# QIAGEN

Sample & Assay Technologies

## New Approaches in Biomarker Detection

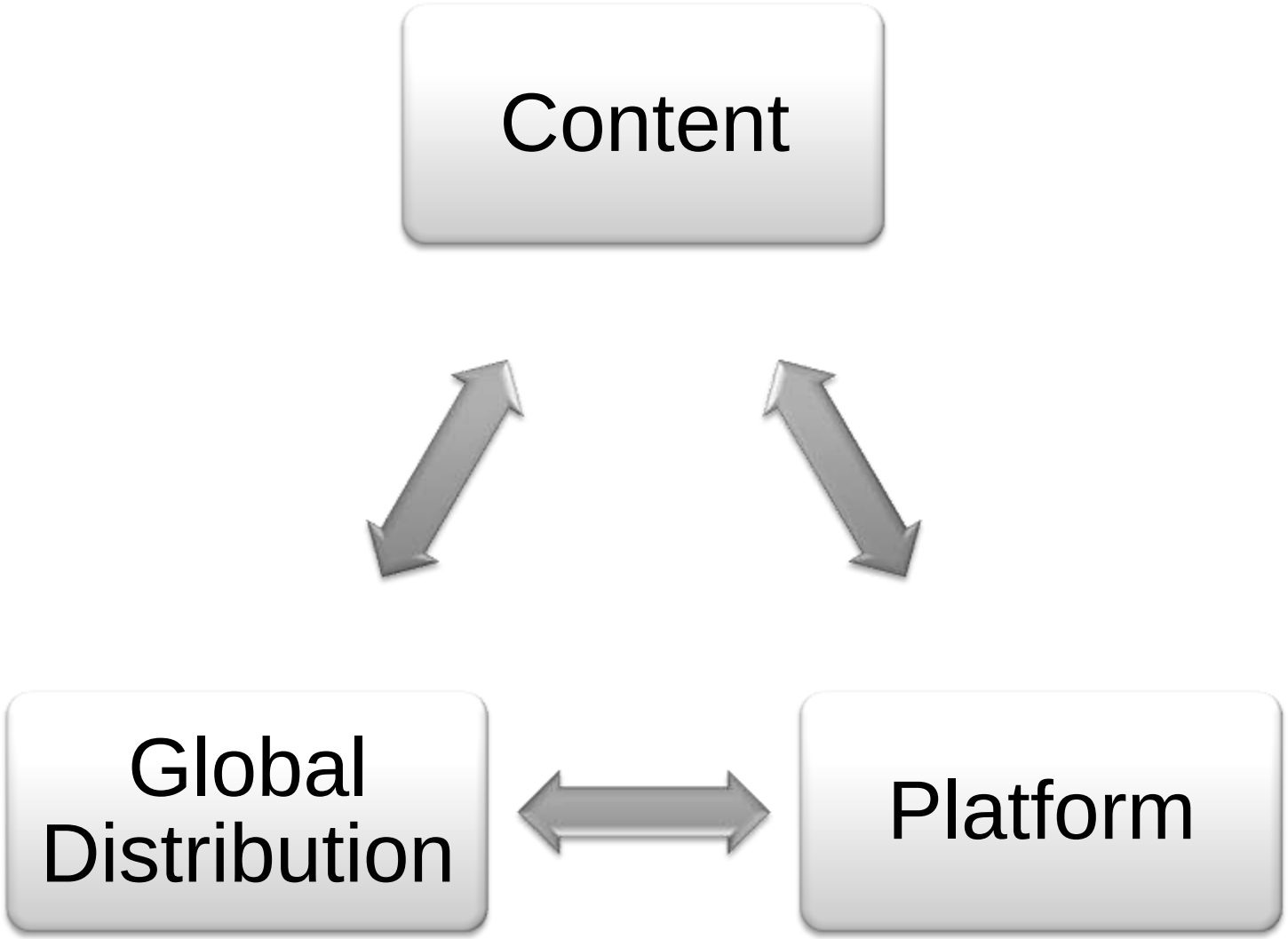
SEAP/SEC/SEPAF
Zaragoza May 2011

Dr. Stephen Little
Vice President Personalized Healthcare

DxS Diagnostic Innovations

**‘DxS is a Personalised Medicine Company that meets the needs of the pharmaceutical industry for biomarkers and companion diagnostics to support the development and then sales of cancer therapies.’**

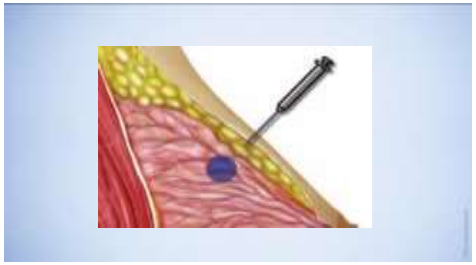
# The Holy Trinity of Successful Molecular Diagnostic Companies



# QIAGEN Sample & Assay Technologies:

## Elucidating information from biological samples

**Complex sample**



**Pure Analyte**

**Information**

# QIAGEN products:
## Sample & Assay Technologies on Automated Platforms

Sample Technologies

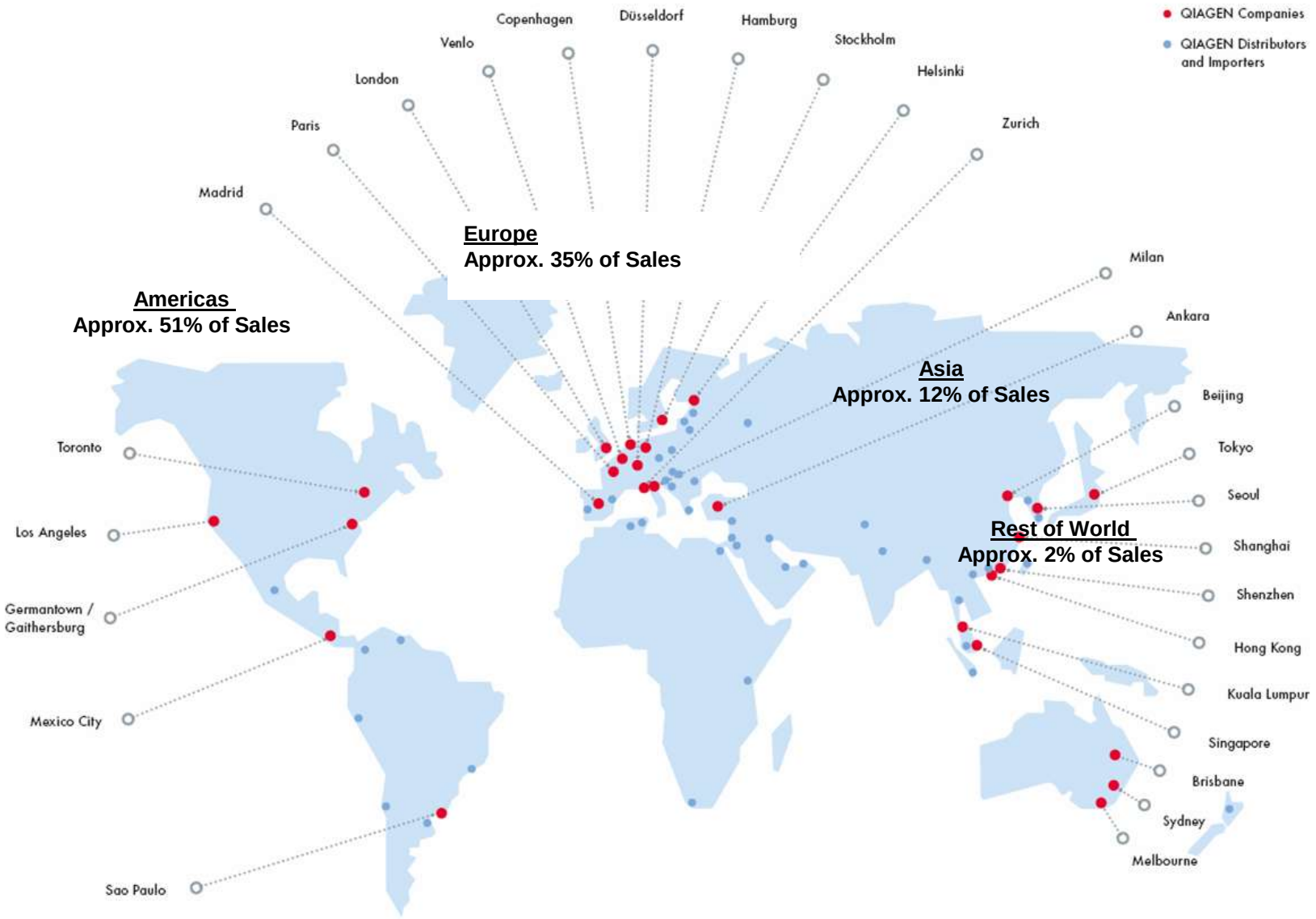
Assay Technologies

Fully Automated Platforms

# QIAsymphony = Our Medium-throughput System…


**…can process up to 200 samples per day – very broad test menu available**

# QIAGEN's Global Footprint



# QIAGEN at a Glance: A focused Market Leader




## Revenues

- $1’010 million
- Industry-leading growth
- 17% from products under 3 years old
- Molecular Sample & Assay Technologies
- Majority of sales in Molecular Diagnostics

## Infrastructure and Innovation

| | |
|---|---|
| Customers | >400,000 |
| Employees | 3’500 |
| R&D | $120 million |
| Presence | Global |

(1) All numbers projected 2008

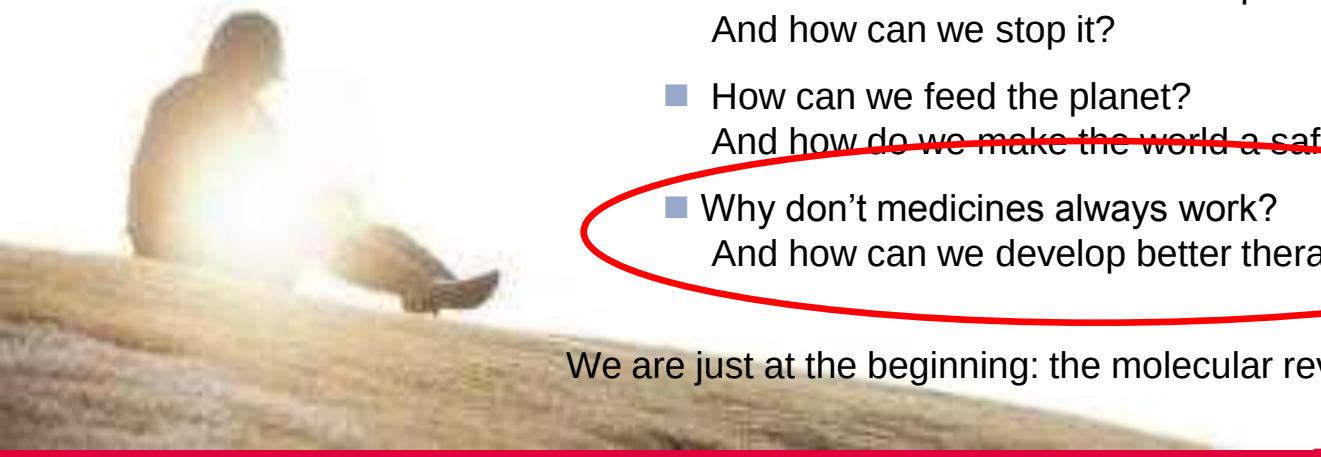
# The Age of Molecular Information

We have entered the age of molecular information.

To understand the molecular basis of life, the global research community invests more than **US$ 120.000.000.000** a year**.**

Molecular information will improve our health, our lives, and our environment

- What makes humans different?
  And what is unique?
- Who will develop disease?
  And how do we prevent it?
- What is the difference between health and illness?
  And how do we diagnose it?
- What causes a cancer to develop?
  And how can we stop it?
- How can we feed the planet?
  And how do we make the world a safer place?
- Why don't medicines always work?
  And how can we develop better therapies?



We are just at the beginning: the molecular revolution has barely started!

# QIAGEN's 4 "P" Framework in MDx

| | LABORATORY BASED TESTING | | | POINT OF NEED |
|---|---|---|---|---|
| | Prevention<br><br>*Asymptomatic patients*<br>*Goal: Early detection* | Profiling<br><br>*Symptomatic patients*<br>*Goal: Confirm* | Personalized Healthcare<br>*Pre-diagnosed patients*<br>*Goal: Guide therapy* | *Rapid turnaround needed*<br>*No laboratory reachable*<br>*Goal: fast result, on spot* |
| Assay Technologies | Narrow portfolio<br>High volume/<$20/assay | Broad portfolio<br>High value,<br>low volume | Growing portfolio<br>High value,<br>low volume | Emerging segment<br>Instrument <$2k,<br>Assays: $3-30 |
| | Examples<br>• HPV<br>• Chlamydia/NG<br>• 5 additional assays in pipeline<br>• More to come | Examples<br>• CMV<br>• EBV<br>• HBV<br>• HIV<br>• HCV<br>• Influenza | Examples<br>• KRAS<br>• EGFR<br>• BRAF<br>• PI3K<br>• Pathogen Genotyping | Examples<br>• careHPV<br>• HAI<br>• Influenza |
| Instruments | High throughput<br>Continuous load | Random access<br>Continuous load | Random access<br>Continuous load | Portable test systems<br>Rapid turn around < 2hrs |
| | QIA*ensemble* | QIA*symphony* | QIA*symphony* | *TBA* |
| Assay Design | Fast, typically isothermal amplification or no amp | PCR<br>Pyrosequencing | PCR<br>Pyrosequencing | Isothermal amplification |

# Focusing on Personalized Healthcare

| | LABORATORY BASED TESTING | | | POINT OF NEED |
|---|---|---|---|---|
| | Prevention<br><br>*Asymptomatic patients*<br>*Goal: Early detection* | Profiling<br><br>*Symptomatic patients*<br>*Goal: Confirm* | Personalized Healthcare<br>*Pre-diagnosed patients*<br>*Goal: Guide therapy* | <br><br>*Rapid turnaround needed*<br>*No laboratory reachable*<br>*Goal: fast result, on spot* |
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| | Examples<br>HPV<br>Chlamydia/NG<br>5 additional assays in pipeline<br>More to come | Examples<br>CMV<br>EBV<br>HBV<br>HIV<br>HCV<br>Influenza | Examples<br>KRAS<br>EGFR<br>B-RAF<br>PI3K<br>Pathogen Genotyping | Examples<br>careHPV<br>HAI<br>Influenza |
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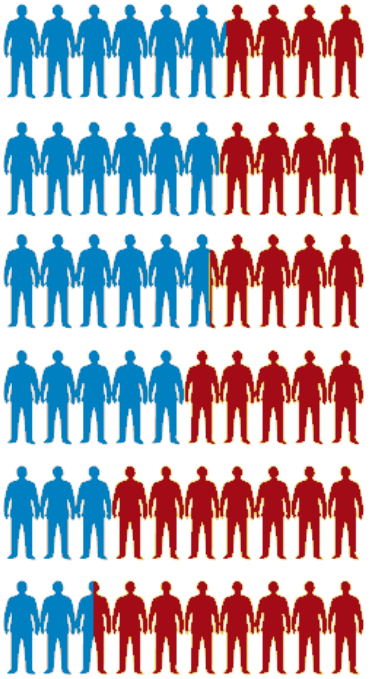
# The problem: Drugs do not always work

| Drug | Efficacy |
|---|---|
| Anti-Depressants | 62% |
| Asthma | 60% |
| Diabetes | 57% |
| Arthritis | 50% |
| Alzheimer | 30% |
| Cancer | 25% |



= Drug does not work

**Good drugs go to the wrong patients**

Quelle Brian B. Spear, Margo Heath-Chiozzi, Jeffrey Huff, "Clinical Trends in Molecular Medicine, Volume 7, Issue 5, 1 May 2001, Pages 201-204

# Personalized Healthcare


The use of a companion diagnostic to predict in advance which patients are most likely to benefit from a particular therapy

# Personalized Healthcare

## The 5 “P”s - Good All Round


| Stakeholder | Benefit |
|---|---|
| Pharma companies | Regulatory approval<br>Competitive advantage<br>Increase cost effectiveness of drug |
| Physicians | Increased safety in treatment decisions<br>Start directly with right treatment and<br>Save valuable time |
| Payers | Increase efficiency of therapies<br>Save money in healthcare systems |
| Patients | Best therapy available<br>Avoid unnecessary side-effects |
| Providers<br>(Dx companies, labs) | New market opportunities |

**But despite its obvious benefits this has been a challenging business environment**

# Personalized Medicine in 2011
## Three Major Drivers


**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
- Increased sequencing power uncovers more potential biomarkers

**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

# How does the PHC market work?

Market is influenced by other stakeholders

- Patients - better outcomes
- Pharma – sell more drugs
- Providers – spend less money

Diagnostic Tests ordered by Doctors

- Clinical Utility
- Benefit to Patients

Diagnostic Tests are provided by Diagnostic Labs

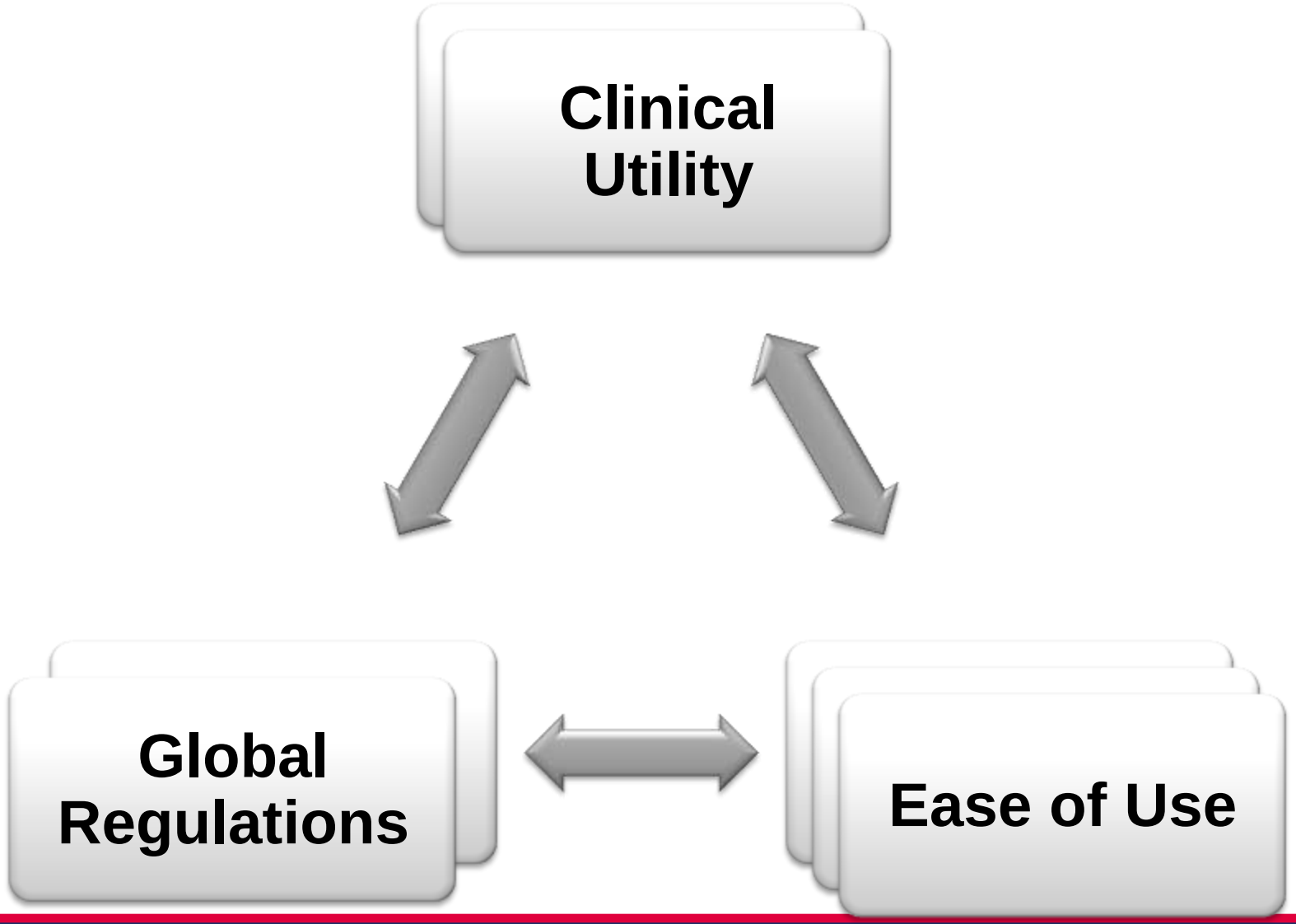
- Major Reference Labs
- Smaller Hospital Labs
- Specialised Labs

Labs can also develop their own tests (LDTs)

Diagnostic Products are supplied by Diagnostic Companies

- Small number of global players with complete systems
- Larger number of companies offering partial solutions

# 4 Critical Success Factors for translation of biomarker to Companion Diagnostics



# Cost of Diagnostic Product Development


**$40M**
**Plus additional cost of drug clinical trial**

# Understanding the Market Segments
## 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 and pharmacy benefit managers
- 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

# Drug/Diagnostic Partnerships are driving the field forward

- Share the cost of CDx development
- Clinical utility issue solved
- Drug success guarantees market
- Unique content encourages platform uptake
- Co-marketing with Pharma

and..

- QIAGEN has infrastructure
- QIAGEN has platforms, flanking menu and Sample & Assay Technologies needed

# Understanding the needs of Pharma – high speed and low risk


1. Don’t let the <u>development</u> of the diagnostic slow up drug development

2. Don’t let <u>regulatory</u> approval of the diagnostic  slow up drug approval

3. Don’t let the <u>availability</u> of the diagnostic limit uptake of the drug

# The CDx roadmap - 3 stages in the life of a CDx

| Tools for Biomarker Selection | Development and Regulatory Expertise | Platform and product distribution and marketing |
|---|---|---|

**Identify Biomarkers** → **Develop Approved CDx** → **Sell CDx**

**Used by pharma on preclinical and clinical samples**

**Used by pharma on clinical trial patients**

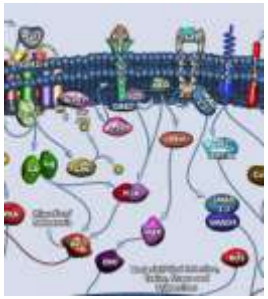
**Used by diagnostic labs on samples of „real“ patients**

**Drug development Phase I and II** → **Drug development Phase II and III** → **Sell Drugs**

Rx pathway

# Stage I – Biomarker selection and CDx strategy

**Identify Biomarkers**



**Drug development Phase I and II**

- **Which biomarkers correlate with drug response?**
- **Is there a business case for moving forward with a CDx?**
- **If we were to progress to a CDx what would the biomarkers be?**

# Drivers of PHC within the pharmaceutical industry

- Influence of the regulatory authorities
  - No approval without a CDx
- Increased cost-effectiveness
  - Makes reimbursement easier
- More competitive products
  - Doctors prefer drugs that work
- Increased chance of a successful pivotal trial
  - Use of a CDx may not always reduce cost but can increase likelihood of success
- Precedent
  - Several high profiles examples such as Amgen's Vectibix, Lilly's Erbitux and AstraZeneca's Iressa have shown the viability of the approach

# Stage II Co-development and approval of Rx and CDx

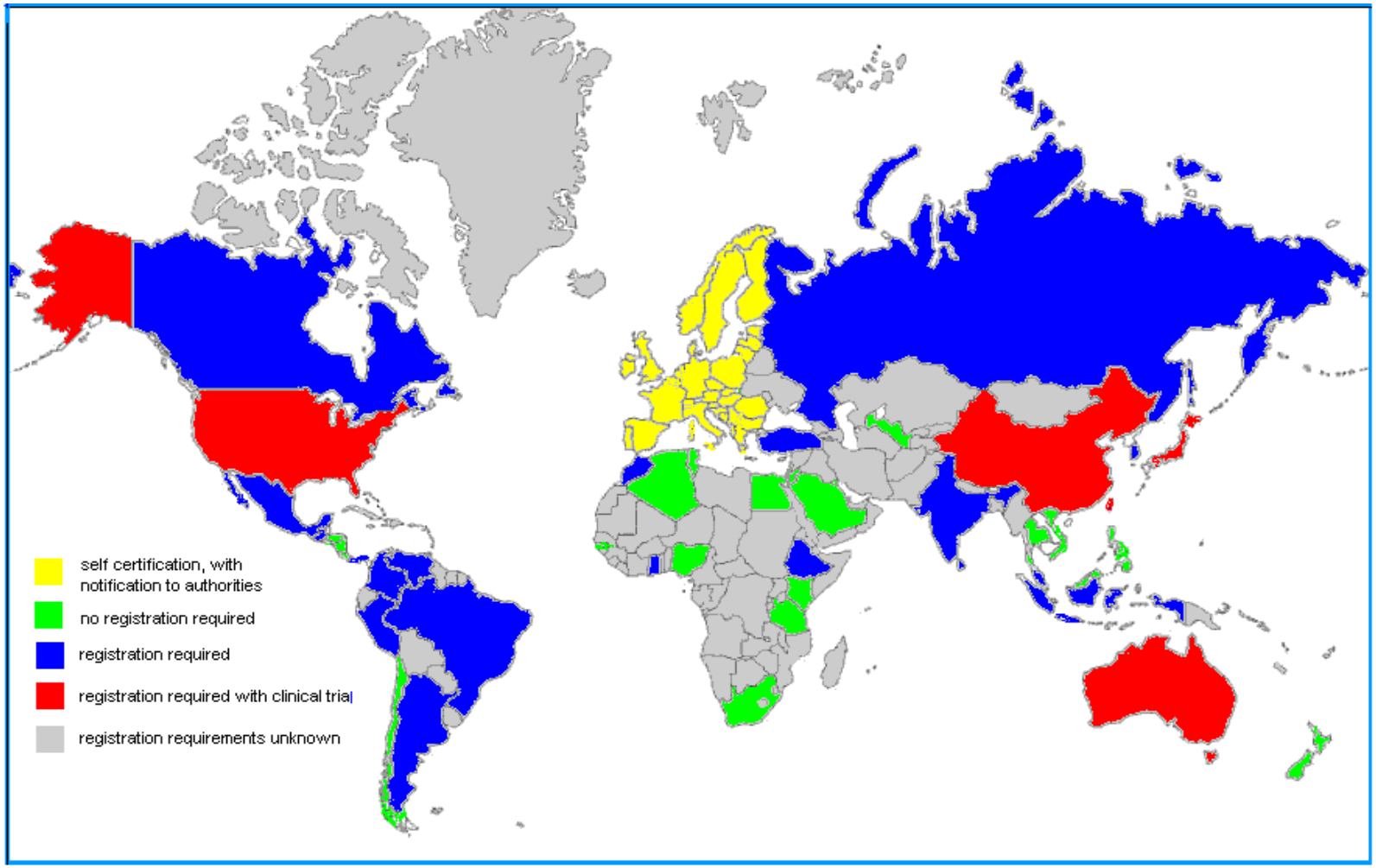
**Develop Approved CDx**

**Used by pharma on clinical trial patients**

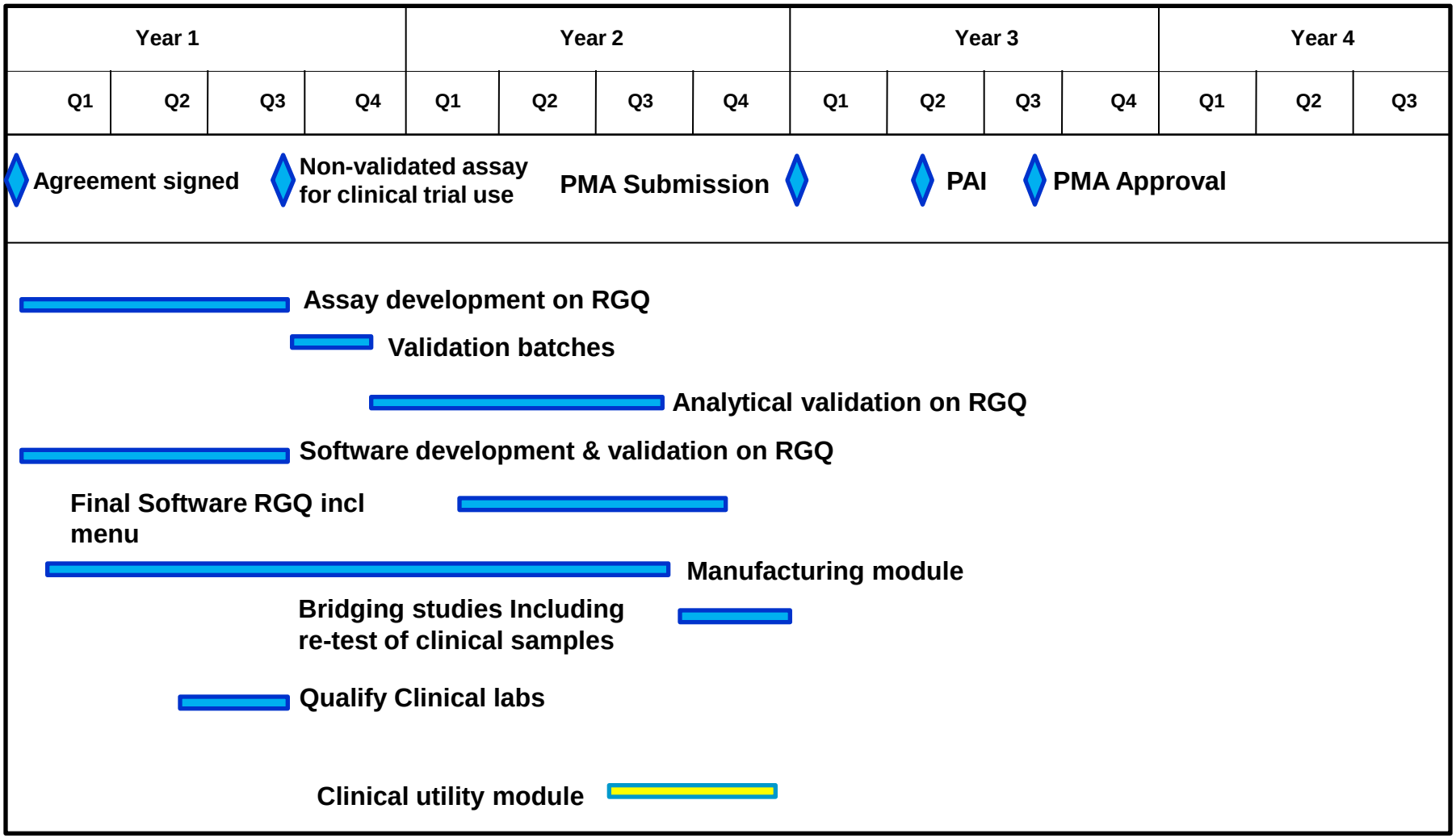
**Drug development Phase II and III**

- **Activities primarily driven by the requirement s of the regulatory agencies**
- **Target markets for the Rx set the regulatory requirements for the CDx**
- **Ideally the final version of the diagnostic will be available for the start of the phIII trial but if not there are bridging and design strategies available**
- **The choice of platform and technology at this stage will have a big impact on future commercial success**

# Global *In vitro* diagnostic regulatory systems



# Companion Diagnostic – Generic Timescale



# Stage III – Co-marketing

**Sell CDx**

**Used by diagnostic labs on samples of „real“ patients**

**Sell Drugs**

**• The CDx product must be readily adopted by the laboratories which will offer the test to the medical community**

- Reimbursement and Price
- Regulatory status
- Platform footprint
- IP
- Workflow

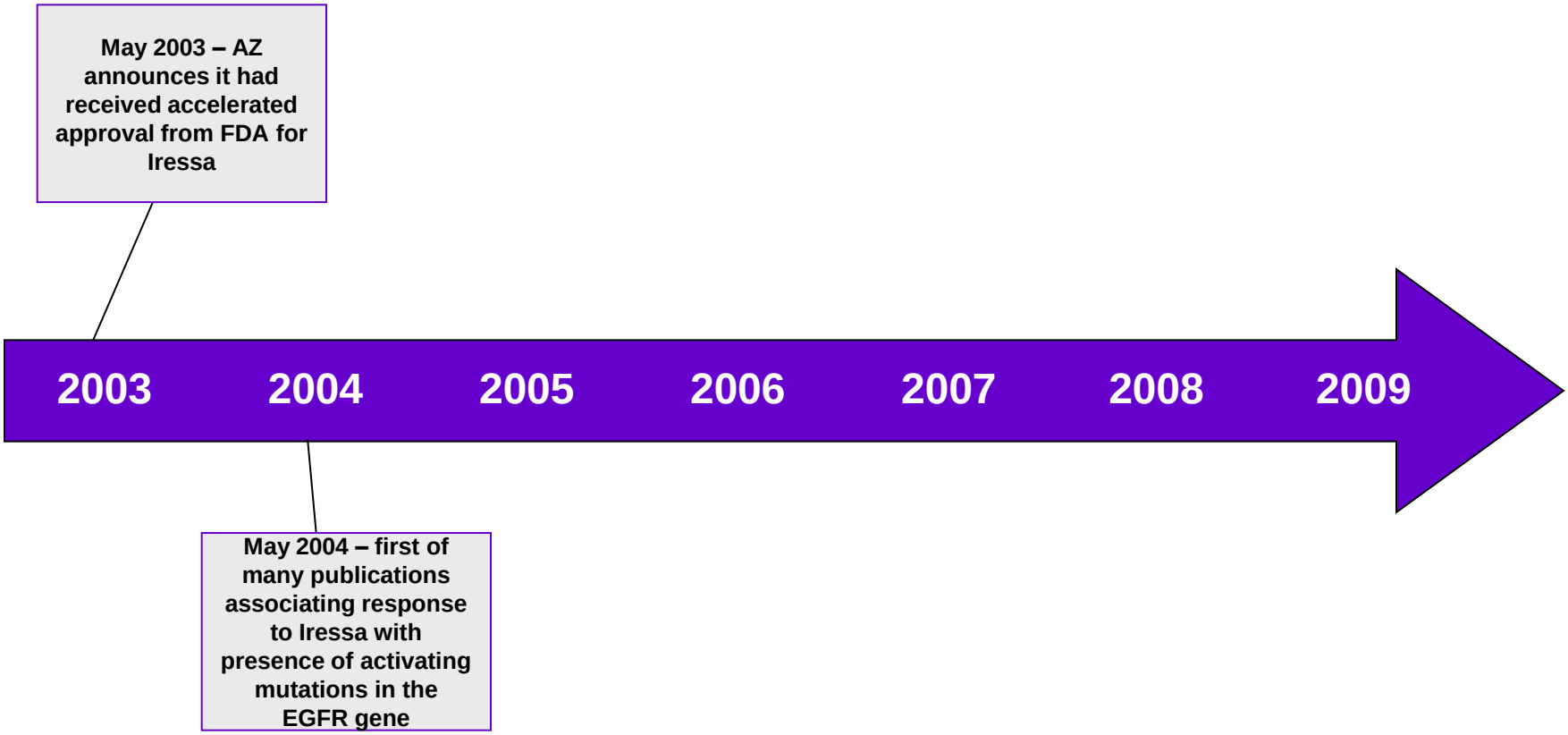
**•The test must be seen to be valuable by the medical community**

- Clinical utility
- Advocacy
- Professional organisations

# Iressa


30
IRESSA
(gefitinib tablets)
250 mg
For Oncology Use Only
AstraZeneca

# Iressa time-line



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

# Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

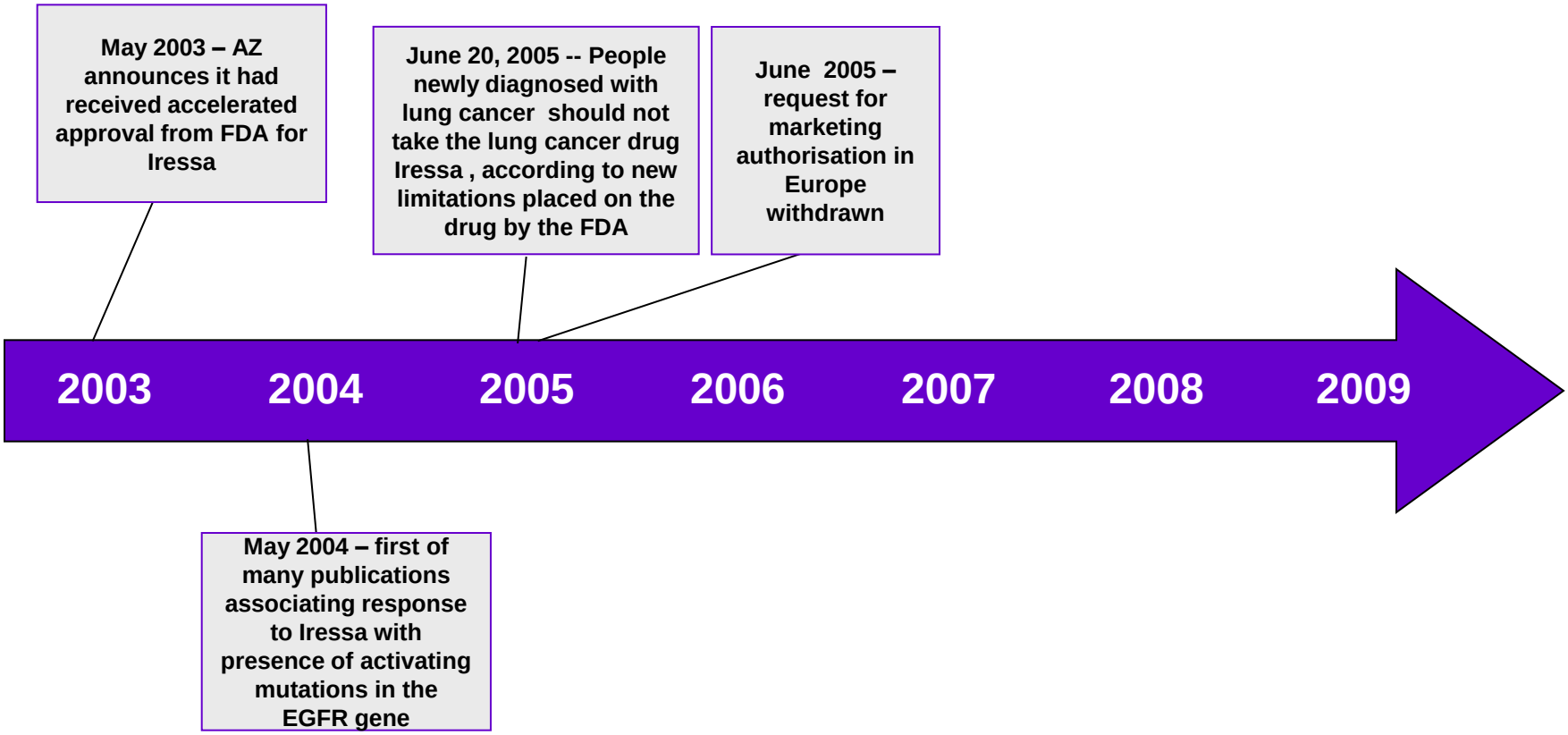
Sciencexpress Report

## *EGFR* Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

[1]Departments of Medical Oncology and Cancer Biology, Dana-Farber Cancer Institute, Boston, MA 02115 USA. [2]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA 02115, USA. [3]Departments of Pathology and Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA 02115, USA. [4]The Broad Institute at MIT and Harvard, Cambridge, MA 02142, USA. [5]Genetics Branch, National Cancer Institute, National Naval Medical Center, Bethesda, MD 20889, USA. [6]Department of Pathology, Brigham and Women's Hospital, Boston MA 02115, USA. [7]Department of Surgery 2, Nagoya City University Medical School, Nagoya 467-8601, Japan.

# Iressa time-line



## FDA ALERT [6/2005]

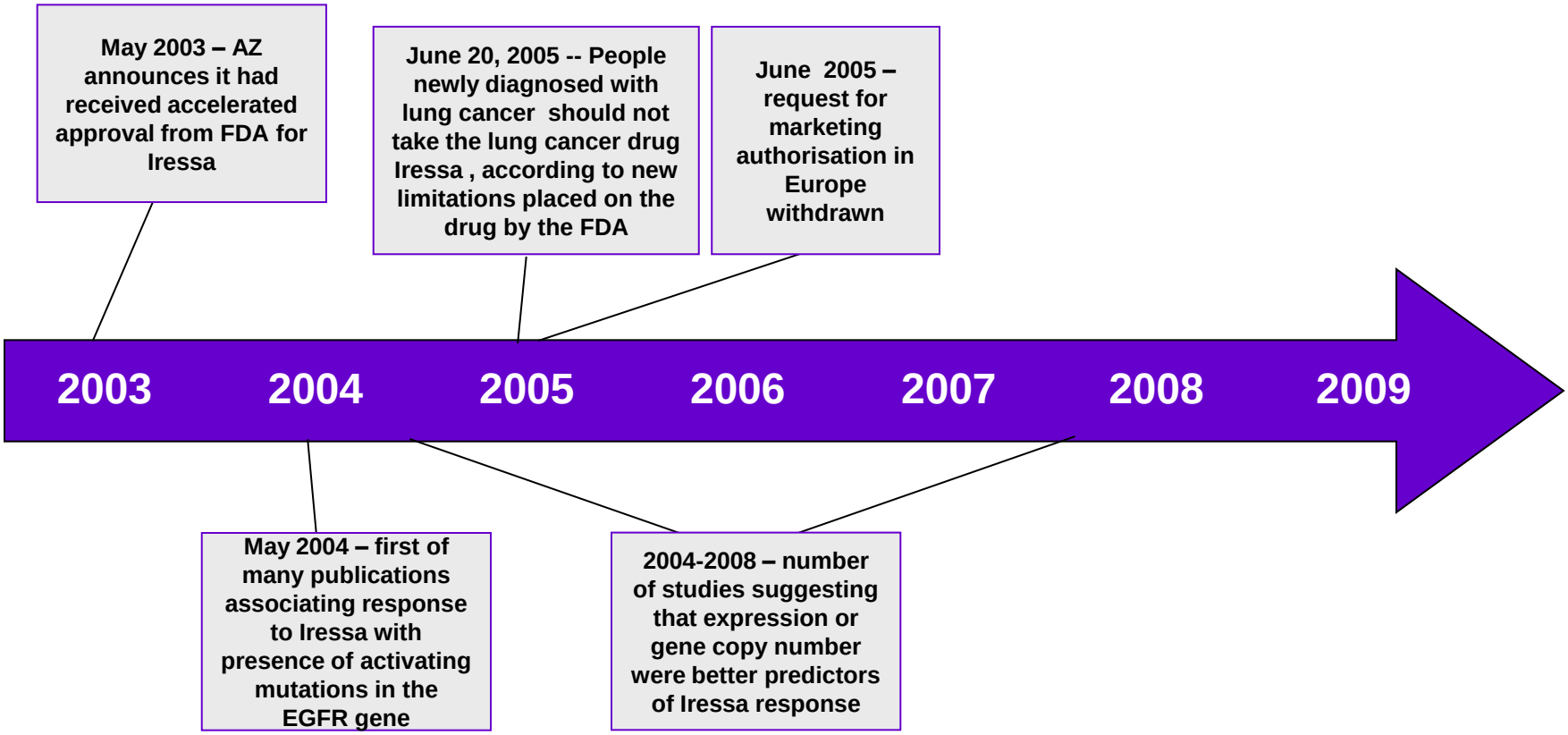
**FDA has approved new labeling for Iressa that states the medicine should be used only in cancer patients who have already taken the medicine and whose doctor believes it is helping them. New patients should not be given Iressa because in a large study Iressa did not make people live longer. There are other medicines for non-small cell lung cancer (NSCLC) that have shown an ability to make people live longer.**

## GEFITINIB (IRESSA™) MARKETING AUTHORISATION APPLICATION WITHDRAWN IN EU

**06/01/05**

**AstraZeneca today announced that it is withdrawing the European Marketing Authorisation Application (MAA) for IRESSA™ (gefitinib) in treating patients with non-small cell lung cancer (NSCLC) from the European Medicines Agency (EMEA**

# Iressa time-line



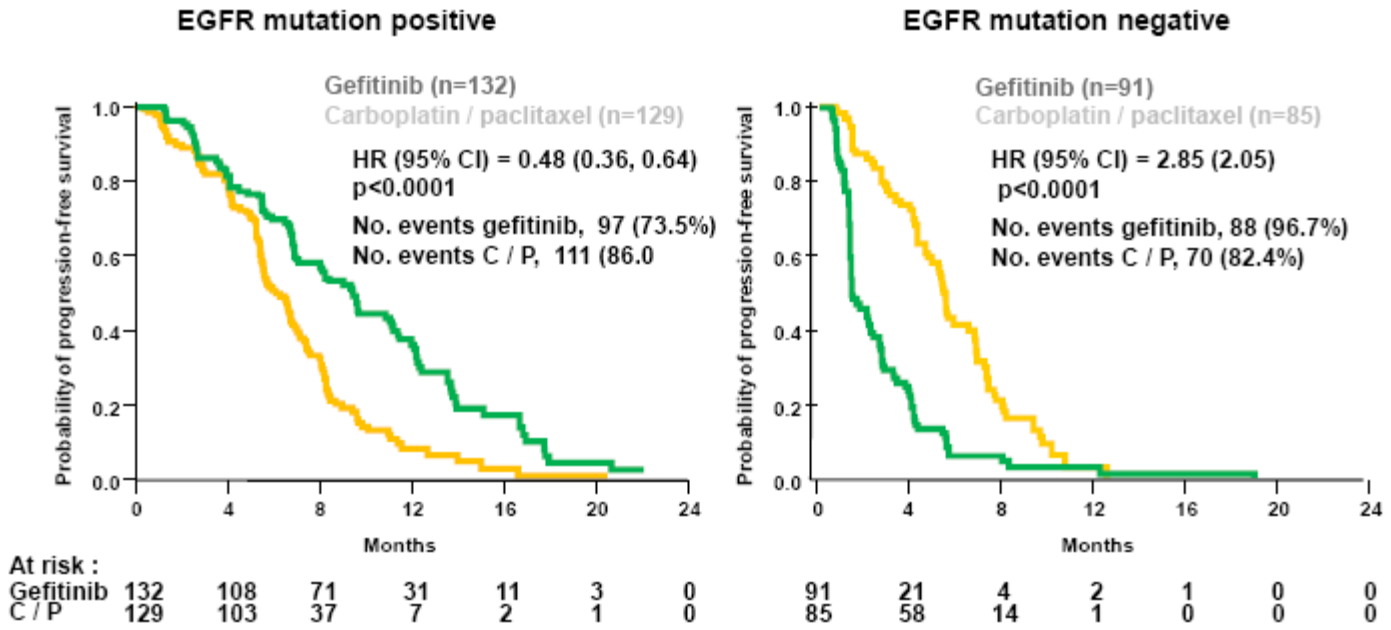
# IPASS – good science is good business

## IPASS Press Conference

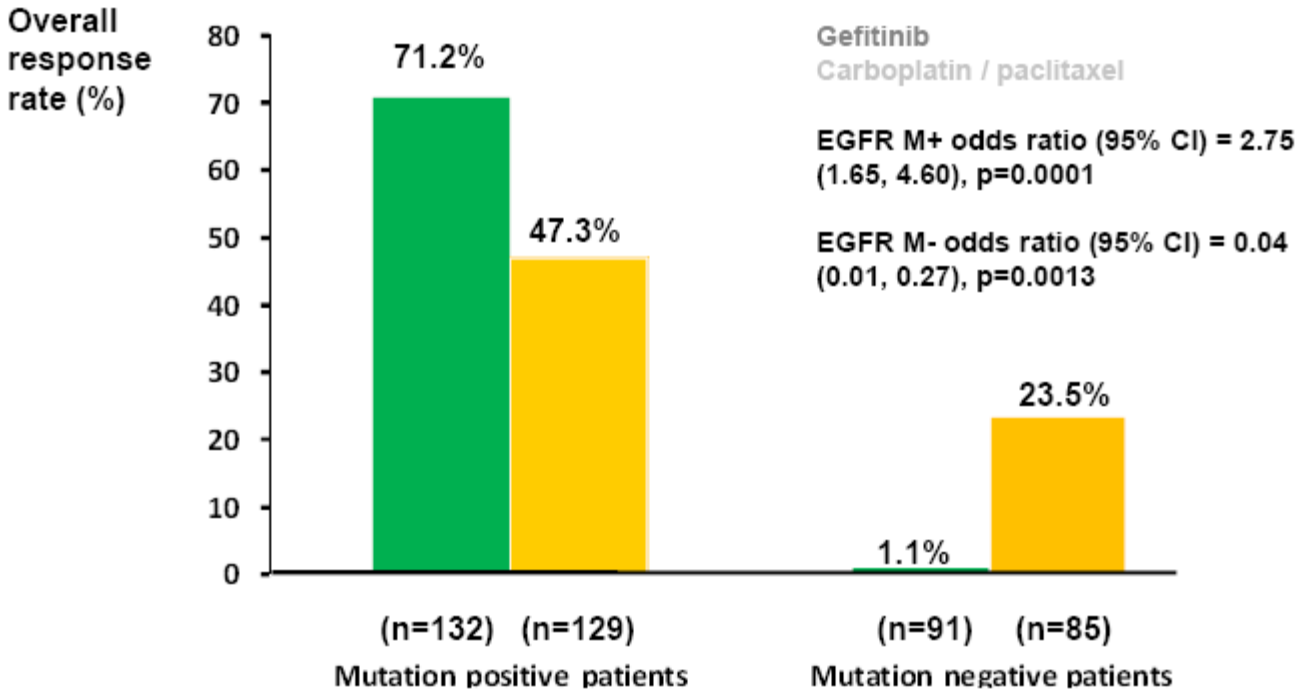
**Professor Tony Mok, Chinese University of Hong Kong**


Phase III, randomised, open-label,
first-line study of gefitinib vs carboplatin / paclitaxel in clinically selected patients with advanced non-small cell lung cancer (IPASS)

# Progression-free survival in EGFR mutation positive and negative patients



# Objective response rate in EGFR mutation positive and negative patients



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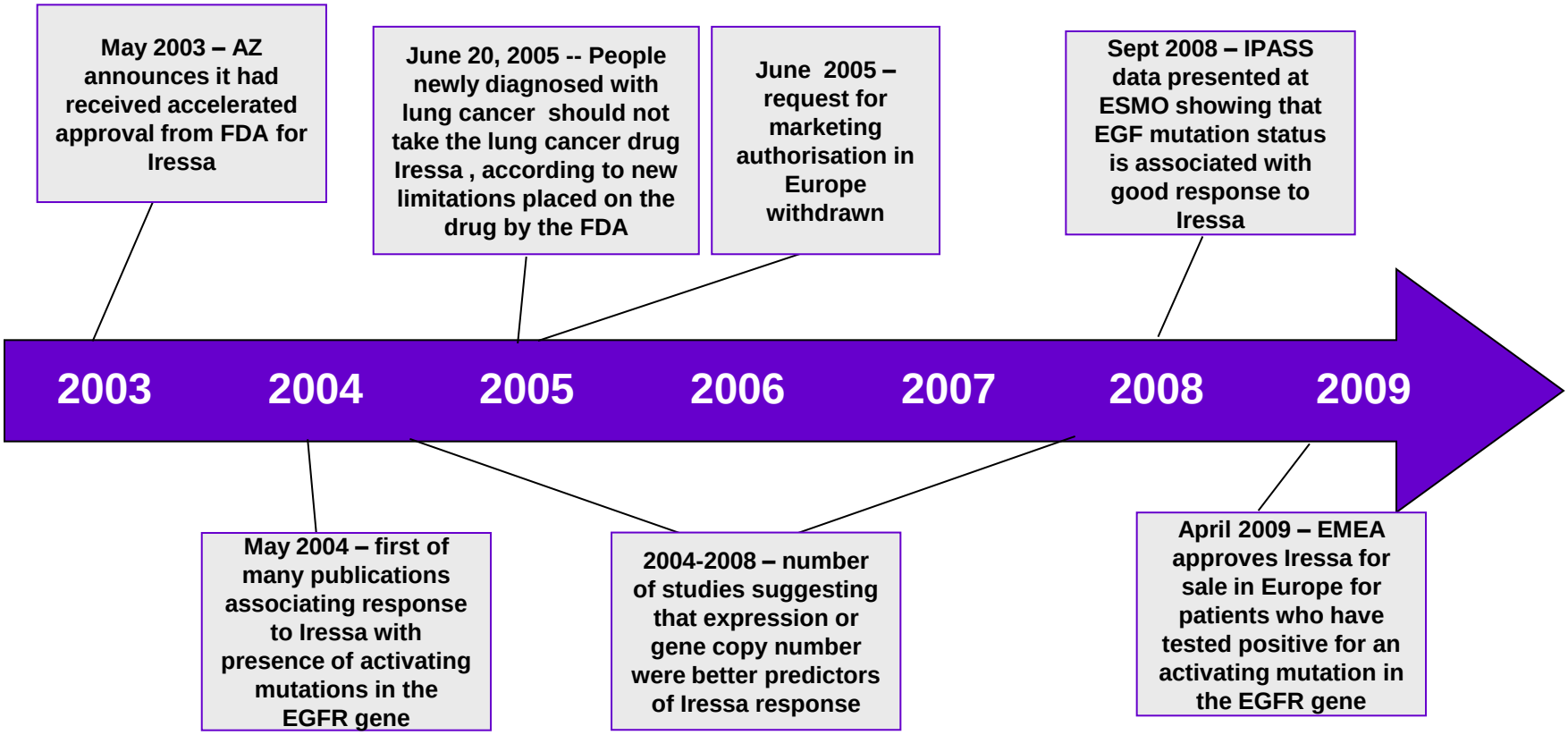


# AstraZeneca announces plan to withdraw US NDA for IRESSA; current US patients have continued access

**February 1, 2011 – Wilmington, DE –** AstraZeneca announced today that it has informed US patients taking IRESSA® (gefitinib), and their prescribing physicians that patients currently benefitting from IRESSA therapy will be able to continue to receive treatment through a clinical study. This action was announced after AstraZeneca informed the US Food and Drug Administration (FDA) that it will be withdrawing the Accelerated Approval New Drug Application (NDA) for IRESSA, effective September 30, 2011. AstraZeneca does not plan to pursue approval for IRESSA in the US.

Patients or physicians in the US with questions about the clinical trial program can call the Information Center at AstraZeneca at 1-800-236-9933.

- ENDS -

**NOTES TO EDITORS:**

**About IRESSA**



# What have we learnt from Iressa and EGFR


- Personalised healthcare becomes a reality when the pharmaceutical and diagnostic industries align
- Following on from pioneering initiatives like IPASS the Rx/Dx business model is now well established and there are many more examples in development
- The more pragmatic view of the European regulators compared to their American cousins appears to encourage innovation
- Data is essential – don't make assumptions about clinical utility

# Why has it taken so long

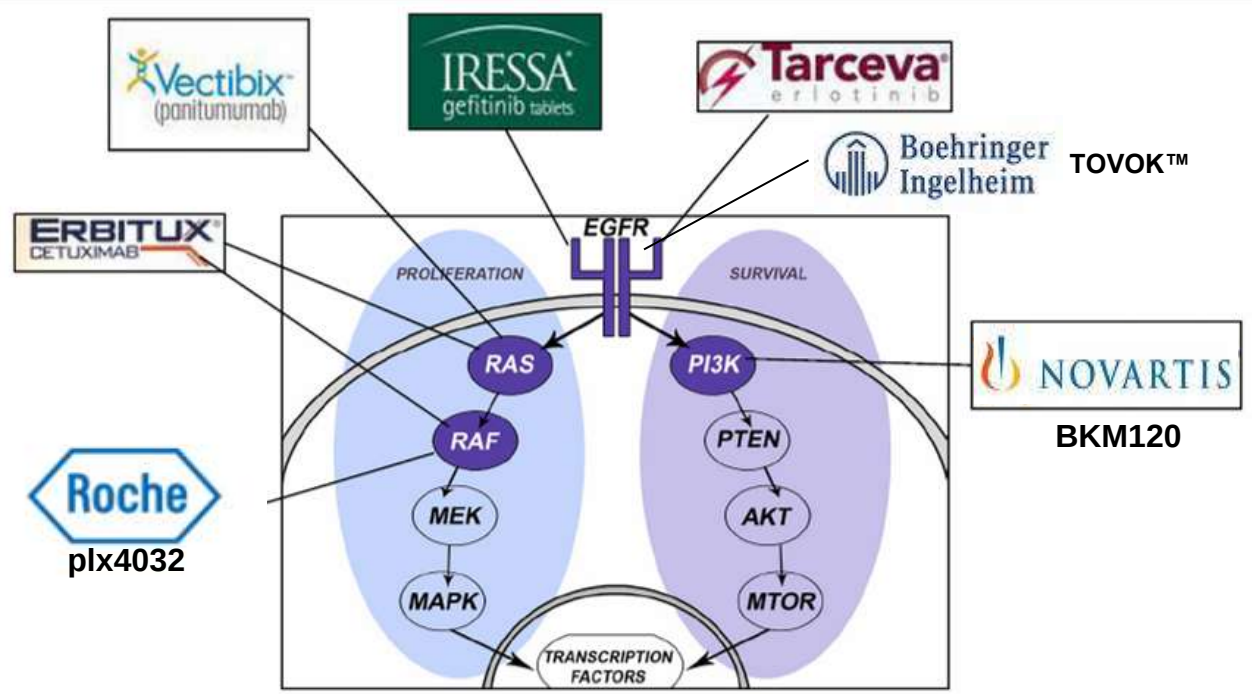
**Pharmaceutical Industry**

- Concerns about market size
- Complexity
- Conservatism

**Diagnostics Industry**

- Cost
- Reward
- Access to Clinical Samples

# Therapies Addressing the EGFR pathway




QIAGEN partners:

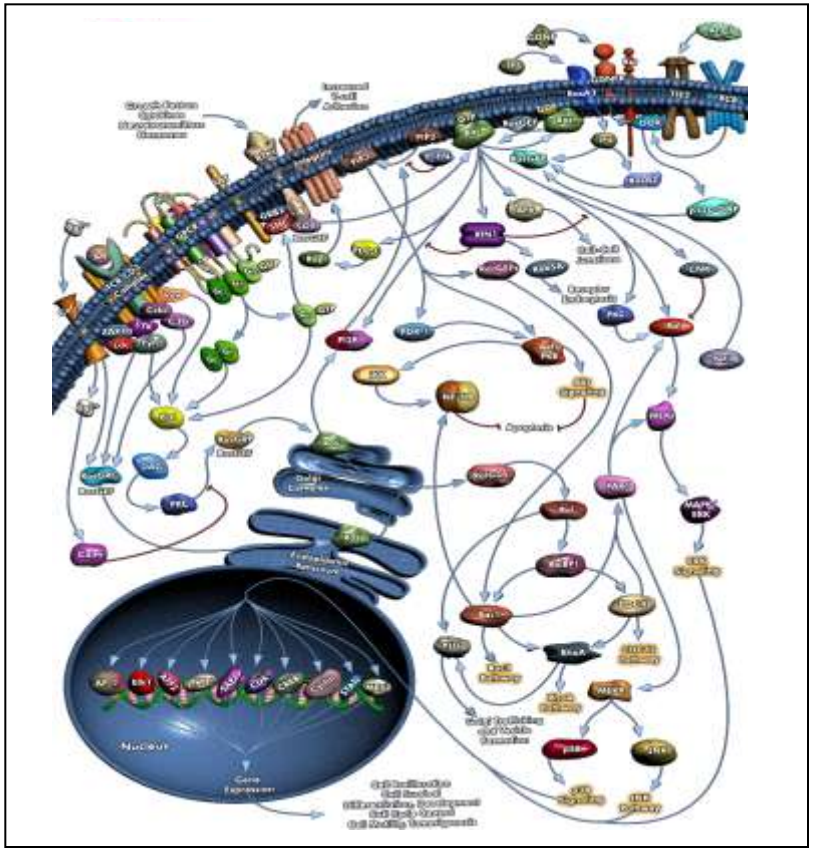
AMGEN AstraZeneca Bristol-Myers Squibb Company Boehringer Ingelheim ImClone Systems Incorporated Lilly MERCK and many more ...

Source: QIAGEN

EGFR = Epidermal Growth Factor Receptor

# Tumor Profiling in the Future

## Pathway Knowledge



## Tumor Panel - Example DNA Analysis

### Predictors of response or resistance or therapy

| | | | | |
|---|---|---|---|---|
| ABL | FGFR3 | MAP2K2 | PTEN | NRAS |
| BRAFT | FGFR4 | MAP2K4 | RETT | HRAS |
| FGFR1 | FLT3 | MET | SRC | AR |
| FGFR2 | MAP2K1 | PIK3CA | MCL1 | ERBB3 |
| AKT1 | AKT2 | AKT3 | ERCC1 | ERBB4 |
| ESR1 | EGFR | KRAS | RARAT | KIT |
| CEBPA | JAK2 | NMP1 | PDGFR | BRCA |

### Indicators of Prognosis

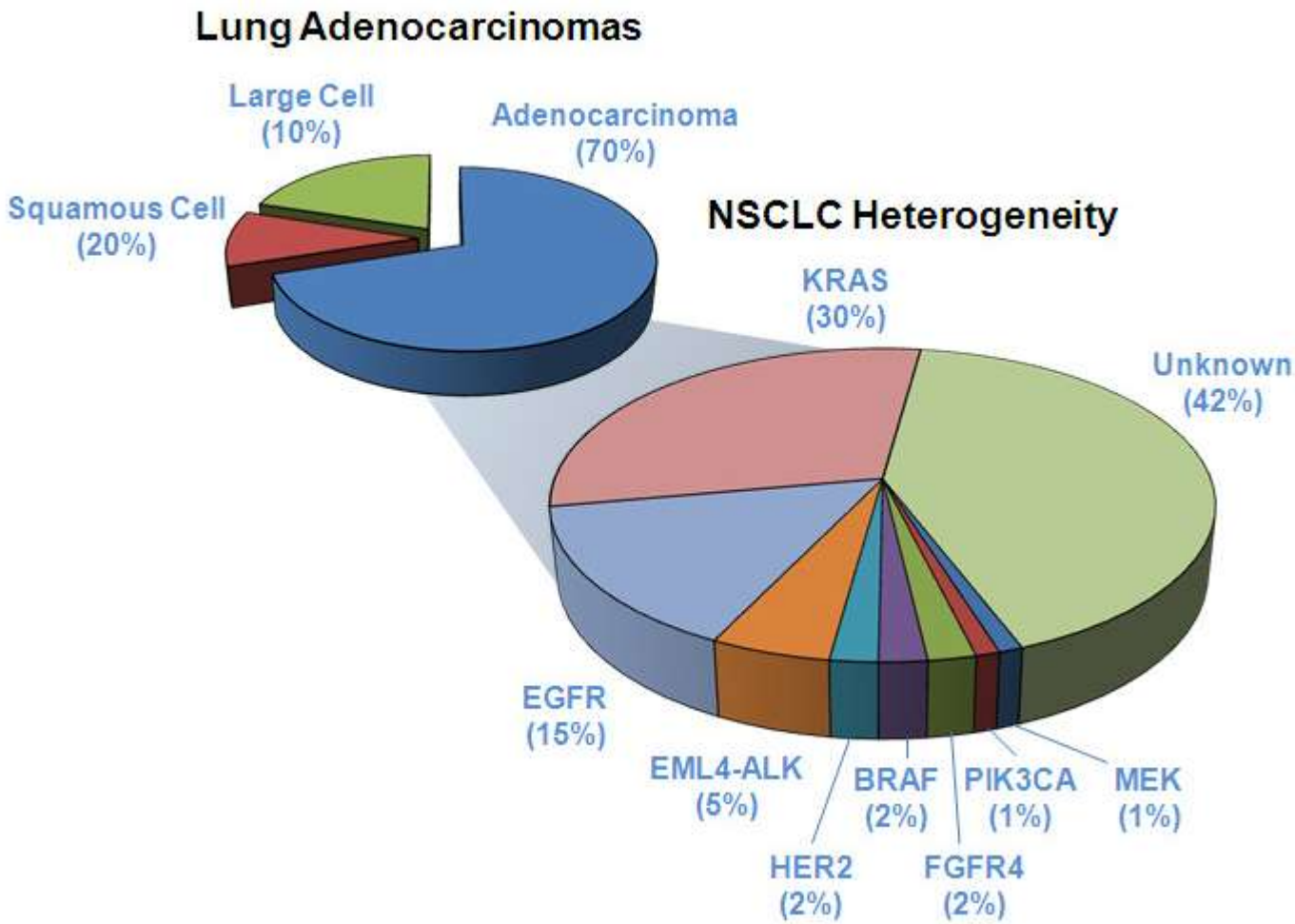
| | | | | |
|---|---|---|---|---|
| APC | CCND1 | MLH1 | MSH2 | CDKN2A |
| MSH6 | MYC | TP53 | MCL1 | MGMT1T |

### Markers for Toxicity or Pharmacokinetics

| | | | | |
|---|---|---|---|---|
| CYP2D6 | UGT1A1 | TMPT | DPYD | CYP3A5 |
| CYP1B1 | ESR2 | MTHFR | S0D2 | ERCC2 |
| CYP2C19 | FGGR3A | NQ01 | SULT1A1 | MAN1B1 |
| CYP2C8 | GSTP1 | NRP2 | TYMS | SLC22A2 |
| CYP3A4 | ITPA | SLC19A1 | UMPS | SLC01B3 |

**Additional Marker sets for Viral diseases, Gene Expression or miRNA required**

# Genetic Variation in Lung Cancer



# The technical, clinical and regulatory challenges of increasing complexity

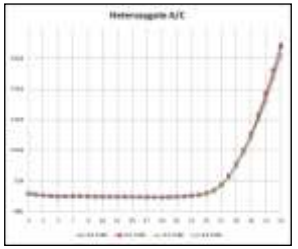

- Technical
  - How do we measure it
- Clinical
  - What does it mean
  - Evidence > Implication
- Regulatory
  - “The claim you prove is the claim you get”

Understanding how these issues will play out will be essential for platform companies as they develop new instruments for molecular diagnostics

# Technical Requirements of Companion Diagnostic Systems

1. Measures an appropriate number of genetic variants
    1. BRAF -1
    2. KRAS – 7
    3. EGFR -29
    4. Lung – 50-100


2. Can deal with the challenge of sample variability
    1. Blood
    2. FFPE Biopsy
    3. Cytology



3. Is easy to use and reliable
    1. Throughputs
    2. Automation

# Clinical Utility and Regulatory Approval

- EGFR contains 29 mutations
- What level of clinical validation is appropriate?
  - Demonstration that the panel predicts response to Iressa
    - clinical population to screen to find 5 EG+pts is about 50
  - Demonstration that each individual mutation within the panel predicts response to Iressa
    - Clinical population to screen to find at least 5 of each of the 29 mutations in the panel is about 3000
- As the complexity of mutation and biomarker profiles increases this problem becomes more of a challenge – in the worst case it could impede the development of the very valuable field of personalised health care

# PHC Summary

- The personalised healthcare market is real, expanding and sustainable
- The opportunity is substantial but it requires a thorough understanding of the market and the customers to make a successful business
- Success requires consideration of
  - Content
  - Platform
  - Distribution


Thank you!

# Why has it taken so long

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