Companion Diagnostics: Aligning Development, Commercialization, and Market Access

March 27, 2013 - Webinar
Outline

• Companion Diagnostics Overview
  - Regulatory Landscape

• Laboratory/Test Distribution Dynamics

• Market Access
  - Evidence/HTA/Cost Impact

• Case Study

• Aligning Development and Commercialization

• Moving Forward
Companion Diagnostics Overview
Types of Rx/Dx Combinations

- The core U.S. personalized medicine market (diagnostics, therapeutics, lab services, and test sales) has been estimated to be $24 billion and is predicted to grow 10 percent a year to $42 billion by 2015*

- The majority of the over 20 personalized medicine drugs are cancer therapies but other areas such as cardiovascular disease, neurology (Alzheimer’s), etc., are currently being explored

- There are several types of companion diagnostics (CDx):
  - Tests co-developed/launched with diagnostic development partners (novel)
  - Tests which have clinical value independent of therapy selection that are brought to market separately (existing)
  - Tests that have been launched as CDx or Rx/Dx combinations for other therapies (existing)
  - Proprietary tests commercialized by innovators/laboratories with intellectual property rights to key biomarkers (uncommon) and non-proprietary markers (common)

Success of Rx/Dx combination requires alignment between test and drug during both development and commercialization

*Source: “The new science of personalized medicine: Translating the promise into practice” Price Waterhouse Coopers 2009
CDx / Rx Requires the Merging of Two Different Development / Regulatory and Commercialization Paradigms

**Pharma**
15 years and $1.2 Billion investment
- FDA approval through rigorous evidence development

**Diagnostics**
2 to 3 years and $7 to $10+ million investment
- Expeditious regulatory clearance with minimal evidence development

**Development**

**Commercialization**

**Pharma**
- Distribute and sell products globally
  - Immediate market access
  - Substantial market access resources (managed markets, health econ)

**Diagnostics**
- Seeking broad platform use
  - Minimal market access support
  - Iterative reimbursement process (coding / funding lag)

**Widespread Market Access**

Very different approaches in terms of regulatory pathway, investment, evidence development, and commercialization between Dx and Rx yield different expectations for development and market access for CDx
CDx Regulatory Environment Overview

Regulatory Pathways for Novel CDx

Government Agency Approval (i.e., FDA Approval of IVD kits, ANVISA in Brazil, etc.)

i.e., test kits are reviewed for safety/efficacy and cleared by government agency

Laboratory Developed Tests (LDT)/ “Home-brew” Laboratories have the ability to create novel tests (in some cases reviewed by laboratory level accreditation programs)

Regulated by Clinical Laboratory Improvements Amendments (CLIA) in U.S.

Many current examples of CDx rely on post-marketing regulatory approval of tests or the assays are not FDA approved (i.e., LDT). The joint FDA review/approval of Zelboraf and Xalkori drugs and kits was precedent setting.
Development / Regulatory Partner Selection

- In July 2011, the FDA issued draft guidance describing the approval process for In Vitro Companion Diagnostics
  - It describes joint regulatory approval of the specific CDx assay for use with therapy
  - Tests can use device clearance processes: predicate (510k) or secure premarket approval (PMA)
  - Labels of CDx drugs may mention use of FDA approved tests but do not name specific test products/manufacturers
  - Labels of CDx diagnostics will link to specific drugs in the intended use statement
  - This guidance document is expected to be finalized in the near future

- A range of factors influence the timing and decision to select a partner for a particular CDx related initiative:
  - Platform/methodology/technological capabilities, unique ability to address a scientific research need, experience/knowledge or alignment with underlying scientific basis of therapeutic (i.e., disease pathway, metabolomics/proteomics)
  - Prior experience/success in bringing a companion test product through the FDA
  - Commercial know-how, market access and product launch experience

CDx development/regulatory partners may bring unique technological capabilities but often the first objective is simply regulatory approval so the initial partner may not be the best partner to launch/commercialization a CDx product
How Development Partnerships May Not Align With Commercial Needs

1) During development a particular test platform is selected due to its potential for highly accurate results (next-generation sequencing, FISH, etc.)
   - Platform may not have clear regulatory approval pathway. Post-launch it is determined that only a limited number of labs globally have the relevant testing capability. An alternative method of patient testing/selection (PCR, IHC) is developed during post-launch phase.

2) Scientific team includes element in clinical development test protocol that involves unique steps that enhance the sample available for molecular testing
   - Commercial labs around the world question need for sample enhancement step. Labs disregard. Payers wonder if they are getting the right population selected because actual test used is different than that used in trial.

3) Pharmaceutical and diagnostic company partner to bring an assay through joint FDA review but need to focus on only certain frequently occurring mutations to enhance prospects for regulatory approval.
   - Physicians want more expansive list of mutations so they order laboratory developed tests with varying levels of accuracy/quality

May be misaligned incentives: Reduced regulatory risk and best chance of approval versus commercially viable test platform
Laboratory/Test Distribution Dynamics
CDx can be performed in a variety of settings/locations. Often a combination of different distribution models are needed globally-- not one size fits all.
Globally, labs will often use "research only" or "investigative use only" for clinical diagnosis. Business objectives for IVD (sell kits/platforms) and Pharma (broad market access) may not align. **Key question**: what approach actually results in highest level of accuracy? It may not always be the FDA approved version.
Market Access
## Global Health Technology Assessment Review Approaches: CDx

<table>
<thead>
<tr>
<th>Approach</th>
<th>Description</th>
</tr>
</thead>
</table>
| National/Joint review of both test and drug   | • Both test and drug are examined together  
• Can be done by separately or jointly by a single organization          |
| Mixed National and Regional review            | Often divided between private (regional) and public payers (national) with private going first |
| Regional review of test                       | Local payers/entities                                                        |
| No formal process for review                  | No explicit review of test for market access                                  |

Market access for CDx is often an iterative process in which labs simply bill for the test and attempt to get paid without formal HTA review.
ACCE Model (Analytic Validity, Clinical Validity, Clinical Utility and Associated Ethical, Legal and Social Implications)

- **Analytic validity:**
  - Ability to accurately and reliably measure the genotype of interest

- **Clinical validity**
  - The test’s ability to detect or predict the associated disorder (phenotype)

- **Clinical utility**
  - Risks and benefits associated with its introduction into routine practice including health outcomes

- **Ethical, legal, and social implications**

Evidence needed to support test can be quite different than that needed for a drug. In the U.S. there is no standard submission process, although a dossier format has been suggested.
Maximizing the Clinical and Economic Potential of Companion Diagnostics Requires Careful Attention to Real-world Performance Characteristics

- Sensitivity
- Specificity
- Prevalence of Disease
- Predictive Value
**Health Economic Dynamics Can Support Access for Test and Drug, Test Accuracy is Critical to Value**

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Response Rate</th>
<th>Number of Responders</th>
<th>Total Cost*</th>
<th>Cost/Respondent*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected</td>
<td>20%</td>
<td>2000</td>
<td>$500 million</td>
<td>$250,000</td>
</tr>
<tr>
<td>Accurate Test</td>
<td>80%</td>
<td>8000</td>
<td>$405 million</td>
<td>$50,625</td>
</tr>
<tr>
<td>Inaccurate Test</td>
<td>Test identifies 80% for tx; but only 60% respond</td>
<td>6000</td>
<td>$405 million</td>
<td>$67,520</td>
</tr>
</tbody>
</table>

Cost of Drug: $50,000 (give only to projected responders)
Cost of Test: $500 (test all eligible patients)

Drug company may need test component to secure market access for therapy because 20% response rate in an untested population does not justify the expense. However, if payers do not typically pay more or less for more accurate tests does the estimated cost per responder match reality?

*inclusive of testing
Pharma funding can be attractive outside of the United States but there are questions about its long-term sustainability.
Case Study
Vectibix, Erbitux and KRAS Timeline

In Europe, while Erbitux was Approved Early On, Vectibix was Initially Not Approved until KRAS Data Were Provided

2004: Erbitux approved by FDA and EMEA

May 2007: EMEAs CHMP recommends against Vectibix approval based on evidence that drug may not work if KRAS is mutated

Sept 2006: FDA grants accelerated approval to Vectibix (no diagnostic test data)

June 2007: Amgen resubmitted to the EMEA but this time included genetic marker data

June 2007: EMEA approves Vectibix for patients with non-mutated KRAS

May 2008: EMEA changes Erbitux’s label to say only non-mutated cases should get drug

June 2008: U.S. physicians begin to use KRAS gene tests regularly

December 2008: In an unusual joint move both Amgen and BMS and Lilly request label change so sales reps can speak to genetic information

May 2008: EMEA changes Erbitux’s label to say only non-mutated cases should get drug

June 2009: After some debate about the validity of retrospective data analysis FDA approves label change for both drugs

June 2009: After some debate about the validity of retrospective data analysis FDA approves label change for both drugs

2008: FDA did finally approve a test kit for KRAS in 2012 but it is currently only approved for Erbitux
## KRAS Test Methods

<table>
<thead>
<tr>
<th></th>
<th>Real-time and Clamp PCR approaches</th>
<th>Melting curve analysis</th>
<th>Pyro-sequencing</th>
<th>Direct Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology</strong></td>
<td>PCR</td>
<td>PCR</td>
<td>Sequencing</td>
<td>Sequencing (bi-directional)</td>
</tr>
<tr>
<td><strong>Sensitivity (limit of detection)</strong></td>
<td>1%-5%</td>
<td>5%-10%</td>
<td>5%-10%</td>
<td>20-30%</td>
</tr>
<tr>
<td><strong>Mutations</strong></td>
<td>7-12</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>High sensitivity, rapid, closed, reduces contamination risk</td>
<td>Rapid, closed PCR system</td>
<td>Detects all possible mutations</td>
<td>Gold standard, can detect all possible mutations</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Only detects specific mutations, requires more tissue for analysis as compared with other methods</td>
<td>Occasionally difficult to distinguish between mutation types</td>
<td>Requires strict control for contamination</td>
<td>Low sensitivity, poorly quantitative, prolonged turnaround, requires strict control for contamination</td>
</tr>
</tbody>
</table>

KRAS is currently performed using numerous approaches with varying levels of accuracy. These differences are lost on physicians.
US Coding: KRAS Medicare Carrier Payment Assignment based on New MoPath CPT Codes

2012: Stacked Coding

<table>
<thead>
<tr>
<th>Quest</th>
<th>LabCorp</th>
<th>ARUP</th>
<th>Genzyme</th>
<th>Mayo</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR and Sequencing</td>
<td>PCR Kit</td>
<td>PCR and Pyrosequencing</td>
<td>Single nucleotide primer extension</td>
<td>PCR Kit</td>
</tr>
<tr>
<td>$263.06</td>
<td>$268.61</td>
<td>$202.43</td>
<td>$345.44</td>
<td>$259.06</td>
</tr>
</tbody>
</table>

2013: New Gene-specific Codes Available for Use

CPT 81275 KRAS

2013: Carrier-specific Payment Assignment

Palmetto GBA LDT = $225.88
Cahaba GBA = $235.00

Palmetto, using Z-codes, can distinguish between FDA-approved versions of tests and LDT versions, and assign payment for FDA-approved tests at differentiated rates.
Topline Estimate of Economic Impact of KRAS Testing to Guide Therapy for mCRC

- “In the treatment group, progression-free survival (PFS) was 12.3 weeks for those with wild-type KRAS, and 7.4 weeks for those with mutant KRAS. In the control group, median PFS was 7.3 weeks in both KRAS groups”¹

- In a hypothetical cohort of 100 patients, the use of the KRAS biomarker (excluding the cost of the test) would account for the following potential cost offsets:
  - 40 patients with KRAS mutation - avoid average 7.4 weeks of panitumumab therapy
  - Usual dose (6mg/kg weeks * 70kg) ~ $4,000 WAC q 2 weeks * 4 doses = $16,000/patient * 40 patients = $640,000 expenditure avoided for therapy where response not expected and alternative therapy could be considered*
  - Improved treatment outcomes is expected in 60 patients where response is predicted based on KRAS mutation analysis

¹http://www.ecco-org.eu/News/News/EJC-news/Need-for-a-paradigm-shift-in-clinical-trial-design/page.aspx/483
*Estimates based on estimated dosing and price information anticipated at time of launch
Aligning Development and Commercialization
Potential Timing of Engagement between IVD and Pharma

• Given the complexity and work involved in developing an IVD assay, early partnering with an IVD company is usually better

• However, an IVD company cannot lock in on a design until the key biomarkers are understood/selected

• If a particular platform is selected too early a platform transition may be needed

• Some pharma prefer to develop assay concept, then secure IVD Partner and do bridging study/IVD assay development/validation during Phase IIA/III

• The risk here is that the diagnostic company may not have enough time to validate the assay prior to therapy approval/launch
Pharmacodiagnostic offerings are being deployed by a range of players with varied capabilities in development and commercialization.

- Much of the focus of Dx / Rx partnerships has focused on product development, however commercial execution risk is not well understood.

<table>
<thead>
<tr>
<th>Platform</th>
<th>Content</th>
<th>CDx Development</th>
<th>CDx Lab Service / Distribution</th>
<th>CDx Commercial Execution</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Developing CDx based on platform capabilities&lt;br&gt;  • In vivo&lt;br&gt;  • In vitro&lt;br&gt;  • Informatics</td>
<td>• Pharma proprietary&lt;br&gt;  • Novel assay discovery</td>
<td>• Develop assays&lt;br&gt;  • Support regulatory approval / clearance&lt;br&gt;  • CRO support&lt;br&gt;  • Biobanking</td>
<td>• Provide testing services</td>
<td>• Provide test “pull through”&lt;br&gt;  • Execute testing distribution strategy&lt;br&gt;  • Optimize market access for test</td>
</tr>
</tbody>
</table>
Activity Coordination Timeline

Discovery/Development

- Focus on science, understanding pathways and relationship between test and drug
- Conduct preliminary health economic analyses to outline value add potential of CDx
- Potential IVD partners should have blend of technical, regulatory, and potentially commercial capabilities

Regulatory Approval

- Focus on validation of assay, relying on late phase drug studies to provide bulk of data
- Ensure drug labeling and indication/intended use is well-aligned with needs of both pharma and Dx partner
- Assess relative fit of test methodology with available test platforms/options globally
- Assess quality metrics relative to alternative approaches including LDTs to determine whether additional studies highlighting quality of FDA approved test is needed post-launch

Commercialization

- Answer two questions prior to launch: 1) who will be doing the test (test distribution) and 2) how will they be paid/funded
- Prepare for iterative distribution and market access process and align activity between Rx and IVD partner

Payment from Pharma to Dx in Fee for Service Model

Return on Investment Calculations Determine Need for Pharma Funding

Try for payer payment but be understand that pharma pays model may be necessary

Stage-appropriate activities can be conducted by Dx and Pharma partners to improve chances for success in CDx partnerships and product launch
Moving Forward
**Key Question:** What should innovators be doing to influence the shape of the evolving companion diagnostic market access landscape?

<table>
<thead>
<tr>
<th></th>
<th>Current</th>
<th>Possible Near Future</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available drugs</strong></td>
<td>Limited examples of Rx/Dx combinations</td>
<td>A host of new therapies, each with their own sets of correlated biomarker targets</td>
</tr>
<tr>
<td><strong>Biomarkers</strong></td>
<td>Individual pairing between single genes and single drugs (i.e, HER-2/Herceptin) assessed using limited test methodologies (PCR, IHC)</td>
<td>Multi-biomarker panels which describe use of different drugs, sometimes using next-generation sequencing or other multiplex technology</td>
</tr>
<tr>
<td><strong>Evidence</strong></td>
<td>Evidence of clinical utility of CDx largely developed by Rx during drug trials. Quality of testing is often in question.</td>
<td>Evidence of test value established independently by labs which create simple yet sophisticated service offering. Independent test quality review made mandatory.</td>
</tr>
<tr>
<td><strong>Regulatory</strong></td>
<td>Blend of LDT and regulatory agency approved approaches</td>
<td>Joint regulatory approval of tests and drugs. Still open question of enforcement of use of approved test.</td>
</tr>
<tr>
<td><strong>Market Access</strong></td>
<td>Non-standardized HTA review. Non-specific coding means some tests are paid without review. Pharma pays model widely deployed OUS.</td>
<td>More standardized HTA review. Transitions from pharma pays models to payer pays.</td>
</tr>
<tr>
<td><strong>Quality</strong></td>
<td>Payers lack clarity into what tests are done and why</td>
<td>Test quality becomes increasing metric of potential CDx drug success, particularly in competitive therapeutic areas</td>
</tr>
</tbody>
</table>
Contact

Thomas Goss, Pharm.D.
Senior Vice President
tgoss@bostonhealthcare.com

Charles Mathews
Vice President
cmathews@bostonhealthcare.com

www.bostonhealthcare.com