Impact of Personalized Medicine MDx tests on Oncology Therapeutics

By Scientia Advisors
Acronyms

• Dx = *In vitro* Diagnostics
• MDx = Molecular Diagnostics
• Rx = Therapeutics
• SNP = Single Nucleotide Polymorphism
• Thx = Theranostics
• WW = Worldwide
What is Personalized Medicine?

The Right Therapy for the Right Patient, at the Right Time

Best responders to therapy identified using Personalized Medicine Tests and then given the Targeted Rx at the right time to maximize efficacy and minimize adverse reaction.
Index

• Overview of Oncology Rx

• Overview of personalized medicine tests
  » Early Detection
  » Prognosis
  » Theranostics (Thx)

• Conclusion
Fewer drug approvals & impending patent expirations plague Pharma’s prognosis.
Combination with personalized medicine tests could be one way to reinvigorate the industry.

Key Takeaways

• Pharma has not had much luck with new products
  » R&D spending is increasing as number of molecules approved are decreasing
  » Fewer molecules are submitted to the FDA for approval every year
  » An increasing number of molecules are going off patent

• “Personalized Medicine already is impacting the basic information we have about new drugs and the patients who take them. This will steadily increase, becoming the background information for every new drug.”
  – Dr. Brian Spear, Abbott

• “Approaches like personalized medicine tests that get drugs to the right patient, while predicting toxicity and ensuring patient compliance is going to be a tremendous help to the industry.”
  – Dr. Peter Corr, Pfizer
Oncology Rx is one of the most attractive areas in therapeutics…

- Total Rx sales in 2006 was ~$560B growing at 15+% CAGR
- Cardiology Rx sales are predicted to fall ‘06-’12 with a CAGR of -2%, due to the introduction of generic versions of existing therapeutics, and newer therapies needing a few more years in the development phase
- Metabolic Disease Rx is the fastest growing sector with a high CAGR in both Diabetes and Obesity Rx sales (11% and 22% respectively)
- Infectious disease Rx increases at a moderate rate due to newer quinolones and antivirals
- Oncology Rx is one of the faster growing sectors in Rx sales (9% CAGR ‘06-’12); driven by targeted Rx

Key Takeaways

Source: Scientia analysis, Therapeutic categories outlook SG Cowen Securities March 2007, Nature drug discovery review
Targeted oncology Rx has a higher CAGR as compared to traditional oncology Rx

<table>
<thead>
<tr>
<th>Year</th>
<th>Traditional Rx</th>
<th>Targeted Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>$55B</td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>$86B</td>
<td></td>
</tr>
</tbody>
</table>

Source: Scientia analysis, 2007 Cowen report on therapeutics

Key Takeaways

- Targeted oncology Rx have a higher growth potential than traditional oncology Rx.
- Thousands of cancer patients are already benefiting from several targeted Rx such as Avastin and Gleevec, personalized medicine tests will enhance the safety and efficacy of these targeted Rx.
- Targeted oncology Rx are most likely to be influenced by personalized medicine tests.
  - Example: BCR/ABL test enhances the efficacy of Gleevec.
  - Example: UGT1A1 test improves the safety of Irinotecan.
- High growth potential of targeted Rx will in turn drive the growth of personalized medicine tests.
- In addition to oncology, infectious disease Rx such as HIV Rx have also readily adopted personalized medicine tests (e.g. HIV viral load, resistance tests).
Pharma oncology pipeline: Increased prevalence of targeted therapeutics which will in turn drive the growth of personalized medicine tests.

Source: Scientia Analysis; SG Cowen & Co Report; Company Websites; ClinicalTrials.gov
Plagued by low efficacy & safety; Oncology Rx will be one of the chief adopters of personalized medicine tests

Oncology Rx problem: low efficacy & safety

Oncology Rx have low efficacy

Current Oncology Rx unmet needs

- 50% of oncology Rx are not as efficacious for the entire population as prescribed
- Oncology Rx has the lowest efficacy compared to other Rx
  » Historically, oncology compounds tend to have a significantly lower success rate in clinical development than compounds in other areas, such as cardiovascular disease

Solution: Personalized medicine tests

- Fewer rates of adverse reactions
- Better response to Rx, with correct dosages
- Rx provided only when necessary; leading to reduced healthcare costs
- Faster approval of drugs, with smaller test population, in shorter period
- Faster rate of R&D with improved drug discovery targets
- Revival of drugs that failed in the past

Oncology Rx have low safety profile

“Cancer Rx, Fentoral is tied to several deaths”
“London Cancer Rx Trial Goes Horribly Wrong”
“Smart cancer Rx Sunitinib may have toxic effects on heart”
“FDA severely limits access to cancer drug Iressa”

Source: Scientia analysis, Trends in Molecular Medicine, Journal of clinical oncology, CDC
Index

• Overview of Oncology Rx

• Overview of personalized medicine tests
  » Early Detection
  » Prognosis
  » Theranostics (Thx)

• Conclusion
MDx personalized medicine tests

- Definition:

  MDx personalized medicine tests include early detection tests that enable early and accurate detection of disease, prognosis tests that provide disease recurrence free survival information, and theranostics tests that enable increased treatment efficacy and reduced adverse events.
Overall cancer care cycle

*Most solid tumors\(^\wedge\) follow a fairly standard patient care cycle*

- **Suspicious mass** identified by imaging
- **Biopsy of suspicious mass**
- **Positive Diagnosis & Staging**
- **Surgery**
- **Node -**
  - **Radiation**
  - **Therapy (Chemo or Targeted)**
- **Node +**
  - **Further surgery**
  - **Second line of treatment**
  - **First line of treatment**
- **Histo\(^*\)**

\(^*\) Histology

\(^\wedge\) excludes Hematopoietic tumors such as leukemia and lymphoma

Source: Scientia Analysis
MDx personalized medicine tests have a large impact on oncology care cycle and greatly influence Rx decisions.

**MDx Screening**: large scale screening of general population periodically

**Diagnosis & Staging**

**Surgery & axillary lymph node analysis**

**2nd line of treatment**

**3rd line of treatment**

- **Imaging**
  - Biopsy of suspicious mass
  - Positive Diagnosis & Staging
    - Surgery
      - Histo*
        - Node -
          - Radiation
        - Node +
          - Further surgery
    - Therapy (Chemo or Targeted)

**MDx Predisposition**
- Test that screens for cases linked to familial cancer cases (e.g. BRCA)

**MDx Detection**
- Test that predicts the aggressiveness of cancer (e.g. Genomic Health’s Oncotype Dx)

**MDx Prognosis**
- Test that indicates patient’s response to prescribed therapy (e.g. HER2/Neu test for Herceptin)

**MDx Theranostics**

**Personalized medicine tests**

* Histology

**Screening**: large scale screening of general population periodically

**Source**: Scientia Analysis

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E.g. The breast cancer patient care continuum has been enhanced by MDx personalized medicine tests

- MDx based early detection will dramatically increase the use of Rx and bundling with early detection tests will give pharma an opportunity to allow Rx to be introduced earlier in the cancer care paradigm
- The use of MDx in prognosis will reduce unnecessary therapies; thus reducing healthcare costs
- The use of MDx theranostics will lead to better drugs that can in turn command premium price
- The breast cancer care cycle of MDx personalized medicine is almost complete; Scientia believes that lung and colorectal cancer will follow suit

Source: Scientia Analysis

* Immunohistochemistry
Index

• Overview of Oncology Rx

• Overview of personalized medicine tests
  » Early Detection
    » Prognosis
      » Theranostics (Thx)

• Conclusion
Early detection
Improved methods of detection and better understanding of disease leading to higher oncology Rx sales

• Detection of cancer is currently done using Pathology
  » Based on an optical method of detection
  » Only detects one cancer cell in 200 normal cells
  » Can lead to mis-classification of tumors

• MDx personalized medicine test will improve the detection/staging of Cancer
  » More sensitive than optical methods of detection, can detect one cancer cell in 10 million normal cells; leading to earlier detection of cancer
  » More accurate classification of tumors
  » Early cancer detection will not only lead to increased patient population implying higher oncology Rx sales, but will also give pharmaceutical companies access to a wider range of patients at an earlier point of the cancer care paradigm

Source: Scientia Analysis
Breast cancer detection

*Today’s detection methods (Histology) may miss micro metastatic levels of cancer leading to poor prediction of disease outcome and treatment.*

STAGE 0 (LCIS /DCIS)  
STAGE I  
STAGE II  
STAGE III (III A/B)  
STAGE IV

Unmet Needs

- Current methodologies may misclassify tumor as benign/localized based on histologic appearance (at least one cancer cell must be present in every 200 normal cells for detection) when the tumor could have micro metastatic levels of cancer cells
- Unfortunately 30% of patients considered to have benign/localized cancer end up developing metastatic cancer (due to misclassification)

- **Promise of MDx is very sensitive detection (ability to detect one cancer cell in $10^7$ normal cells) and accurate quantification of clinically relevant micro metastatic cells**
- **No clinically validated biomarkers available for detection yet**

Index

- Overview of Oncology Rx
- Overview of personalized medicine tests
  - Early Detection
  - Prognosis
  - Theranostics (Thx)
- Conclusion
Prognosis

A reduction in unnecessary therapies; thus reducing healthcare costs

- Predicts aggressiveness of cancer, which was not possible by traditional pathology methods, thus addresses an unmet need in oncology today
- Identifies patients with high risk of recurrence who may benefit from adjuvant chemotherapy (improved recurrence-free and overall survival)
- Applies only to early stage patients with inherently good chances of survival (who may be cured with local/regional therapy alone)
- Will reduce unnecessary chemotherapies, leading to fewer adverse side effects
- Are not theranostic tests, but influence key therapy decisions

Source: Scientia Analysis
Prognosis^ tests are high value* diagnostics that reduce healthcare expenditure
e.g. Oncotype Dx from Genomic Health

Key Features

- Predicts likelihood of recurrence and benefit of chemotherapy for early stage (N- ER+) breast cancer
- Test based on algorithm and proprietary 21-gene panel using quantitative RT-PCR
- Genomic Health Financials:
  - ~$25M Revenue 2006, $120M expected by 2008
  - $3,460 price per test

Drivers of Success

- 7 studies with over 2600 patients, published in peer-reviewed journals and presented at national meetings validate the correlation between test results and the need for chemotherapy
- Studies have been conducted with Kaiser Permanente to show economic benefit
- Sales modeled around sales for big pharmaceutical companies, with clinical validation to help secure reimbursement
- Increasing adoption and reimbursement
  - Over 27,000 tests have been ordered by over 5,500 Physicians since 2004
  - Approximately 80% of the population is covered for the test

Source: Scientia Analysis; Genomic Health company financials

^ Other breast cancer prognosis tests provided by Agendia, ABT-CRA, Ipsogen, Exagen, Aviara; with Veridex (JnJ) and Roche entering the market in the future

* Provide critical information that helps physicians make clinically relevant decisions; as a result command premium prices

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Index

• Overview of Oncology Rx

• Overview of personalized medicine tests
  » Early Detection
  » Prognosis
  » Theranostics (Thx)

• Conclusion
Theranostics (Thx) are therapy specific diagnostics that can be used to select patients for treatments that are particularly likely to benefit them and to minimize side-effects.

Thx can also provide an early and objective indication of treatment efficacy in individual patients, so that (if necessary) the treatment can be altered with minimum delay.
The two types of theranostic tests

*Both are essential for improved outcomes*

<table>
<thead>
<tr>
<th>Theranostic Tests</th>
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<tbody>
<tr>
<td><strong>Adverse Drug Reaction Tests</strong></td>
</tr>
<tr>
<td>• These tests identify people likely to have adverse drug reactions to particular drugs, reducing the number of people reporting side effects</td>
</tr>
<tr>
<td>• Adverse Drug Reactions is the 6th leading cause of death</td>
</tr>
<tr>
<td>• These are one-time tests that cost between $300 and $800.</td>
</tr>
<tr>
<td>• E.g. CYP 450 test, UGT1A1 tests</td>
</tr>
</tbody>
</table>

| **Drug Responder Category Tests** |
| • These tests distinguish between responders and non-responders to a specific drug or set of drugs |
| • When combined with the adverse reaction tests, they can provide a comprehensive response profile, which can be used for treatment decisions |
| • E.g. Her2/Neu test, BCR/ABL test |

Source: Scientia Analysis

* Treatments for most diseases follow this method, with the exception of some oncology treatments
Theranostics provides clear cost-to-benefit ratios and quality-of-life payoffs for all stakeholders of healthcare.

- Guides Rx decisions
- Higher efficacy of treatment, with fewer adverse side effects

- Clinical utility changes medical practice increasing payers' willingness to pay
- When paired with Dx test results, more efficient payment decision

- Increase in Dx volume and revenue
- Potential for higher pricing due to higher efficacy
- Enables focused trials – smaller group for shorter periods with better results

- Faster approval process due to focused trials

Source: Scientia Analysis
Therapies accompanied by Thx command a premium price in the market

Thx driven Rx command premium pricing over traditional Rx…

• **High efficacy**: Herceptin showed that it reduced the risk of recurrence by as much as 52%.

• **Reduced adverse events by excluding non-responders**: Adverse events cause >2 million hospitalizations today with a cost of $100 billion to the healthcare system.

Target population in US:
- **Herceptin**: $24K
  - 13K*
- **Taxol**: $15K
  - Not driven by Thx

Source: Scientia Analysis; 2003 Commerzebank report on Roche “Tamoxifen Breast Cancer Prevention Has Small Mortality Effect”; Drugs.com; Roche corporate presentation; Genentech
Index

• Overview of Oncology Rx

• Overview of personalized medicine tests
  » Early Detection
  » Prognosis
  » Theranostics (Thx)

• Conclusion
The overall MDx personalized medicine landscape
Numerous players emerging with novel biomarkers
FDA and payors are pushing for integration of Rx with personalized medicine tests

- On Aug. 22, 2006, the FDA approved UGT1A1 test, for use in identifying patients that may be at increased risk of adverse reactions to irinotecan HCl.
- On Dec. 24, 2004, the FDA approved AmpliChip CYP450 test, the first FDA approved PGx test.
- On Feb. 6, 2007, the FDA approved Agendia’s MammaPrint Dx for breast cancer recurrence, the first IVDMIA test.
- On Sept. 18, 2007, the FDA approved the first genetic test for Warfarin sensitivity, “Verigene.”
- On Dec. 12, 2007, the FDA relabeled Carbamazepine to include recommendation of genetic test for patients with Asian ancestry.
- Payors reimburse Genomic Health’s OncoType Dx assay for breast cancer recurrence.
Case studies on pharma’s perception of integrated personalized medicine tests

*Roche appears to be the only Pharma with integrated Rx-Dx offering*

<table>
<thead>
<tr>
<th>Rx-Dx Collaborations</th>
<th>Integrated Rx and Dx Divisions</th>
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<tbody>
<tr>
<td><strong>Genentech</strong></td>
<td><strong>Roche</strong></td>
</tr>
<tr>
<td>Collaboration with Abbott/Vysis and DakoCytomation for Her2/Neu testing for Herceptin (first FDA approved Thx)</td>
<td>Integrated Rx/Dx: close cooperation between Rx and Dx to validate novel Oncology markers for personalized medicine tests</td>
</tr>
<tr>
<td><strong>Novartis</strong></td>
<td><strong>Abbott</strong></td>
</tr>
<tr>
<td>Collaboration with Genzyme genetics BCR/ABL testing for chronic myeloid leukemia (CML) Rx</td>
<td>Partial Control with limited Rx/Dx integration (Abbott Dx &amp; Vysis)</td>
</tr>
<tr>
<td><strong>Pfizer</strong></td>
<td><strong>Johnson &amp; Johnson</strong></td>
</tr>
<tr>
<td>Collaboration with Monogram Biosciences for HIV drugs</td>
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<tr>
<td>Monogram’s Trofile Assay is used to test CCR5 which is instrumental in the decision to administer Pfizer’s recently approved Maravirocs</td>
<td>Partial Control with limited Rx/Dx integration (Veridex and Ortho Clinical Diagnostics)</td>
</tr>
<tr>
<td><strong>Lilly</strong></td>
<td></td>
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<tr>
<td>Collaborated with University of North Carolina at Chapel Hill for breast cancer studies on Gemzar. Lilly used a breast cancer prognosis test that predicts need for Gemzar in early stage breast cancer patients</td>
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</table>

Source: Scientia Analysis; Company Corporate Presentations; Press Releases
Beyond Oncology: Some emerging trends in Infectious and personalized medicine

By providing early diagnosis, MDx is enabling the delivery of right therapy at the right time

Sepsis Causing Pathogens Example:

- Broad Antibiotic therapy: $50-200/agent/day
- MDx
- Day 1: Specific therapy starts immediately
- Patient quarantined immediately preventing the spread of infection
- Fewer ICU stays
- Total cost/patient: $50-100K
- % mortality: 5%
- Day 2: Specific therapy given on Day 3
- Infection spread in ICU and general ward
- Extended ICU stays
- Total cost/patient: $180K
- % mortality: 13%
- Day 3: Culture

Key Take-Aways

- Historically, in critical care infectious diseases such as sepsis, ICU\(^*\) physicians have to wait 2-3 days to get accurate information about specific pathogens in patient samples. With the introduction of MDx tests, results would be available in about 6 hours, thus ICU\(^*\) stays will be shortened; reducing costs and associated risks for the patients
- Hospital acquired infections such as MRSA is a growing healthcare concern; Rx for multi-drug resistant, hospital acquired infection is a major opportunity for pharmaceutical companies
  - MDx is facilitating this opportunity by enabling the early detection of these pathogens
  - Pfizer’s Zyvox is the only IV/Oral MRSA Agent; however Zyvox is plagued by safety concerns associated with intravascular catheter infections
- MDx provides early diagnosis; thus enabling the delivery of right therapy at the right time

*Intensive Care Unit

"My top of mind issue is early and accurate diagnosis...I only get information from Pharma on therapy but I wish someone could educate me about early diagnosis using MDx to enable delivery of right therapy at the right time" - ICU physician, Methodist hospital

Source: Scientia analysis and interviews with hospitals
Key conclusions

• Today, Oncology and certain Infectious diseases such as HIV Rx seem to be the first to adopt personalized medicine tests
  » Personalized medicine tests are likely to become prominent in other therapeutic areas including cardiology, CNS, respiratory, and psychiatric disorders over the next decade

• MDx personalized medicine tests are influencing Rx sales by:
  » Improving the early detection of cancer, leading to higher Rx sales
  » Providing a method to predict prognosis of early stage oncology patients, hence helping reduce unnecessary Rx and adverse side effects
  » Improving efficacy and reducing side effects of targeted therapies

• Changing points of view
  » Traditionally pharma companies have not looked diagnostic tests as key influencers of Rx sales
  » While Pharma Companies have taken an initial step toward Personalized Medicine, they need to take a strategic look at how their markets will be impacted by it. Our thesis is that Pharma Companies will be increasingly pressured to control a broader portion of the PharmacoGenomics value chain and to create more efficient processes and discover and validate novel biomarkers
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- market strategy and positioning
- valuation
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