# QIAGEN’s 4 “P” Framework in MDx

## LABORATORY-BASED TESTING

<table>
<thead>
<tr>
<th>Prevention</th>
<th>Profiling</th>
<th>Personalized Healthcare</th>
<th>POINT OF NEED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic patients</td>
<td>Symptomatic patients</td>
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<td>Rapid turnaround needed</td>
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### Assay Technologies

<table>
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<tr>
<th></th>
<th>Narrow portfolio</th>
<th>Broad portfolio</th>
<th>Growing portfolio</th>
<th>Emerging segment</th>
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<tbody>
<tr>
<td></td>
<td>High volume/&lt;$20/assay</td>
<td>High value, low volume</td>
<td>High value, low volume</td>
<td>Instrument &lt;$2k, Assays: $3-30</td>
</tr>
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### Examples

- Narrow portfolio: HPV, Chlamydia/NG, 5 additional assays in pipeline, More to come
- Broad portfolio: CMV, EBV, HBV, HIV, HCV, Influenza
- Growing portfolio: KRAS, EGFR, BRAF, PI3K, Pathogen Genotyping
- Emerging segment: careHPV, HAI, Influenza

### Instruments

- High throughput: Continuous load
- Random access: Continuous load
- Portable test systems: Rapid turn-around < 2hrs
- TBA

### Assay Design

- Fast, typically isothermal amplification or no amp
- PCR
- Pyrosequencing
- Isothermal amplification

---

Sample & Assay Technologies
# Focusing on Personalized Healthcare

## Laboratory-Based Testing vs. Point of Need

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## Assay Technologies

| Narrow portfolio               | Broad portfolio            | Growing portfolio       | Emerging segment |
| High volume/<$20/assay         | High value, low volume     | High value, low volume  | Instrument <$2k, |
|                                |                            |                         | Assays: $3-30    |

## Assay Technologies Examples

- **HPV**
- Chlamydia/NG
- 5 additional assays in pipeline
- More to come

- **CMV**
- EBV
- HBV
- HIV
- HCV
- Influenza

## Instruments

- **High throughput**
- **Continuous load**

## Assay Design

- Fast, typically isothermal amplification or no amp
- PCR
- Pyrosequencing

- Random access
- Continuous load
- Random access
- Continuous load
- Portable test systems
- Rapid turn-around < 2hrs
- TBA
- Isothermal amplification

- **QIAensemble**
- **QIAsymphony**

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Current trends in Personalized Healthcare

Three sectors of Personalized Healthcare
- Pharma
- Providers
- Patients

QIAGEN’s focus in PHC
The use of a **companion diagnostic** to predict in advance which patients are most likely to benefit from a particular therapy.
90% of drugs work in 30–50% of individuals

$770B annual global drug sales in 2008 (IMS Health)

$350B annually spent on ineffective medicines globally

Many novel therapies are very effective but only in a proportion of the target population

Identifying a sub-group of patients likely to respond can dramatically increase cost effectiveness of a drug

Personalized Medicine in 2010
Three Major Trends

**Political - Effectiveness to Cost Effectiveness**
- WW acceptance: Money spent on healthcare is finite
- Increased emphasis on health technology assessment (HTA)
  Aim: Increase cost effectiveness of treatments
- Pharmaceutical companies are responding
  Trend: Development of companion diagnostics (CDx)
  to increase cost effectiveness of drugs

**Scientific - Therapies to Targeted Therapies**
- Advancement in understanding of disease processes lead to
target drugs, more closely to specific molecular targets
- Increasing demand for diagnostic tools to identify patients
  with specific disease sub-types, likely to respond to the therapy

**Regulatory - Passive to Active Regulation**
- Regulatory Authorities realized benefits CDx can bring to patients
- Both EMEA and the FDA encouraging pharmaceutical companies
to explore the use of CDx during drug development
- Dx-Rx combination will become an obligate element of
  NDA/BLA submission and product labeling
Example: KRAS Test
KRAS Mutations Predict Non Response to EGFR Inhibitor Therapies

KRAS mutant
no benefit

KRAS normal
significant benefit

“Routine use of KRAS mutational testing in colorectal cancer patients could save the health care system more than $600 million in drug costs alone”
Example: IRESSA
Effective in EGFR+ Patients but Appears to Harm EGFR-ve

Progression-free survival in EGFR mutation positive and negative patients

EGFR mutation positive

Gefitinib (n=132)
Carboplatin / paclitaxel (n=129)
HR (95% CI) = 0.48 (0.36, 0.64)
p<0.0001
No. events gefitinib, 97 (73.5%)
No. events C / P, 111 (86.0)

EGFR mutation negative

Gefitinib (n=91)
Carboplatin / paclitaxel (n=85)
HR (95% CI) = 2.85 (2.05)
p<0.0001
No. events gefitinib, 86 (96.7%)
No. events C / P, 70 (82.4)
Therapies Addressing Epidermal Growth Factor Receptor

Diagnostic Solutions for the EGFR Pathway are Highly Relevant For Many Current and Future Therapies in Oncology

Source: QIAGEN

EGFR = Epidermal Growth Factor Receptor
Exclusive Licence for Biomarker PI3K from John Hopkins University

- QIAGEN to develop RT-PCR and Endpoint-PCR assays for companion diagnostic use with certain cancer treatments
- Provides QIAGEN pharma partnering opportunities to develop and market tests for new cancer drug candidates
- Expands opportunity to develop a series of personalized healthcare diagnostics based on proprietary platform

BKM120

XL147

GDC0941

GSK1059615

PX-866

CAL101
Drugs targeting the EGFR pathway represent <2% of drugs in development
New Wave of Safety Biomarkers

Drugs with pharmacogenetic safety markers

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company</th>
<th>Safety marker</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>GSK</td>
<td>HLA B5701</td>
<td>Rash</td>
</tr>
<tr>
<td>Antibody flucloxacillin</td>
<td></td>
<td>HLA B5701</td>
<td>Liver injury</td>
</tr>
<tr>
<td>Allopurinol</td>
<td></td>
<td>HLA B5801</td>
<td>Severe adverse events</td>
</tr>
<tr>
<td>Carbemazapine</td>
<td></td>
<td>HLA B1502</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>VKORC1</td>
<td>Dose</td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td>CYP2C9</td>
<td>Dose</td>
</tr>
</tbody>
</table>

- Novartis submitted lumiracoxib (Prexige, COX2 inhibitor) and a safety genetic marker (DQA1*0102) to predict liver toxicity for the management of osteoarthritis pain to the European regulatory authorities in December 2009. FDA discussions planned.

- Exanta, an AstraZeneca oral direct thrombin inhibitor which was withdrawn from development in 2006 due to liver toxicity. This was shown to be associated with HLA alleles DRB1(*)07 and DQA1(*)02 but AZ has not announced any plans to try to use a pharmacogenetic test to rescue this drug.
**Personalized Healthcare – Seems to Be Good All Round**

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Increased effectiveness of therapies</td>
</tr>
<tr>
<td>Doctors</td>
<td>Increased safety in treatment decisions</td>
</tr>
<tr>
<td>Healthcare providers</td>
<td>Better outcomes for less cost</td>
</tr>
<tr>
<td>Pharma companies</td>
<td>Regulatory approval and competitive advantage</td>
</tr>
<tr>
<td>Diagnostic companies</td>
<td>New market opportunities</td>
</tr>
</tbody>
</table>

…but Personalized Healthcare has been a challenging business environment
Understanding the Customers’ Needs
Key to Commercial Success

Pharma wants to sell drugs
- Focus on meeting the needs of the Pharma industry
  - Custom develop companion diagnostic tests
  - Win regulatory approval
  - Distribute and sell products globally

Providers want to save money
- Focus efforts on meeting needs of national health services pharmacy benefit managers and
  - Generate convincing pharmaco-economic data

Patients want better results
- Focus on reducing unnecessary drug usage or selecting best treatment
- Find way of selling benefits to patients and doctors
- Be prepared to invest in marketing
Deliver Companion Diagnostics
Seven Critical Issues

Clinical
- Sufficient data to demonstrate the clinical utility

Technical
- Assays need to be reliable, robust, and compatible with diagnostic lab operations

Regulatory
- Approval needed for the drug, the diagnostic, and (in USA) the instrument

Availability
- Needs to match the distribution of the drug – global if there is a pharma partner

Reimbursement
- Who will pay for the test and how much

Legal
- Are all technology and gene licenses in place

Commercial
- Different models needed depending on level of drug company involvement
The Economics of Companion Diagnostic Development

Demonstrating “clinical utility” requires a clinical trial of both the drug and the diagnostic

- A Phase III trial of a cancer drug can cost over $100M
- A standalone clinical trial for the companion diagnostic can easily run over $20M
- Using typical reimbursement prices, the market for a typical cancer drug companion diagnostic is $20-50M per annum

The need to demonstrate clinical utility linked to a specific drug means that diagnostic companies cannot normally develop their own companion diagnostics.
Five Ways to Demonstrate Clinical Utility

1. **Stand alone**
   Diagnostic company can identify a way to gain IP on an assay and generate sufficient returns to pay for the investment in discovery and clinical development.

2. **Partnership (Piggy Back)**
   Drug industry requires a companion diagnostic to effectively market its therapies and works with a partner to make this happen.

3. **FDA assent**
   FDA are eager to promote personalized medicine and have relabeled a number of drugs to include a reference to personalized medicine e.g. Warfarin, Irinotecan, or 6MP.

4. **One-stop shop**
   Integrate Drug and Diagnostic Delivery.

5. **Short cut**
   Introduce tests based on early data – prior to rigorous demonstration of clinical utility.
# Features of CDx Business Models

<table>
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<tr>
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<th>Stand alone</th>
<th>Partnership</th>
<th>FDA Assent</th>
<th>Short cut</th>
<th>One-stop shop</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs</td>
<td>High - Dx co-funded clinical</td>
<td>Revenue generating</td>
<td>Low – no clinical</td>
<td>Medium – minimal clinical</td>
<td>High – part of drug development</td>
</tr>
<tr>
<td>Revenues</td>
<td>High – Dx driven</td>
<td>Medium - Rx driven</td>
<td>Low – Dx driven</td>
<td>Low - medium</td>
<td>Low – not significant</td>
</tr>
<tr>
<td>Marketing</td>
<td>Independent</td>
<td>Rx co-supported</td>
<td>Independent if generic</td>
<td>Independent or payor</td>
<td>Rx/Dx partnership</td>
</tr>
<tr>
<td>Exclusivity</td>
<td>IP driven</td>
<td>Clinical trial and IP</td>
<td>None or IP driven</td>
<td>None or IP driven</td>
<td>Clinical trial or IP</td>
</tr>
<tr>
<td>Risk</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
<td>Medium</td>
<td>High</td>
</tr>
<tr>
<td>Regulatory Pathway</td>
<td>LDT or 510K</td>
<td>IVD - PMA</td>
<td>IVD – 510K</td>
<td>LDT</td>
<td>IVR - PMA</td>
</tr>
<tr>
<td>Examples</td>
<td>Genomic Health, XDx, etc.</td>
<td>QIAGEN, (DxS), Monogram, Dako</td>
<td>Osmetech Third Wave</td>
<td>Caris, Clarient</td>
<td>Roche</td>
</tr>
<tr>
<td>Location</td>
<td>Geographic</td>
<td>Global</td>
<td>USA</td>
<td>USA</td>
<td>Global</td>
</tr>
</tbody>
</table>
Pharma Partnership
The Most Attractive for QIAGEN

- Funding for CDx development
- Clinical utility issue solved
- Drug success guarantees market
- Reimbursement levels increasing
- Co-marketing with Pharma and...
- QIAGEN has infrastructure
- QIAGEN has platforms, flanking menu, and Sample & Assay Technologies needed
## QIAGEN – Best Partner for Pharma

Pharma’s Options for Partnered Companion Dx

<table>
<thead>
<tr>
<th></th>
<th>QIAGEN</th>
<th>Small Dx Company</th>
<th>Large Dx Company</th>
<th>Reference Laboratory</th>
<th>Specialized, Small Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Technology Options</strong></td>
<td>Broad</td>
<td>Limited</td>
<td>Limited (in Mdx)</td>
<td>Broad</td>
<td>Limited</td>
</tr>
<tr>
<td><strong>Platform presence</strong></td>
<td>Broad</td>
<td>Limited</td>
<td>Broad</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Independency from Pharma</strong></td>
<td>Fully independent</td>
<td>? Can change fast</td>
<td>Mostly NOT given</td>
<td>Given</td>
<td>? Can change fast</td>
</tr>
<tr>
<td><strong>CDx Experience</strong></td>
<td>Yes</td>
<td>Possibly</td>
<td>Selectively</td>
<td>Possibly</td>
<td>Possibly</td>
</tr>
<tr>
<td><strong>Global presence</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Regulatory</strong></td>
<td>Yes</td>
<td>Limited</td>
<td>Yes</td>
<td>Selectively</td>
<td>Limited</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Yes</td>
<td>Limited</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Menu options</strong></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Access to physicians</strong></td>
<td>Yes</td>
<td>Limited</td>
<td>Rare</td>
<td>Yes</td>
<td>Possibly</td>
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## Meeting the Needs of Pharma
### High Speed and Low Risk

<table>
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<th>Requirement</th>
<th>Solution</th>
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<tr>
<td>Regulatory strength and experience with the FDA</td>
<td>QIAGEN are setting the agenda with KRAS and EGFR PMAs</td>
</tr>
<tr>
<td>Technology, platform and assays</td>
<td>Own both chemistry and instrumentation</td>
</tr>
<tr>
<td>Rapid and reliable development and approval process</td>
<td>Tried and tested process</td>
</tr>
<tr>
<td>Access to biomarker IP</td>
<td>Part of the QIAGEN strategy to discover and to license</td>
</tr>
<tr>
<td>Route to market for the CDx</td>
<td>Own sales channels</td>
</tr>
<tr>
<td>Expertise and experience</td>
<td>World leaders</td>
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Partnering with the Pharmaceutical Industry

Dx pathway

Identify Relevant Biomarkers (GeneGlobe, SABiosciences)
Used by pharma on preclinical and clinical samples

Develop Approved CDx products (DxS)
Used by pharma on clinical trial patients

Sell Companion Diagnostics (QIAGEN)
Used by diagnostic labs on samples of "real" patients

Rx pathway

Drug development Phase I and II

CDx co-development agreement in place

Drug development Phase II and III

Sell Drugs

Coordinated submissions to FDA

CDx co-development agreement in place

Coordinated submissions to FDA

QIAGEN Analyst and Investor Day, February 11, 2010
Sample & Assay Technologies
QIAGEN’s value proposition for Pharma partners:

- A significant supplier to Pharma discovery and development
- Owner of vast technology portfolio in molecular sample and assay technologies
- Full infrastructure for pharma co-developments
- A leader in molecular diagnostics
  - Own diagnostic platforms with installed base
  - Regulatory depth
  - Sales channel strength
  - Intellectual property – platform and content
  - Global reach
- Independence
Development Agreement with Pfizer Inc

- EGFRvIII companion diagnostic for Phase II immunotherapy vaccine against Glioblastoma multiforme (GBM)
  - GMB is most common and most aggressive primary brain tumor in adults
  - GMB occurs in ~25,000 patients annually
  - EGFRvIII mutated in 25-40% of GMB tumors
- RT-PCR assay to identify tumors with mutated EGFRvIII
### QIAGEN in the Wider Personalised Healthcare Market

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<th>Pharma Partnership</th>
<th>Provider Cost Saving</th>
<th>Patient Outcomes</th>
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<tr>
<td>Global leader in companion diagnostics</td>
<td>Provide reagents</td>
<td>Monitor opportunities</td>
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<tr>
<td>Full infrastructure for partnerships</td>
<td>QIAGEN not active in reference lab market</td>
<td>Sensitive to changes in reimbursement practice</td>
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<td>Highest priority</td>
<td>Seek partnerships to productise lab tests</td>
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- Global leader in companion diagnostics
- Full infrastructure for partnerships
- Highest priority
- Provide reagents
- QIAGEN not active in reference lab market
- Seek partnerships to productise lab tests
Summary

QIAGEN is currently the world leader in the provision of companion diagnostics

The opportunity exists to maintain this lead as the market expands, thereby creating a substantial companion diagnostics business

The challenges for the future are all about managing growth and delivering on expectations
Thank you!