The Molecular Diagnostic Market and development of personalized molecular tests

Dr. Iris Simon
Sr. Director Research & Development, Agendia NV, Amsterdam NL and Irvine CA
• Agenda - Who are we
• Molecular Diagnostic Market
  • Opportunities and Challenges
• Development of Molecular Diagnostics (ColoPrint)
  • Development
  • Validation
  • Product Development
  • Regulatory
  • Marketing
• What’s next
Agendia, the Company

- Molecular cancer diagnostic company
- Four products on the market
- Development and commercialization of diagnostic tests using tumor gene expression profiling
- MammaPrint is first FDA-cleared prognostic test
- 40,000 specimen lab capacity
- CLIA-certified lab in US and NL
- ~120 employees
Nothing can be done without strategic alliances.
Why Molecular Diagnostics
Terminology

- **IVD** = In Vitro Diagnostic
- **Molecular Diagnostic (MDx)**
  - clinical application of molecular technologies to diagnose and monitor human diseases based on DNA, RNA, proteins
  - More complex, more information
  - Fastest growing segment of IVD market
- **IVDMIA**: In Vitro Diagnostic Multivariate Index Assay
1. Molecular Diagnostics (MDx) are one of the fastest growing markets

**Revenue Forecasts**

- Revenues from sales of molecular diagnostics are forecasted from 2009 to 2014. The revenues for the Global Molecular Diagnostics Market were $3,708.8 million in 2009 and are expected to reach $6,209.8 million by 2014 with a CAGR of 10.9 percent.
- Revenues continue to be driven by strong growth in HPV, Genomics and bacteriology testing.

**Molecular Diagnostics Market: Revenue Forecasts (World), 2007-2014**

<table>
<thead>
<tr>
<th>Year</th>
<th>Revenues ($Million)</th>
<th>Revenue Growth Rate (%)</th>
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<tbody>
<tr>
<td>2007</td>
<td>3,032.2</td>
<td>--</td>
</tr>
<tr>
<td>2008</td>
<td>3,387.0</td>
<td>11.7</td>
</tr>
<tr>
<td>2009</td>
<td>3,708.8</td>
<td>9.5</td>
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<tr>
<td>2010</td>
<td>4,079.7</td>
<td>9.5</td>
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<tr>
<td>2011</td>
<td>4,508.0</td>
<td>10.5</td>
</tr>
<tr>
<td>2012</td>
<td>5,003.9</td>
<td>11.0</td>
</tr>
<tr>
<td>2013</td>
<td>5,569.3</td>
<td>11.3</td>
</tr>
<tr>
<td>2014</td>
<td>6,209.8</td>
<td>11.5</td>
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CAGR (2009-2014): 10.9%

*Note: All figures are rounded; the base year is 2009. Source: Frost & Sullivan*
2. Paradigm shift in treatment creates high growth MDx opportunity

- Benefit from drugs is less than 25% in most indications
- New targeted drugs are only beneficial in small numbers of patients with specific characteristics
- Consequently, treatment is rapidly shifting from a “one size fits all” approach to a more personalized approach
- Requires the development of appropriate molecular diagnostics (MDx) tests that help physicians to decide who and how to treat
3. Health Care Cost must be reduced

Valuable Service
- Small component of total cost influences large percentage of clinical decisions
- Screening, early detection, and monitoring reduce downstream costs
- Companion diagnostics improve drug efficacy and reduce adverse drug effects

2008 Projected US Health care Spend $2.4 Trillion
- 2-3% of spend influences 70-80% of physician decisions

Source: Centers for Medicare & Medicaid Services, Office of the Actuary, and company estimates.
Molecular diagnostics bring new challenges

- **Traditional diagnostics**
  - Methods developed over decades and centuries
  - Often used at local hospital
  - Single marker
  - cheap
  - Simple and understandable (patients, doctors, health care)
  - Established by tradition

- **Molecular Diagnostics**
  - Methods developed in less than 10 years
  - Often requires centralized lab
  - Multiple markers
  - Complex and complicated (method and application)
  - Requires new regulations and high quality control
  - Usefulness has to be demonstrated by clinical studies
Major challenges

- Society is willing to pay €50,000 for treatment of patients
  - but not €5000 for a MDx that would help identifying those patients who will benefit from it

- Many MDx have big influence on patient’s life
  - but there are no validation standards and no stringent regulatory requirements for MDx

- Validation, clinical studies, safety data and education are required - similar to efforts required for new drugs
  - but this can not be provided without big costs for companies and support from community
  - and health insurances need to establish (better) rules how to reimburse MDx
The making of a new molecular diagnostic test
Clinical Need Business Plan

Research: Profile Development

Research: Profile Validation

Product Development & logistic

Quality Control Regulatory Approval

Launch & Marketing Education

Prospective Implementation Study

Sales
Research: Profile Development

Research: Profile Validation
1. Whole genome microarray profiling

2. Identification of genes correlated with CRC recurrence

3. Train a classification algorithm to predict status of new samples

4. Apply signatures to independent cohorts

5. Evaluate performance (+/- clinical variables)

6. Combine results with results from other technologies
The Idea: Genomic Profile

- Expression profiling provides a global “map” of the tumor
  - The pattern of gene expression is different in patients with different outcome (e.g. aggressive vs. indolent)

- The difference in expression allows the identification of “signature” genes

- The correlation of an “unknown” tumor sample with the signature genes is called genomic profiling
<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
<th>Institutions/Details</th>
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<tbody>
<tr>
<td><strong>Whole Genome Array</strong></td>
<td></td>
<td></td>
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<tr>
<td>Training Set (stage I-IV) (n=188)</td>
<td></td>
<td>Netherlands Cancer Institute, Leiden Medical Center, Slotervaart</td>
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<tr>
<td>Selection of Final 18-Gene Set &amp; Algorithm</td>
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<td></td>
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<tr>
<td><strong>Standardization of Analytical Methods</strong></td>
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<td></td>
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<tr>
<td>In-silico Validation Study (stage I-III)</td>
<td></td>
<td>public datasets (n=322)</td>
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<tr>
<td>Clinical Validation Study I (stage I-III)</td>
<td></td>
<td>Institute Catala d’Oncologia Barcelona (n=206)</td>
</tr>
<tr>
<td>Clinical Validation Study II (stage II-III)</td>
<td></td>
<td>Munich Hospital Rechts der Isar (n=233)</td>
</tr>
<tr>
<td>Clinical Validation Study III (stage II-III)</td>
<td></td>
<td>MD Anderson, Vall d’Hebron, others - ongoing</td>
</tr>
<tr>
<td>PARSC Prospective Study (stage II + III)</td>
<td></td>
<td>ongoing US, Asian, and European Center (N ~600 stage II)</td>
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Product Development & logistic

Quality Control
Regulatory Approval
The diagnostic microarray

- 8-pack custom array produced by Agilent Technologies
- Each subarrays has 15,000 genes
- Per subarray the genes of the prognostic profiles are printed 5-times
- Additionally, each subarray includes hundreds of normalization genes and data points for hybridization and quality control
Technical Validation of ColoPrint as a reproducible and standardized test

Repeated runs of three samples over 20 days performed by different operators = less than 5% variation

ColoPrint uses the same technology, methods and QC as FDA-cleared MammaPrint assay

Validation experiments and criteria are set up and performed according to FDA and NCCLS guidelines
Regulatory Requirements: Lab

MammaPrint is the first multi-variate molecular diagnostic test cleared by FDA

ISO 17025 accredited and CE marked for European market

CLIA registered

College of American Pathologists (CAP) Accredited
Regulatory Requirements: Device (EU)

- Laboratory Testing: not regulated in EU
  - EMEA approval: Not applicable - EMEA only regulates drugs

- Materials used: regulated
  - CE Marking: Agendia is in control of design, sub-contracts Agilent (U.S.) for production, imports micro-array chip into EU, is the manufacturer according to EU law, and is responsible for registration.
Regulatory Requirements: Device (US)

- FDA approval (product specific safety & effectiveness)
- CLIA accredited or certified (Laboratory General Quality program)
- QSR compliance (GLP) (product specific procedural quality)

- Prognostic Profile (who to treat) was classified as Class II device

- Predictive Profile (how to treat) will most likely be classified as Class III device (most stringent regulatory category for devices)
PARSC Study: *Prospective Assessment of Risk Stratification by ColoPrint*

**Principal Investigators:**
Europe: Dr. R. Salazar (ICO Barcelona)
US: Dr. J. Marshall (Georgetown)
PARSC Study: Prospective Assessment of Risk Stratification by ColoPrint

- **Objective:**
  - validate the performance of ColoPrint in estimating the 3-year relapse rate in patients with stage II colon cancer.
  - compare the risk assessment in stage II patients using ColoPrint profile vs a clinical risk assessment based on Investigator’s assessment of risk and ASCO high-risk recommendations.
  - investigate therapy as a potential confounding factor for ColoPrint results
  - assess the performance of ColoPrint in estimating the 3-year relapse rate in patients with stage III colon cancer.
PARSC Study Current Status:

- Aim 575 eligible stage 2 patients
- Status March 30th 2012:
  - 34 sites open (EU 15, Asia 2, US 17)
  - 366 eligible Stage II
    - 150 patients already with first follow completed
  - 300 eligible stage 3
- Expected last patient enrollment: Dec’12
- FFPE addendum study submitted for IRB in top 5 centers

<table>
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<tr>
<th>Event</th>
<th>Date</th>
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<tbody>
<tr>
<td>First patient entered PARSC trial</td>
<td>September 2008</td>
</tr>
<tr>
<td>Last patient entered study</td>
<td>December 2012</td>
</tr>
<tr>
<td>Database locked (3 yrs survival)</td>
<td>March 2016</td>
</tr>
<tr>
<td>Final report (3 yrs survival)</td>
<td>June 2016</td>
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What’s next in colon cancer?

- Signature to identify patients with MSI-H status
- Mutation Analysis
- Molecular Subtypes to classify patients (EMT)
- Response signatures to identify patients with likely response to specific treatments
- Development of companion diagnostics with big Pharma
Acknowledgement

- Many thanks to all patients and hospitals participating in PARSC and our research studies
- Many thanks to our collaborators