QIAGEN – Research & Development Pipeline 2008/2009

QIAGEN Analyst and Investor Day 2009
Dr. Joachim Schorr,
Senior Vice President Global Research & Development

New York, February 12th, 2009
Agenda

Launches 2008

- R&D Budget and Programs 2009
- NextGen HPV Screening Assay and Platform
- NextGen Genotyping Assays
- QIAGEN’s Content Programs
Selected Product Launches 2008

**Applications**

- **DNA**
  - CompactPrep megagiga
  - EpiTect MethyLight Assays
  - EpiTect MethyLight PCR Kit
  - EpiTect Control DNA
  - EpiTect WBA Kits
  - EpiTect MSP PCR Kits
  - QIAsymphony system
  - EZ1 Advanced
  - QIAxcel system/cartridges
  - QIAcube: additional protocols
  - TopTaq Mastermix
  - EpiTect HRM Kit
  - Multiplex Genotyping Kit
  - SNP qPCR Kit

**RNAi**

- FlexiPlate Gene Family updates
- Human WG/DG siRNA Set v 4.0
- AllStars hs cell death control
- miScript additions
- New DNA transfection reagent
  - Next generation Lipofection & Nanofection
- HiPerFect for miRNA
- Online transfection protocols

- FlexiPlate & custom assays for miScript
- Synthetic miRNAs & miRNA inhibitors
- HiPerFect for primary cells

**Gene Expression & Function**

- QuantiFast Multiplex PCR Kit
- AllPrep DNA/RNA 96
- RNeasy 96 Plus
- RNeasy protect animal blood

- QuantiFast Multiplex RT-PCR Kit
- QuantTect HTP Eva Green Kit
## Selected Product Launches 2008

<table>
<thead>
<tr>
<th>Product</th>
<th>Regulated Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AutoSys</strong></td>
<td><strong>Product</strong></td>
</tr>
<tr>
<td>QIAsymphony system</td>
<td>QIAcard FTA (Marie McClusky)</td>
</tr>
<tr>
<td>EZ1 Advanced</td>
<td>QIAsafe (Marie McClusky)</td>
</tr>
<tr>
<td>QIAxcel System/cartridges</td>
<td>VET BVDV PCR Screening Kit</td>
</tr>
<tr>
<td>QIAcube: additional protocols</td>
<td>VET BVDV PCR Subtyping Kit</td>
</tr>
<tr>
<td><strong>QIAsymphony system</strong></td>
<td>VET Taylorella PCR Kit RUO</td>
</tr>
<tr>
<td><strong>EZ1 Advanced</strong></td>
<td><strong>QIAcube: PAX Blood RNA RUO</strong></td>
</tr>
<tr>
<td><strong>QIAxcel System/cartridges</strong></td>
<td><strong>QIAamp DSP Virus Kit Modif. CD&amp;US</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>QIAcube: additional protocols</strong></td>
</tr>
<tr>
<td><strong>QIAxcel System/cartridges</strong></td>
<td><strong>artus Enterovirus LC PCR</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>artus Borrelia LC PCR</strong></td>
</tr>
<tr>
<td><strong>QIAxcel System/cartridges</strong></td>
<td><strong>artus Malaria LC PCR</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>artus B.antrax</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>artus L.Pneumophila LC PCR</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>artus WNV LC PCR</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>artus HIV RG CE</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>ResPlex II RUO</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>Olerup SSP FDA</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>SBTExcellerator CE + FDA</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>QIAamp 24 plate + RUO protocols BR MDx</strong></td>
</tr>
<tr>
<td><strong>QIAcube: additional protocols</strong></td>
<td><strong>QIAamp esoteric (bacDNA, vNA)</strong></td>
</tr>
</tbody>
</table>

- EZ14 (14 channel instrument) – BMR, MDx
- QIAxcel PAX Blood RNA RUO
- QIAxcel gDNA Blood RUO
- QIAxcel Respiratory/Oral RUO
- QIAxcel Virus RUO
- QIAxcel Stool/Urine Media RUO
- QIAcube: additional protocols

- QIAamp 24 plate + RUO protocols BR MDx
- QIAamp esoteric (bacDNA, vNA)
Launches 2008

R&D Budget and Programs 2009

NextGen HPV Screening Assay and Platform

NextGen Genotyping Assays

QIAGEN’s Content Programs
R&D Cost Budget by Customer Class
QIAGEN Group Budget 2009

* R&D Administration, Basic Research, Patent & Licensing, Business Development
DNA Methylation Analysis
Key Technologies (Epigenetics, Methylation)

- Bisulfite treatment of gDNA
- Determine methylation pattern
- Screening of CpG island
  - High resolution melting
- Specific CpG positions
  - MSP PCR
  - Pyrosequencing
- Quantification of CpG methylation
  - Pyrosequencing
  - Methylight PCR
  - Next Generation Sequencing
Pyrosequencing Application
Workflow Overview

Primer Design → PCR → Purification → Sequence-based Assay Run → Data Analysis

- Primer Design
  - Software
    - Primer design for PCR and sequence based assay development

- PCR
  - Rotor-Gene Q Cycler

- Purification
  - Vacuum Prep Station
    - beads
    - buffers
  - Denaturation of Biotinylated PCR
  - Purification of ssDNA for sequence based assay reaction

- Sequence-based Assay Run
  - PyroMark™ Q24

- Data Analysis
  - PyroMark instruments to conduct the assays
    - PyroMark Gold
      - APO protein
      - MTH receptor
      - K-ras gene
      - BRAF gene
      - p16
      - MLH1
      - MGMT
      - Line 1
      - PyroMark MOTT
      - PyroMark Funghi

- Software
  - Read-out of data on instrument
Pyrograms of the SNRPN locus from Angelman Syndrome patients, Prader-Willi Syndrome patients compared to normal controls.

Analysis of allelic methylation differences at the small nuclear ribonucleoprotein polypeptide N (SNRPN) locus can differentiate the maternally and paternally inherited chromosome 15 and can be used as a diagnostic test for Angelman Syndrome and Prader-Willi Syndrome.
Multiple infection of HPV-16 and HPV-18 in 3 unrelated clinical samples sequenced by the multiple sequencing primer method and genotyped by sequence-pattern-recognition.
K-ras is an oncogene involved in signal transduction pathway
- Cell growth regulated via EGF-ras-raf signal transduction
- EGFR-Inhibitors against EGF Receptor block cell growth
- Oncogenic ras mutations in 4 critical positions
- Patient stratification increases efficacy of Anti-EGF drugs
- PyroMark K-ras v2.0 is a pyrosequencing based assay that detects all mutations in relevant positions

![Graph showing wt K-Ras and Mutated K-Ras](image-url)

From Magnus Sundström, PhD Molecular Pathology at Uppsala University Hospital, Sweden
Oncogenic Ras-Genes Play Major Role in Cancer

Oncogenic ras mutations found in up to 30% of all human tumors
- 15-50% of lung cancers
- 72-90% of pancreatic cancers
- 35-45% of colon cancers

Colon and rectum cancer is a major disease burden: No 2 cancer
- Global Incidence: 1,020,000 cases
- Global Mortality: 530,000 deaths
- Incidence in western world: 456,000 cases

Pharma with strong pipeline for colon cancer as well as Anti-EGFR
- Colon cancer: 60+ candidates in clinical phases
- EGFR inhibitors: 140+ trials citing EGFR inhibitors

Pyrosequencing outperforms qPCR in terms of
- Targets: Identifies known and unknown mutations
  Identifies variations in mutations
  Covers several key mutations
- Technology: Easy set-up
  Very fast – direct signal

Regulatory strategy
- US: RUO followed by FDA submission
- EU: CE labeling
Agenda

- Launches 2008
- R&D Budget and Programs 2009
- NextGen HPV Screening Assay and Platform
- NextGen Genotyping Assays
- QIAGEN’s Content Programs
### Beyond hc2: Assay Improvements in NextGen

<table>
<thead>
<tr>
<th><strong>digene hc2 HPV Screening Assay</strong></th>
<th><strong>NextGen HPV Screening Assay</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Handling:</strong></td>
<td></td>
</tr>
<tr>
<td>Four hour assay</td>
<td>Two hour assay, fully automated</td>
</tr>
<tr>
<td>4 ml PC sample volume per assay</td>
<td>1-2 ml PC volume per assay</td>
</tr>
<tr>
<td>Two-plate assay</td>
<td>Single-plate assay</td>
</tr>
<tr>
<td><strong>Performance:</strong></td>
<td></td>
</tr>
<tr>
<td>13 high risk subtypes</td>
<td>15 high risk subtypes (+ types 66 and 82)</td>
</tr>
<tr>
<td>Acceptable analytical sensitivity</td>
<td>Improved analytical sensitivity!!</td>
</tr>
<tr>
<td>Known LR-analytical specificity</td>
<td>Improved analytical specificity!!</td>
</tr>
<tr>
<td><strong>Technology:</strong></td>
<td></td>
</tr>
<tr>
<td>Complex Ab coating to plates</td>
<td>Simple Ab linkage to beads</td>
</tr>
<tr>
<td>Lot dependent components</td>
<td>Lot-independent components</td>
</tr>
<tr>
<td>Reagent on-board stability: 8 hours</td>
<td>Reagent on-board stability: &gt; 7 days</td>
</tr>
</tbody>
</table>
QIAensemble Product Configuration
Future HPV & CT System

High-Throughput Ensemble Workcell
Throughput = 1 to 2000 Tests/Shift

Bar-coded Sample
LBC

Pre-analytical + De-capper
CE1000

Manual plate transfer

QIAensemble (JE2000)
STM
Sample

CCU = Central Control Unit

Assays:
- High Risk HPV Screening
- HPV Type 16, 18, 45 Probes
- CT/GC
- Future menu

Urine

QIAensemble Product Configuration
Future HPV & CT System
QIAensemble Product Configuration
Future HPV & CT System

Classic Ensemble Workcell
Throughput = 1 to 400 Tests/Shift

QIAensemble (JE800) QIAsymphony SP
Sample

Assays:
- High Risk HPV Screening
- HPV Type 16, 18, 45 Probes
- CT/GC
- Future menu

CCU = Central Control Unit

Bar-coded Sample

LBC

Urine

De-capper TBD

Manual plate transfer
### QIAensemble Status/Timeline

<table>
<thead>
<tr>
<th>Ensemble System Component</th>
<th>Current Status</th>
<th>Clinical Trials CE Mark</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR HPV Screening Assay</td>
<td>Performance testing; Formulation lock</td>
<td>Initiate Clinical Trials 2009; CE Mark 2010</td>
</tr>
<tr>
<td>Probe Set (16,18,45)</td>
<td>Assay Development</td>
<td>Initiate Clinical Trials 2009; CE Mark 2010</td>
</tr>
<tr>
<td>QIAensemble (JE2000)</td>
<td>Prototypes assay integration testing;</td>
<td>Initiate Clinical Trials 2009;</td>
</tr>
<tr>
<td>Pre-anlytiker &amp; De-capper (CE1000)</td>
<td>Early prototype assay integration;</td>
<td>Initiate Clinical Trials 2009</td>
</tr>
<tr>
<td>System Software</td>
<td>Lock down software specifications</td>
<td>Initiate Clinical Trials 2009</td>
</tr>
<tr>
<td>QIAensemble (JE800)/ QIAsymphony</td>
<td></td>
<td>Instrument Migration Study to Follow QIAensemble (HT) FDA approval; CE Mark 2010</td>
</tr>
<tr>
<td>QIAensemble (JE2000) Plus + CT/GC with tHDA</td>
<td>Feasibility/prototype development</td>
<td>TBD</td>
</tr>
</tbody>
</table>
# Regulatory Approval Projects

**USA**

<table>
<thead>
<tr>
<th>PROJECT QUARTER</th>
<th>YEAR</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Q1</td>
<td>Q2</td>
<td>Q3</td>
</tr>
<tr>
<td>artus CMV RG 6000</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>artus HSV 1/2 RG 6000</td>
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<tr>
<td>HLA</td>
<td></td>
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<tr>
<td>NextGen HPV Screening</td>
<td></td>
<td>Pre-IDE</td>
<td></td>
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</tr>
<tr>
<td>DML 3000</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AX pH QIAsymphony for HC 2.0</td>
<td></td>
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</tr>
</tbody>
</table>

- **Running / planned project**
- **Clinical trials begin**
- **510K Submission**
- **PMA Submission**
- **Estimated Approval/Launch** (typically 15 months after submission for PMA, 6 months for 510K)

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**Notes:**
- Project changed due to Corbett acquisition.
- Submitted April 08 Approval expected for Feb 09
- Combined Project: NextGen with 16, 18, 45 probe set genotyping.
- Submission done. Approval expected Q109
- New project
## Selected Regulatory Approval Projects
### Europe

<table>
<thead>
<tr>
<th>Project</th>
<th>Year</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>artus HIV RG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EZ1 upgrade virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cador BVDV TM RT Kit</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>QIAplex ResPlex II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NextGen</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>HPV Genotyping</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- **artus HIV RG**
  - Submitted March 08
  - Approved June 08
- **EZ1 upgrade virus**
  - Launched in March 08
- **Cador BVDV TM RT Kit**
  - Approved in Jan 09
- **QIAplex ResPlex II**
  - RUO Launch T3 08 CE launch planned for T3 09
- **NextGen**
  - RUO Launch followed by CE mark shifted to 2010
- **HPV Genotyping**
  - RHA stript assay
  - RUO launched Jan 09
  - CE launch planned for Sep 09
Agenda

Launches 2008

R&D Budget and Programs 2009

NextGen HPV Screening Assay and Platform

NextGen Genotyping Assays

QIAGEN’s Content Programs
QIAGEN HPV Genotyping Test Strategy

**Positive HC2** → **Genotyping Reflex**
- QIAensemble
  - High Risk: 16, 18, 45
  - >70% of all HPV infections

**Probe Set Genotyping Assay**
- Run on QIAensemble instrument
- Genotypes 16, 18, 45
- Hybrid Capture format
- Cytology labs: no PCR capability
- Reagents: reflex on instrument
- Seamless protocol with screening assay

**LQ & RH HPV Genotyping Assay**
- 1° Customers: Reference Labs
- Genotype 18 High Risk types
- Initial Clinical utility: 16, 18, 45 triage
  - Persistence for other HR types
  - Vaccine monitoring
- GP 5+/6+ consensus primers
- Luminex-based
- Reverse Hybridization – based (RH)

Customers: Reference Labs
- Genotype 18 High Risk types
- Initial Clinical utility: 16, 18, 45 triage
- Persistence for other HR types
- Vaccine monitoring
- GP 5+/6+ consensus primers
- Luminex-based
- Reverse Hybridization – based (RH)

LQ & RH
- 18 High Risk Subtypes
# Genotyping Projects Overview

<table>
<thead>
<tr>
<th>Project</th>
<th>Projected Launch Date</th>
<th>Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modified HCII</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>digene</em> HPV Genotyping PS Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>digene</em> HPV Genotyping PS Test (ASR)</td>
<td>June 2009</td>
<td>Sold as ASR in the U.S.</td>
</tr>
<tr>
<td><em>digene</em> HPV Genotyping PS Test (CE)</td>
<td>Jan 2010</td>
<td>Sold as CE-marked kit in Europe similar to hc2 assay protocol and reagents as possible.</td>
</tr>
<tr>
<td><strong>PCR line blot</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>digene</em> HPV Genotyping RH Test</td>
<td></td>
<td></td>
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<tr>
<td><em>digene</em> HPV Genotyping RH Test (RUO)</td>
<td>Nov 2008</td>
<td>Sold only ex U.S. as RUO and CE</td>
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<tr>
<td><em>digene</em> HPV Genotyping RH Test (CE)</td>
<td>July 2009</td>
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<tr>
<td><strong>PCR luminex</strong></td>
<td></td>
<td></td>
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<tr>
<td><em>digene</em> HPV Genotyping LQ Test</td>
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<td></td>
</tr>
<tr>
<td><em>digene</em> HPV Genotyping LQ Test (RUO)</td>
<td>Dec 2008</td>
<td>Sold only ex U.S. as RUO and CE</td>
</tr>
<tr>
<td><em>digene</em> HPV Genotyping LQ Test (CE)</td>
<td>July 2009</td>
<td></td>
</tr>
</tbody>
</table>

PS = Probe Set  
RH = Reversed Hybridization  
LQ = Luminex based
Addressing HPV in Developing Countries

- careHPV designed for use in low resource countries
  - Simple to run
  - Rapid, accurate results
  - Requires minimal infrastructure
  - Affordable for public-health programs in those countries

Developed by QIAGEN in close partnership with:

PATH

And funding from:

BILL & MELINDA GATES FOUNDATION
Current Timeline for *care*HPV and PG Biotech assays

- Initiate SFDA clinical trial enrollment and testing
  Q1 2009
- Submit for SFDA approval early H2 2009
- Apply for commercial license in India immediately upon receiving SFDA approval
Agenda

Launches 2008

R&D Budget and Programs 2009

NextGen HPV Screening Assay and Platform

NextGen Genotyping Assays

QIAGEN’s Content Programs
# Diagnostic Content is Key for Medical Value

<table>
<thead>
<tr>
<th>Infectious Disease</th>
<th>Near-term</th>
<th>Mid-term</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>ResPlex II artus assays on RG</td>
<td>GastroPlex, BK, Adenovirus, JC, Candida, Aspergillus</td>
<td>Predisposition to Infection</td>
<td></td>
</tr>
<tr>
<td>Oncology</td>
<td>K-ras, B-raf</td>
<td>A/C-raf, MEK-1/2, p53, EGFR, BCR-ABL, N-ras, PI3-Kinase, N/H-RasAKT, BCR, PTEN et al Companion diagnostics for cancer therapeutics</td>
<td>Screening for colon cancer</td>
</tr>
<tr>
<td>Women's Health</td>
<td>HPV Genotyping, HPV HC2 Symphony care HPV (3rd world)</td>
<td>HPV NextGen CT/NG NextGen Progression marker</td>
<td>Panel for reproductive tract infections, Screening for breast cancer</td>
</tr>
<tr>
<td>Other</td>
<td>Blood screening (China)</td>
<td>MRSA, cDiff, VRE Pseudomonas, Acinetobacter, other bacteria</td>
<td>Meningitis, Sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Factor II, V</td>
<td>Cytochrome p450</td>
</tr>
</tbody>
</table>
Tumor Characterization
Cancer Biomarker Discovery & Standardization Using XenoBase*

- Tumors are indistinguishable according to classical classification!
- Tumors can be differentiated on a molecular level (see red cloud)!

\[\text{luminal} \ll< \text{CK5/CK18} >\gg \text{basal} \]

\[\text{vimentinreich} \ll< \text{CK/VM} >\gg \text{keratinreich} \]

- Good clinical progression (G)
- Bad clinical progression (B)

41 x G (72%)
24 x B (39%)

*XenoBase Software is licensed from the van Andel Institute*