The Health Industry Forum

October 12, 2006

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President
Genzyme Genetics
Themes for today

- Diagnostics (both genetic and non-genetic) to play larger role in the future
- Evolving toward sustainable business models
- Policy decisions needed today to support innovation and improved outcomes
Diagnostics: Key to unlocking the power of genome data
### U.S. Laboratory Industry, 2001 – 2003

<table>
<thead>
<tr>
<th>Testing segment</th>
<th>Description</th>
<th>Revenues, 2003</th>
<th>Growth, 2001-2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine</td>
<td>Relatively simple and common tests</td>
<td>28.5 $Billions</td>
<td>71 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 % CAGR</td>
</tr>
<tr>
<td>Anatomic pathology</td>
<td>Requires board-certified pathologist. Includes complex cancer diagnostics</td>
<td>5.8 $Billions</td>
<td>14 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7 % CAGR</td>
</tr>
<tr>
<td>Esoteric</td>
<td>Too complex &amp; low volume for most hospitals, physician offices and routine independent labs</td>
<td>3.7 $Billions</td>
<td>9 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15 % CAGR</td>
</tr>
<tr>
<td>Cytology</td>
<td>Predominantly Pap testing</td>
<td>1.3 $Billions</td>
<td>3 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 % CAGR</td>
</tr>
<tr>
<td>Drugs of abuse</td>
<td>Predominantly urine tests required by employers</td>
<td>0.9 $Billions</td>
<td>2 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(5) % CAGR</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>40.2 $Billions</td>
<td>100 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 % CAGR</td>
</tr>
</tbody>
</table>

Genetic testing accounted for ~$1.2 billion in 2003

Source: Lab Industry Strategic Outlook 2005; Frost & Sullivan
Diagnostics:
Genetic testing spans multiple disease areas

U.S. genetic testing market, 2003
100% = $1.2 billion

- 63% Infectious disease
- 25% Prenatal & newborn screening
- 7% Predictive testing
- 6% Pharmacogenetic testing

Source: Frost & Sullivan
Diagnostics:
Valuable information at modest cost

CMS Clinical Laboratory Fees in real terms, 1984 – 2004
Index: 1984 = $1.00

Rx & Dx as components of national healthcare spending, 2000 – 2003
$ billions

Testing is <5% of expenditure, but drives >70% of decisions

Source: Lab Industry Strategic Outlook 2005; AdvaMed
<table>
<thead>
<tr>
<th>Clinical decision being made</th>
<th>Examples Dx-Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Diagnosis &amp; Stratification</strong></td>
<td></td>
</tr>
<tr>
<td>What is the most accurate diagnosis?</td>
<td>• BCR-Abl – Gleevec®</td>
</tr>
<tr>
<td>• How severe is their disease?</td>
<td>• ER/PR – Tamoxifen</td>
</tr>
<tr>
<td>• Are they at risk for disease?</td>
<td>• 5Q deletion - Revlimid®</td>
</tr>
<tr>
<td><strong>2 Drug selection</strong></td>
<td></td>
</tr>
<tr>
<td>What Rx is appropriate for this patient?</td>
<td>• HER2 expression – Herceptin®</td>
</tr>
<tr>
<td>• What drug will they respond to?</td>
<td>• EGFR expression – Erbitux®</td>
</tr>
<tr>
<td>• Will they have an adverse reaction?</td>
<td>• EGFR mutation – Tarceva®, Iressa®</td>
</tr>
<tr>
<td>• BCR-Abl mutation – Gleevec®</td>
<td></td>
</tr>
<tr>
<td><strong>3 Dose selection</strong></td>
<td></td>
</tr>
<tr>
<td>What dose is appropriate for this patient?</td>
<td>• UGT1A1 polymorphism – Camptosar®</td>
</tr>
<tr>
<td>• CYP450 polymorphism – Multiple</td>
<td></td>
</tr>
<tr>
<td><strong>4 Patient monitoring</strong></td>
<td></td>
</tr>
<tr>
<td>Is this patient responding to therapy?</td>
<td>• BCR-Abl RT-PCR – Gleevec®</td>
</tr>
<tr>
<td>• CLL MRD – Campath®</td>
<td></td>
</tr>
</tbody>
</table>
### Need for Change:
**Strong case for personalized medicine**

<table>
<thead>
<tr>
<th>Building the Case for Personalized Medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>US drug spending $250+B per year and growing fast</td>
</tr>
<tr>
<td>50% of drugs not efficacious as prescribed</td>
</tr>
<tr>
<td>US diagnostics spending decreased since 1984</td>
</tr>
<tr>
<td>Adverse drug reactions 6th leading cause of death</td>
</tr>
<tr>
<td>FDA interested in biomarkers and diagnostic algorithms</td>
</tr>
</tbody>
</table>

Nov. 2005 Thomas Weisel Partners report titled Beneficiaries of Personalized Medicine and Market Update
Pharmacogenetics and the concept of individualized medicine published in The Pharmacogenomics Journal (Vol 6, Pg 16-21).
Molecular Diagnostics and Personalized Medicine 2003, Drug & Market Development August 2003*
Successful when it leads to innovation and improves the standard of care.

Fails when we settle for "Trial and Error".

Need for Change: Current system - Cycle of trial and error
Health Care Cost vs. Disease Progression

- Baseline Risk
- Initiating Symptoms
- Earliest Molecular Detection
- Earliest Clinical Detection
- Typical Current Intervention

Source: Model by Ralph Snyderman, Duke University
Increase in antibiotic use

Increase in resistant strains

Limited treatment alternatives
- more antibiotics
- increased mortality

Ineffective empiric therapy
- increased morbidity
- more antibiotics

Increased healthcare resource use

Increased hospitalization
- more antibiotics

Estimated unnecessary cost of resistance = $4B annually

Source: McKinnon, Academy for Infection Management, February 2004
Combining Testing with Treatment

Observation → Test → Action → Predictable Response

A More Direct Answer
### Disease Survival Rates

<table>
<thead>
<tr>
<th>Disease</th>
<th>1 Year Survival</th>
<th>5 Year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer (small cell-non small cell)</td>
<td>36-41%</td>
<td>6-13%</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>60%</td>
<td>39%</td>
</tr>
<tr>
<td>Chronic myeloid leukemia (CML)</td>
<td>93%</td>
<td>80%</td>
</tr>
<tr>
<td>Heart failure (male-female)</td>
<td>76-72%</td>
<td>41-55%</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>78%</td>
<td>38%</td>
</tr>
</tbody>
</table>

1. **2005 USRDS Annual Data Report**
### Need for Change: Payors wasting money on drugs that are not working

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Frequency of Absent or Incomplete Efficacy (%)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Total Market Size</th>
<th>Cost to the Health Care System of Ineffective Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-converting enzyme (ACE) inhibitors</td>
<td>10-30</td>
<td>$3.9B&lt;sup&gt;2&lt;/sup&gt; (2003)</td>
<td>$390M-$1.2B</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>15-25</td>
<td>$2.3B&lt;sup&gt;2&lt;/sup&gt; (2003)</td>
<td>$345M-575M</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>20-50</td>
<td>$11.7B&lt;sup&gt;3&lt;/sup&gt; (2003)</td>
<td>$2.3B-$5.8B</td>
</tr>
<tr>
<td>Statins</td>
<td>30-70</td>
<td>$12.6B&lt;sup&gt;4&lt;/sup&gt; (2004)</td>
<td>$3.8B-$8.8B</td>
</tr>
<tr>
<td>Beta agonists</td>
<td>40-70</td>
<td>$1.4B&lt;sup&gt;5&lt;/sup&gt; (2004)</td>
<td>$560M-$1B</td>
</tr>
</tbody>
</table>

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<sup>1</sup> Ross JS & Ginsburg GS, Am J Clin Pathol 2003;119:26-36

<sup>2</sup> Datamonitor, August 1, 2005

<sup>3</sup> Global Industry Analysts, October 10, 2004

<sup>4</sup> Carnegie Research

<sup>5</sup> Specialty Pharmaceutical Pulse, SG Cowen, October 2005
Past – Macro Level Diagnostic Testing
- Disease defined by location and size
  - Tests differentiated disease from non-disease

Today – Molecular Diagnostic and Prognostic Testing
- Disease defined by individual biology/DNA
  - Tests to subcategorize disease and:
    - predict outcomes of specific Rx
    - screen for adverse events
    - monitor disease

Tomorrow – Predictive Testing
- Predictive testing for development of common diseases
  - Disruptive technologies

Why Now: Testing technology has improved
Why Now:
Disease better understood, segmented, & personalized

60 Years Ago

Leukemia or Lymphoma

Chronic Leukemia
Acute Leukemia
Preleukemia

“Disease of the Blood”

Indolent Lymphoma
Aggressive Lymphoma

50 Years Ago

~38 Leukemia types identified:
- Acute myeloid leukemia (~12 types)
- Acute lymphoblastic leukemia (2 types)
- Acute promyelocytic leukemia (2 types)
- Acute monocytic leukemia (2 types)
- Acute erythroid leukemia (2 types)
- Acute megakaryoblastic leukemia
- Acute myelomonocytic leukemia (2 types)
- Chronic myeloid leukemia
- Chronic myeloproliferative disorders (5 types)
- Myelodysplastic syndromes (6 types)
- Mixed myeloproliferative/myelodysplastic syndromes (3 types)

5 year Survival
~ 0%

70 Years Ago

~51 Lymphomas identified:
- Mature B-cell lymphomas (~14 types)
- Mature T-cell lymphomas (15 types)
- Plasma cell neoplasm (3 types)
- Immature (precursor) lymphomas (2 types)
- Hodgkin's lymphoma (5 types)
- Immunodeficiency associated lymphomas (~5 types)
- Other hematolymphoid neoplasms (~7 types)

Today

~38 Leukemia types identified:
- Acute myeloid leukemia (~12 types)
- Acute lymphoblastic leukemia (2 types)
- Acute promyelocytic leukemia (2 types)
- Acute monocytic leukemia (2 types)
- Acute erythroid leukemia (2 types)
- Acute megakaryoblastic leukemia
- Acute myelomonocytic leukemia (2 types)
- Chronic myeloid leukemia
- Chronic myeloproliferative disorders (5 types)
- Myelodysplastic syndromes (6 types)
- Mixed myeloproliferative/myelodysplastic syndromes (3 types)

5 year Survival
~ 70%

## Why Now: Targeted Rx will drive growth of companion Dx

Projected impact of targeted therapies on genetic testing*

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Stage of Rx development</strong></td>
<td>Phase III</td>
<td>Phase I</td>
</tr>
<tr>
<td><strong>Percent Rx with predictive biomarker</strong></td>
<td>~10%</td>
<td>20-30%</td>
</tr>
<tr>
<td><strong>Time to market</strong></td>
<td>Zero to 4 years</td>
<td>5 to 9 years</td>
</tr>
<tr>
<td><strong>Projected joint Rx/Dx launches</strong></td>
<td>2 to 4 per year</td>
<td>6 to 9 per year</td>
</tr>
</tbody>
</table>

* Assumes ~30 NMEs approved per year

Source: Royal Society’s *Personalised Medicines: Hopes and Realities*; Genzyme analysis
Business models and challenges

- Diagnostic and therapeutic companies both drive innovation
- Active area of venture investment and partnership
- Significant challenges to sustainable business model
**Business Model**

*Dx companies are the primary drivers of innovation*

**Business model**
- Discover or license markers relevant to multiple diseases and therapies
- Invest in clinical validation
- Commercialize assay
- Recoup investment from selling test services or kits

**Challenges**
- Significant, high-risk investment in clinical validation
- Adoption is uneven
- Reimbursement based on activity rather than value of test
- Uncertain regulatory environment

**Primary driver of innovation**

**Significant, high-risk investments difficult to recover**
Venture capital investment in Dx companies, 1998 – 2006
$ millions per quarter

Source: NATURE BIOTECHNOLOGY VOLUME 24 NUMBER 8 AUGUST 2006
Business Model

Rx companies are less likely to develop innovative Dx

Business model

- Discover markers relevant to targeted therapeutics
- Clinically validate marker during development of therapeutic
- License IP for test to diagnostic firm
- Rx profits fund development of Dx

Challenges

- Fear of limiting potential market for therapeutics under development
- Lack skills required for test development
- Face uncertain regulatory environment

Gaining importance

Potentially reluctant to develop genetic tests
Rx and Dx companies are beginning to collaborate

Overview of deals between Rx and Dx companies, 1998 – 2006

New collaborations

<table>
<thead>
<tr>
<th>Year</th>
<th>1998</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
<th>2002</th>
<th>2003</th>
<th>2004</th>
<th>2005</th>
<th>2006 YTD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td>3</td>
</tr>
</tbody>
</table>

Therapeutic areas

- Oncology: 41%
- Neurology: 10%
- CV: 7%
- Metabolic: 7%
- All other: 47%

Even more collaboration is needed in the future

Source: Windhover; Genzyme analysis, as of June 2006
Business Model – Challenge #1
New test development is complex & expensive

Sample Collection
Marker Discovery
Initial Validation Data
Test Development
Research Studies
Lab Developed Test
Clinical Studies
Test Kit Developed
Market Expands

Up to $100M per new test
Physicians & patients
• Poor understanding of how to use Dx info
• Watch and wait approach still acceptable
• Lack of focus for reducing medical costs
• Concerns over misuse of genetic information

Payors
• Little current impact of Rx/Dx on largest areas of drug spend
• Concern that information from Dx will not influence prescribing behavior
• Not enough pharmacoeconomic data to show benefit
• Fear that convergence will drive up Rx prices
Reimbursement based on CPT-codes

<table>
<thead>
<tr>
<th>CPT code</th>
<th>Description</th>
<th>Fee</th>
</tr>
</thead>
<tbody>
<tr>
<td>88368</td>
<td>Morphometric analysis, in situ hybridization (probe #1)</td>
<td>$157</td>
</tr>
<tr>
<td>88368</td>
<td>Morphometric analysis, in situ hybridization (probe #2)</td>
<td>$157</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td><strong>$314</strong></td>
</tr>
</tbody>
</table>

Value based on health outcomes and savings

<table>
<thead>
<tr>
<th>Cost of Herceptin therapy per patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without HER2 test</td>
</tr>
<tr>
<td>With HER2 test</td>
</tr>
</tbody>
</table>

HER2 test delivers healthcare savings that are ~75x its cost

* As measured by FISH and reimbursed by CMS
Business Model – Challenge #4
Current regulatory uncertainty is high

- **FDA**
  - ASR Draft Guidance
  - IVD MIA Draft Guidance

- **CLIA**
  - Genetic Testing Specialty
    - CMS dropped initiative but patient groups are calling for it

- **Legislators**
  - Interest level increasing
Policy Needed to support innovation

- Education, incentives, and system to ensure existing and new diagnostics lead to improved outcomes
- Regulations that support rather than stifle innovation
- Reimbursement based on value rather than activity
### Policy Needed

**System that ensures Dx lead to improved outcomes**

#### Today

- Physicians **don’t understand** how to incorporate information from tests into clinical practice
- Physicians have **little incentive** to steer treatment based on information from tests
- Payors are **unable to verify** that information from tests is being incorporated into treatment

#### Tomorrow

- Unique needs of payors and physicians to be addressed
  - **Pipeline** should be visible for education and preparation
  - **Cost/ Benefit** studies and population outcomes should be encouraged
  - **Utilization management** requirements to be addressed
Policy Needed
Regulations that support rather than stifle innovation

Today

- Yes, there is a focus on quality
  - Oversight by CMS, CLIA & FDA
  - CAP proficiency testing & review
  - State reviews
  - HHS Advisory Committees (SACGHS)

- Significant potential increase in regulation
  - FDA – ASRs & IVD MIAs
  - CLIA – Genetic Testing Specialty

Tomorrow

- Continued focus on quality for all tests

- Resolution of regulatory uncertainty quickly

- Regulations that strike appropriate balances – allow innovation and rapid integration of new scientific data
Today

- Medicare basis for diagnostic codes reimbursement rooted in 1984
- No ability to differentiate testing based upon its complexity or impact
- Costs and complexity not considered when setting reimbursement levels

Tomorrow

- Medicare Director Dr. Mark McClellan said, "Instead of having 10 to 20 percent success rates over a broad population, we want to get to 80 to 90 percent who will benefit, and with fewer side effects"
  - New York Times, November 5, 2004
- National MCO “supports reimbursement for less than ¼ of currently available genetic tests, but believes molecular testing will ultimately become a standard of care for preventative diagnoses and appropriate pharmaceutical utilization”
  - Banc of America Analyst Report, January 2005
- MCOs will not pay for Herceptin® unless a patient has a positive HER2- test
● Embrace Diagnostics For Improved Outcomes
  – Patients
  – Payors
  – System Economics

● Need to Educate ourselves and our constituencies
  – More outcome and pharmacoeconomic data needed

● Policy Needed
  – System that ensures that diagnostics lead to improved outcomes
  – Regulations that support rather than stifle innovation
  – Reimbursement based on value