarker to Companion Dx Assay Development

**Selection, Validation, & Testing**
- Biomarker R&D
- Assay Development
- Technology Transfer
- Novel Biomarkers
- Study Specific Batch Testing

**Scale-up and Global Deployment**
- Assay Commercialization
- Laboratory Developed Test
- IVD Strategy
- High Volume Real-time Testing
Biomarker vs. IVD Development (historical)

Drug Development

<table>
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<tr>
<th>Discovery</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Register</th>
<th>Launch</th>
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Comp Dx Development

Biomarker Development
- Target Identification
- Assay Validation
- Testing

Potential Gap & Risks
- How to move CompDx strategy earlier?

IVD Development
- Research
- Prototype
- Clinical & Mfg Validation
- 510K

- Biomarkers and IVD were not necessarily considered as single development strategy to CompDx
- How to move companion diagnostics strategy earlier in drug development?
Laboratory Developed Test (LDT) can Bridge Biomarker and IVD Development

Drug Development

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<tr>
<th>Discovery</th>
<th>Phase I</th>
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<th>Registration Approval</th>
<th>Global Launch</th>
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<tbody>
<tr>
<td><strong>Biomarker Discovery and Development</strong></td>
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<td>Identification</td>
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<td>Assay Validation</td>
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<td>CT Testing</td>
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<td><strong>LDT Development</strong></td>
<td>Research Prototype</td>
<td>Launch w/drug approval</td>
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<tr>
<td><strong>IVD Development</strong></td>
<td>Research Prototype</td>
<td>Clinical &amp; Mfg Validation, 510K</td>
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- Parallel LDT strategy can bridge timeline between drug and IVD development / approval
- Early involvement and alignment of IVD and biomarker development is critical
How a Central Lab Can Support Companion Diagnostic Development

**Biomarker Development – LDT – IVD**

- Research
- Prototype Assay
- Technical Validation
- Clinical Validation
  - Ph I
  - Ph II
  - Ph III
- Adoption

- **Academic Lab**
- **BM Discovery / Pharma**
- **Large IVD Mfg**
- **Large Ref Lab**

- **CT Central laboratory**
- **Niche CLIA Labs**

**Biomarker Laboratory ➔ Central Laboratory ➔ Reference Laboratory ➔ IVD**
Evolution of a Biomarker Assay to CompDx: Diagnostic Manufacturer Perspective

- Regulatory and validation standards
- Platform selection
- Meaningful Performance criteria
- Specimen availability, collection, handling, storage and stability issues
- Assay robustness
- Assay standardization
- Flexibility for Assay Modification
Early screening and selection
• Multiplex or screening array approach

Mid stage development - LDT
• Defined panels of analytes or single analytes
• Selection based on critical parameters
  - Sample volume
  - Turn-around-time
  - Through-put
  - Sensitivity
  - Specificity
  - Cost
  - IVD Compatibility

Late stage development
• IVD companies may be locked into single platform
• No assay modifications
• Strategies to bridge data for method changes
Case Examples: Laboratory Developed Tests & Companion Diagnostics
ras Mutation Analysis
• H-ras, K-ras, N-ras mutations by DNA sequencing

DxS Therascreen
• CE-marked, but not FDA cleared
• Scorpion technology on ABI 7500
• Detects 7 different mutations
• Improving sensitivity
  ▪ DNA extracted method selection
    o 2-4 5 micron slices
    o Extraction for tumor tissue only
    o QC of extracted DNA
Epidermal Growth Factor Receptor (EGFR) Pathway Mutation Analysis: Therapy Choice

**February 2009 NEJM**
- 11% of RAS mutations missed if only ASCO recommendations were followed

**June 2009**
- Quest Diagnostics launches most complete EGFR pathway testing

**July 2009**
- FDA adds EGFR testing information to Erbitux® & Vectibix® labels

- **KRAS Mutations**
  - Negative
  - Positive
  - Response to Anti-EGFR Unlikely

- **NRAS Mutations**
  - Negative
  - Positive
  - Response to Anti-EGFR Unlikely

- **BRAF Mutations**
  - Negative
  - Response to Anti-EGFR More Likely
  - Positive
  - Response to Anti-EGFR Unlikely

- **Prescribe Erbitux® or Vectibix®**

Patients | Growth | People
Proprietary Assay: IgG FcγRs Polymorphisms

- Genetic polymorphic variants for Fc receptors proteins that predict response of patients with lymphoma to therapy with Rituximab
- Assay is performed via real-time PCR
- Potentially applicable to all Ab therapies that utilize antibody-dependent cell-mediated cytotoxicity
- Sample type: whole blood or tissue to derive DNA


Zhang, et. al., J. Clin. Oncol. 25:3712-3718
ColoVantage™ (Methylated Septin 9 DNA)

Septin 9 gene (SEPT9) involved in cytokinesis and cell cycle control

Abnormal methylation of SEPT9 DNA associated with CRC in case/control studies

Plasma-based test

No patient preparation required before testing

Clinical study (PRESEPT) under way

Is methylated SEPT9 DNA test clinically useful for CRC screening?
Screening for Methylated Septin 9 DNA

The PRECEPT STUDY: Goals and Success Criteria

- Screening population (US-Guidelines)
- Cancer (0.6-0.8%)
- Polyps (30-40%)
- No findings

- 7,500 subjects w/ ~50 cancer cases

PRECEPT

Goal: Evaluate performance and health economic benefit of SEPT9 in CRC screening

SEPT9 Testing in external laboratories:
1) All cases with cancer and larger polyps
2) A random selection of cases with smaller polyps and normals (Expect testing of approx. 1,500 samples in total)

Success criteria:
- >50% Sensitivity (current US screening guideline requirements)
- 85-90% Specificity (health economically acceptable)

Used with permission from Epigenomics.
A Case Study: Colorectal Cancer

EGFR Pathway

Diagnostic

Biopsy

Screening

FIT Septin-9

Testing Opportunity: <50,000

Testing Opportunity: ~300,000

Testing Opportunity: >80 Million

Diagnostic

Prognostic/ Monitoring

Therapy Choice
Simplexa: Example of Comp Dx in Physician Office

Why Simplexa?

- Size and versatility of the instrument
- Scalability & Speed
- Software designed for clinical lab
- Proprietary detection algorithm
- 50-75% reduction of reagent usage
- Service and support with ‘repair by replace’ model
Summary

- Companion Diagnostic assay development is still evolving
- LDTs bridge the gap in development timelines
- Delivering an FDA approved diagnostic test is not without its challenges; timing is critical
- New strategic partnerships across multiple industries are necessary
- Allow for flexibility to adapt to changes in platforms and clinical utility throughout development