Von der Molekulardiagnostik zur Personalisierten Medizin
Industrietrends und Fallstudien

2. DVFA-Life Science Symposium
Frankfurt, 17. Juni 2009

Dr. Thomas Schweins
Vice President Marketing & Strategy
Agenda

QIAGEN: Facts, Business Model & Strategy

Trends Molecular Diagnostics:
- Case Study: Diagnostic HPV Test

Trends Personalized Medicine
- Case Study: Prognostic K-ras Test
## QIAGEN at a Glance: A Focused Market Leader

### Financial overview
- Sales 2008: $893 M
- Gross- / EBIT margin\(^1\): 72% / 29%
- Organic growth: 10% - 15%
- Market capitalization\(^2\): $3.5 B
- Presence: Global

### Customer, Innovation and Employees
- # Customer: 400,000
- R&D: $120 M
- Patents & Licenses: >2,000
- Products < 3 years old: 17%
- Employees: >3,000

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\(^1\) Adjusted figures exclude business integration and relocation related charges as well as amortization of acquired intangibles and equity-based compensation (SFAS 123R).

\(^2\) As of June 9, 2009
QIAGEN With a Strong Financial Performance

(1) Analyst estimates
Source: QIAGEN

CAGR_{2003-2008} = 21%
Typical Products: Instruments = 10% of Sales
Typical Products: Consumables  =  90% of sales
Complex Biological Sample

Sample Preparation

Pure Genes

Results

- Virus detected
  - Yes
  - No

SAMPLE Technologies

ASSAY Technologies
Disseminating Technologies Into Four Markets

- Market leader Academia
  - Life Science Research
- Market leader Pharma
  - Research & Development
- Market leader Applied Testing
  - Routine Testing
- Market leader Molecular Diagnostics
  - Routine Testing

Product and Technology Continuum

SAMPLE Technologies

ASSAY Technologies
Leading Position – Multiple Growth Drivers

- Academia: ~$240M
- Pharma: ~$150M
- Applied Testing: ~$70M
- Molecular Diagnostics: ~$430M

SAMPLE Technologies
ASSAY Technologies

Product and Technology Continuum
Life sciences and molecular technologies have only just started to change the world in which we live.

Molecular information is going to be important and a mega trend

- What makes humans different? And what unique?
- What is the difference between healthy and sick?
- How can we identify viruses and bacteria?
- How can we stop infectious diseases?
- How can we develop better drugs?
- How can we improve the food quality?
- How can we identify criminals?
- How can we stop cancer?
- …

NIH invests 40.000.000.000 $ per annum
EU invests 20.000.000.000 $ per annum
Pharma invests 40.000.000.000 $ per annum
Biotech invests 15.000.000.000 $ per annum
Asia invests 6.000.000.000 $ per annum

> $120.000.000.000 $ per annum
Fast Growing and Very Attractive Market

High value tests increase value ... ... and significance in health care... ... and lead to attractive industry growth

Average price per tests

Share of health care cost

MDx Market Development

Molecular Diagnostics within the Health Care System With Increase Importance
Market Leadership in Molecular Diagnostics

QIAGEN’s market position
- No. 1 in HPV testing
- No. 1 in automated sample processing
- No. 1 in manual sample preparation
- No. 2 in PCR technology in MDx
- No. 2 in HLA testing
- No. 1 in emerging countries
- Largest infectious disease assay portfolio

Technology & Infrastructure
- 120 Mio $ R&D budget in molecular technologies
- IP estate: 2,000+ patents & licenses
- Broad technology platform
- 450 individuals in Sales & Marketing

Molecular Diagnostic Landscape

<table>
<thead>
<tr>
<th>Sales in US$ millions</th>
<th>QIAGEN</th>
<th>Roche MDx</th>
<th>Genprobe</th>
<th>Abbott</th>
<th>Siemens</th>
<th>Cepheid</th>
<th>Hologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>435</td>
<td>350</td>
<td>220</td>
<td>150</td>
<td>140</td>
<td>90</td>
<td>45</td>
<td></td>
</tr>
</tbody>
</table>

(1) Excluding Viral Load and Blood banking business
New Content & Dissemination Drive Market Growth

Molecular Dx parameter and # of MDx laboratories

Increasing Importance of Medical Value Expected

- Increasing testing efficiency
- Improving medical value

Value creation

2000 2010 2020
QIAGEN With Focus on Efficiency and Medical Value

Value creation

- HIV: Test & treat
- Cervical Cx Screening
- MRSA for HAI
- Colon cancer stratification
- Molecular Tumor Staging
- HPV: Test & Vaccinate
- Breast cancer prediction
- POC Antibiotics selection
- New-born predisposition
- Breast cancer prediction
- Ultra-fast sepsis analysis
- Point-of-care testing
- Data integration
- Connectivity
- OTC Tests
- Consumer Tests

Menu breath
- Ease-of-use
- High Resolution
- Integrated workflows
- Integrated systems

Instrument size
- Multiplexing

Sensitivity

Examples

2000 2010 2020

- Increasing Testing efficiency
- Improving Medical value
From Patient Sample To Clinical Results
QIAGEN Provides Advanced Sample And Assay Technologies

Sample and Assay Technologies from Sample to Result
Agenda

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The Cervical Cancer - HPV Connection

HPV and Cervical Cancer Prevalence

Clinical relevance

- Persistent infection with HPV is proven cause of cervical cancer
- 500,000 new cases every year
- 250,000 die of cervical cancer
- Single HPV test in women age 30 and over is an excellent proxy for persistent infections

Source: National Cancer Institute SEER data

The *digene* HPV Test – Preventing Cervical Cancer
HPV Diagnostic - Enormous Market Potential

Global pap test market

- **US** 50-55M
- **Europe** 45-50M
- **Asia/Latin America** 40-50M

Total WW Pap: 145-160M

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HPV market potential

<table>
<thead>
<tr>
<th>Region</th>
<th>Eligible annual tests (1)</th>
<th>Potential IVD Market ($)</th>
<th>Potential Lab Market ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.S.</td>
<td>35 M</td>
<td>$525 M</td>
<td>$1.700M</td>
</tr>
<tr>
<td>Europe</td>
<td>35 M</td>
<td>$455 M</td>
<td>$1.500M</td>
</tr>
<tr>
<td>Asia/Latin America</td>
<td>35 M</td>
<td>$350 M</td>
<td>$900M</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>~100M</td>
<td>~$1.3B</td>
<td>~$3.3B</td>
</tr>
</tbody>
</table>

(1) Age-adjusted for women age over 30
Large Variation in Market Penetration within USA

HPV Screening Market USA - Metropolitan Areas

Total avail. Market kTest p.a.

Penetration in %

0% 20% 40% 60% 80% 100%

Los Angeles

New York

(1) Area not proportional to market potential
Well Established Multi-Channel Distribution

- Patient makes appointment
- Physician detailing
  ~120 professionals
- DTC TV Advertising
  130M impressions
- Women advocacy
- Key Opinion Leaders
- Doctor orders HPV Test
- Lab runs HPV test
- Key Opinion Leaders
- Lab Sales
  ~40 professionals
- Reimbursement
  ~5 professionals
- Patient reimbursed for test
- Physician discuss test results with patient

QIAGEN with Pharma Business Model in Sales and Marketing
Pap Did Not Find the Cervical Disease But The HPV Test Did!
Agenda

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Patient Stratification: A Win-Win Situation

A. Enrichment of responders

- Enrich clinical trials with patients who are more likely to respond to therapy

B. Elimination of side effects

- Exclusion of patients with adverse effects

Benefits for Patients
- Increased efficacy
- Reduced unnecessary treatments
- Increased safety and less side effects

Benefits for Payer and Provider
- Increased in efficiency
- Reduction in health care costs

Potential benefits for Pharma
- Targeted medicine = higher prices
- Increased success rates in clinical trials
- Increased compliance
- Reduced risks for side effects
## Personalized Medicine Becomes Reality

<table>
<thead>
<tr>
<th>Molecular Biomarker Test</th>
<th>Therapy</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCR-ABL</td>
<td>Gleevec®</td>
<td>Chronic myeloid leukemia</td>
</tr>
<tr>
<td>c-KIT</td>
<td>Gleevec®</td>
<td>Gastrointestinal stromal tumor (GIST):</td>
</tr>
<tr>
<td>HER-2/neu receptor</td>
<td>Herceptin®</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>BRCA 1,2</td>
<td>Breast/ ovarian cancer</td>
<td>Pharmaceutical and surgical prevention options</td>
</tr>
<tr>
<td>AlloMap® gene profile</td>
<td>Immunosuppressiva</td>
<td>Monitors immune response to heart transplant</td>
</tr>
<tr>
<td>Familion® 5-gene profile</td>
<td>Pharmaceutical prevention</td>
<td>Inherited cardiac channelopathies: Prevention &amp; drug selection</td>
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<tr>
<td>p16/CDKN2A</td>
<td>Melanoma:Preventive treatment</td>
<td>Pharmaceutical and surgical prevention options</td>
</tr>
<tr>
<td>TruGene®-HIV 1 Genotyping Kit</td>
<td>Anti-retroviral drugs</td>
<td>Guides therapy selection based on resistant HIV mutations</td>
</tr>
<tr>
<td>Oncotype DX™ 21-gene assay</td>
<td>Cancer treatment regimens</td>
<td>Quantifies the likelihood of breast cancer</td>
</tr>
<tr>
<td>UGT1A1</td>
<td>Camptosar®</td>
<td>Drug side effects in colon cancer treatment</td>
</tr>
<tr>
<td>Amplichip® CYP2D6/CYP2C19</td>
<td>Drugs metabolized by P450</td>
<td>Treatment dose for drugs that are metabolized by P450</td>
</tr>
<tr>
<td>Estrogen receptor</td>
<td>Tamoxifen</td>
<td>Relevance of tamoxifen citrate in breast cancer therapy</td>
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<tr>
<td>TPMT</td>
<td>Purinethol®</td>
<td>Dose adjustment in acute lymphoblastic leukemia treatment</td>
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<tr>
<td>HIV enters CD4 cells via CCR5-K-</td>
<td>Selzentry</td>
<td>Show that their type of HIV enters CD4 cells via CCR5</td>
</tr>
<tr>
<td>Ras (B-Raf)</td>
<td>Vectibix, Erbitux</td>
<td>Exclusion of K-Ras mutants increase efficacy</td>
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<tr>
<td><strong>B</strong></td>
<td></td>
<td></td>
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<tr>
<td>CYP2C9 and VKORC1</td>
<td>Warfarin</td>
<td>Helps assess Warfarin sensitivity</td>
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<tr>
<td>HLA-B*5701 allele</td>
<td>Abacavir</td>
<td>Adverse reactions in AIDS patients</td>
</tr>
</tbody>
</table>

Source: Personalized Medicine Coalition, 2008
How to Detect Cancer?

**Normal prostate tissue**

- Prostate glands (white areas)
- Surrounded by epithelial cells (blue)

**Prostate cancer tissue**

- Cancerous tissue completely disorganized
- Uncontrolled growth of malignant cells
- Destroys the normal glandular structure.

Organized structure:

Pathology is used to determine if a tissue has progressed to cancer
Molecular Diagnostics is the Future

Yesterday: Pathology

Future: Molecular Diagnostics

**Macroscopic** observation
- Based on microscope
- Innovative staining reagents (Immunohistochemistry/IHC)

**Molecular** detection
- Changes in expression pattern
- Detection of genetic and epigenetic changes

Molecular Dx Enables Better Diagnosis, Classification and Treatment
Ras-Pathway: Molecular Mechanisms of Cell Growth

Ras–Raf–pathway
Single-Run Identification of Oncogenic K-ras Mutants

Gly12, Gly13

Sequence to analyze: GGT GGC GTA GG

K-ras Sequence Pyrosequencing results for different samples

Wildtype K-Ras

Mutant in 12

Mutant in 12

Mutants in 61 are sequenced in parallel in second well
Personalized Medicine: $14 B With Targeted Therapy

Targeted therapy - Cancer drug sales 2006

<table>
<thead>
<tr>
<th>Company</th>
<th>Sales (US$B)</th>
</tr>
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<tbody>
<tr>
<td>Genentech</td>
<td>5.2</td>
</tr>
<tr>
<td>Roche</td>
<td>3.9</td>
</tr>
<tr>
<td>Novartis</td>
<td>2.6</td>
</tr>
<tr>
<td>BMS</td>
<td>0.8</td>
</tr>
<tr>
<td>Others</td>
<td>2.1</td>
</tr>
</tbody>
</table>
Roche Strategy: Focus on Personalized Medicine

It is an unfortunate fact that medicines are currently not as effective as they could be in an average of around fifty percent of patients, and in certain indications the success rate is even lower. This is why Roche is systematically pursuing personalised medicine.”

Severin Schwan, CEO

Pioneering personalised healthcare

Personalised healthcare has enormous potential to make healthcare better, safer, and more user-effective.

It will still be some time before the potential of personalised healthcare is fully realised, but the market is clearly shifting away from “one size fits all” products.

Medicine is becoming increasingly personalised

Over the last few years, Roche has provided various examples of how intertwining diagnostic and pharmaceutical medicine across the life science value chain can lead to more efficient and effective healthcare.

Acquisition of Ventana

$3.4 Bio USD for $240 Mio USD sales
Roche: Companion Dx Program for Each Project

**Companion Diagnostics program for each project**  
*Strong oncology drug portfolio, combined with diagnostics capabilities uniquely positions Roche to lead in PHC*

<table>
<thead>
<tr>
<th>Roche Oncology Pipeline</th>
<th>Roche Capabilities</th>
<th>Ventana Capabilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late Development/Market</td>
<td>PCR</td>
<td>IHC/ISH</td>
</tr>
<tr>
<td>Herceptin</td>
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<td>Taregko</td>
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<tr>
<td>Mahilhera/ Riluxan</td>
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<tr>
<td>Pertuzumab</td>
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<td>R7204</td>
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<td>R7112</td>
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<td>R1567</td>
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<td>R7160</td>
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<tr>
<td>R7159</td>
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</tbody>
</table>

Very few other pharma companies with Dx competence
Novartis Launches Internal Molecular Dx Unit

In addition to developing companion diagnostics, Novartis is charged with developing "standalone" diagnostics "that have no relationship with our drugs whatsoever."

Novartis has extended and expanded its blood screening collaboration with Gen-Probe until 2025.
More and More Collaboration & Internal Programs Emerge

Pharma – Diagnostics Collaboration

- Collaboration with Abbott/Vysis and DakoCytomation for Her2/Neu testing for Herceptin (first FDA approved Thx)
- Collaboration with Genzyme genetics BCR/ABL testing for chronic myeloid leukemia (CML) Rx
- Collaboration with Monogram Biosciences for HIV drugs
  » Monogram’s Trofile Assay is used to test CCR5 which is instrumental in the decision to administer Pfizer’s recently approved Maraviroc
- 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

Integrated Rx and Dx Divisions

- Integrated Rx/Dx: close cooperation between Rx and Dx to validate novel Oncology markers for personalized medicine tests
- Partial Control with limited Rx/Dx integration (Abbott Dx & Vysis)
- Partial Control with limited Rx/Dx integration (Veridex and Ortho Clinical Diagnostics)

Source: Company reports
Sample & Assay Technologies

Strong push towards personalized medicine

Guidance for Industry
Pharmacogenomic Data Submissions

Draft
Preliminary Concept Paper — Not for Implementation

Drug-Diagnostic Co-Development Concept Paper
Draft — Not for Implementation

Opening the Door to the Next Generation of Medicine

Genomics has the potential to revolutionize the practice of medicine, but despite significant scientific advances, very few genomic-based tests or treatments have reached consumers. Source: Obama introduced the Genomics and Personalized Medicine Act to overcome the scientific barriers, adverse market pressures, and regulatory obstacles that have stood in the way of better medicine.

Genomics and Personalized Medicine:
Tests are only beginning to understand how our genetic makeup affects our predisposition for certain diseases and can help guide our health care decisions. Today, the typical black-and-white drug prescription is effective for 40-60% of patients prescribed it. Meanwhile, serious adverse drug reactions kill 32,000 people and kill 250,000 people a year in the U.S.:

1. Could clinicians help predict which patients will go sick, diagnose illness earlier, and patients to determine which drugs will be effective and safe. Doctors may eventually hire science to personalize drug treatment in an individual patient’s genetic makeup, thereby improving health care outcomes and quality. Drug compliance, meanwhile, will be better anticipated which new medication will work, speeding up drug discovery.

Examples of Genomics Medicine:
Example: Pneumonitis Parwater is a discovery for kids with leukemia, but in 11 percent of cases, an effective, economic, and safe alternative. By the 1990’s, researchers identified a variant that prevents affected patients from properly breaking down Parwater, leading to serious patients and adverse drug reactions that can be reduced. Pneumonitis is a bloodstream cancer drug that tends to induce in crianças. However, researchers after discovering a genetic difference in one breast cancer patient who had the drug very effective in 30 of 32 cases. Today, doctors combine a genetic test with genomic testing, with significantly improved survival for women with this type of cancer. "Genomic research advances have improved the treatment of breast cancer," the researchers have said for the development of new drugs like herceptin.

Potential Unfolding:
As scientists were beginning to identify genes associated with diseases, such as with the American Cancer Society predicted, "This is the biggest single breakthrough in a century of all time." In 2000, Dr. Francis Collins, the head of the Human Genome Project, said to güzel USA, he said, "Genomic medicine makes the dream promise of customizing the diagnostic and treatment of every disease." Thus, here, the genomic medicine has not yet happened. Relatively few drugs or tests based on genomics have reached the market.
Questions?