

# *Growing trends in the retrospective analysis of clinical trial samples*

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BioStorage Symposium  
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# Topics



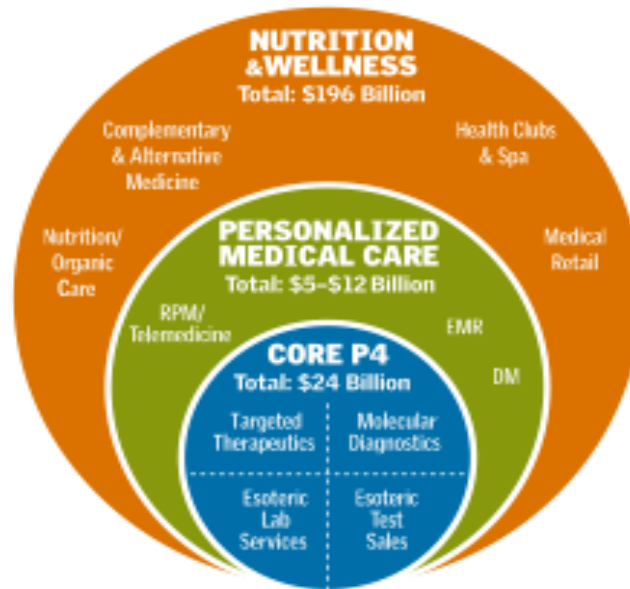
- Pharma challenges and opportunities
- Role for retrospective analysis
  - no samples, no science
- London Genetics Limited

# The future – niche not blockbusters

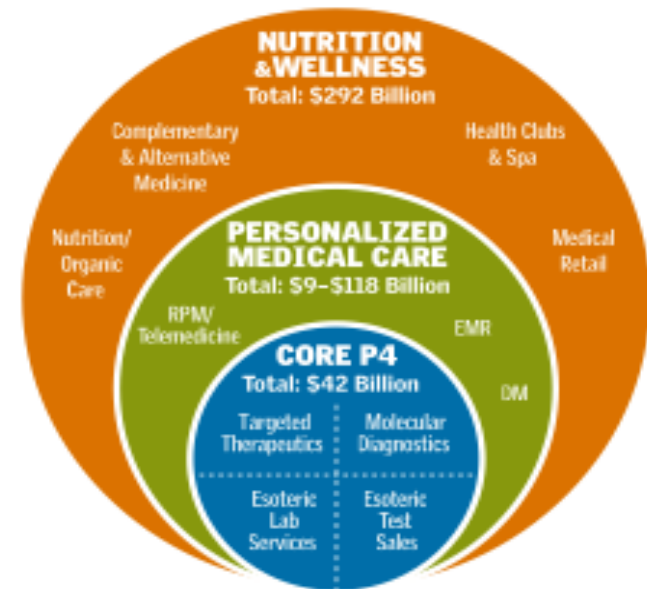
**Personalized Medicine  
Market Size,  
2009 and 2015**

[+]  
Roll over each category  
to reveal dollar costs.

**2009 TOTAL MARKET:  
\$225-\$232 Billion**



**2015 TOTAL MARKET:  
\$344-\$452 Billion**

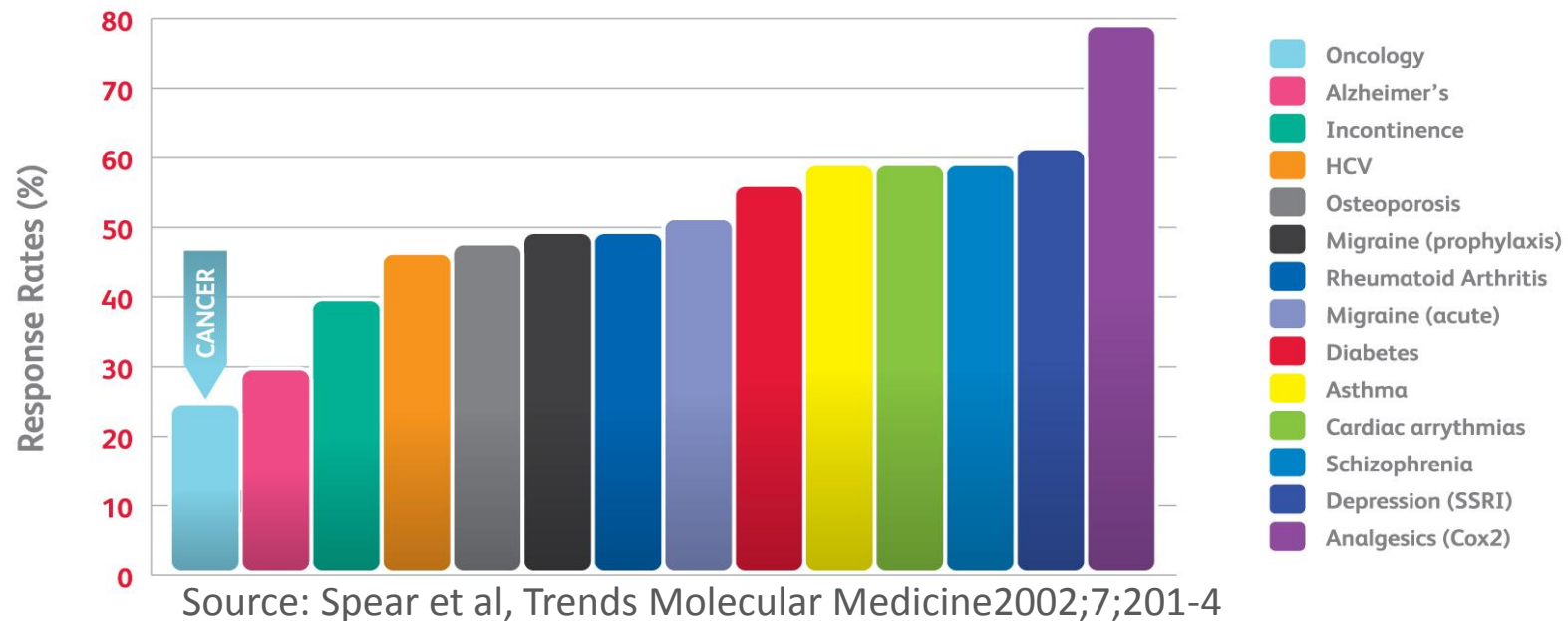


Totals may differ due to rounding.  
Source: PricewaterhouseCoopers analysis.

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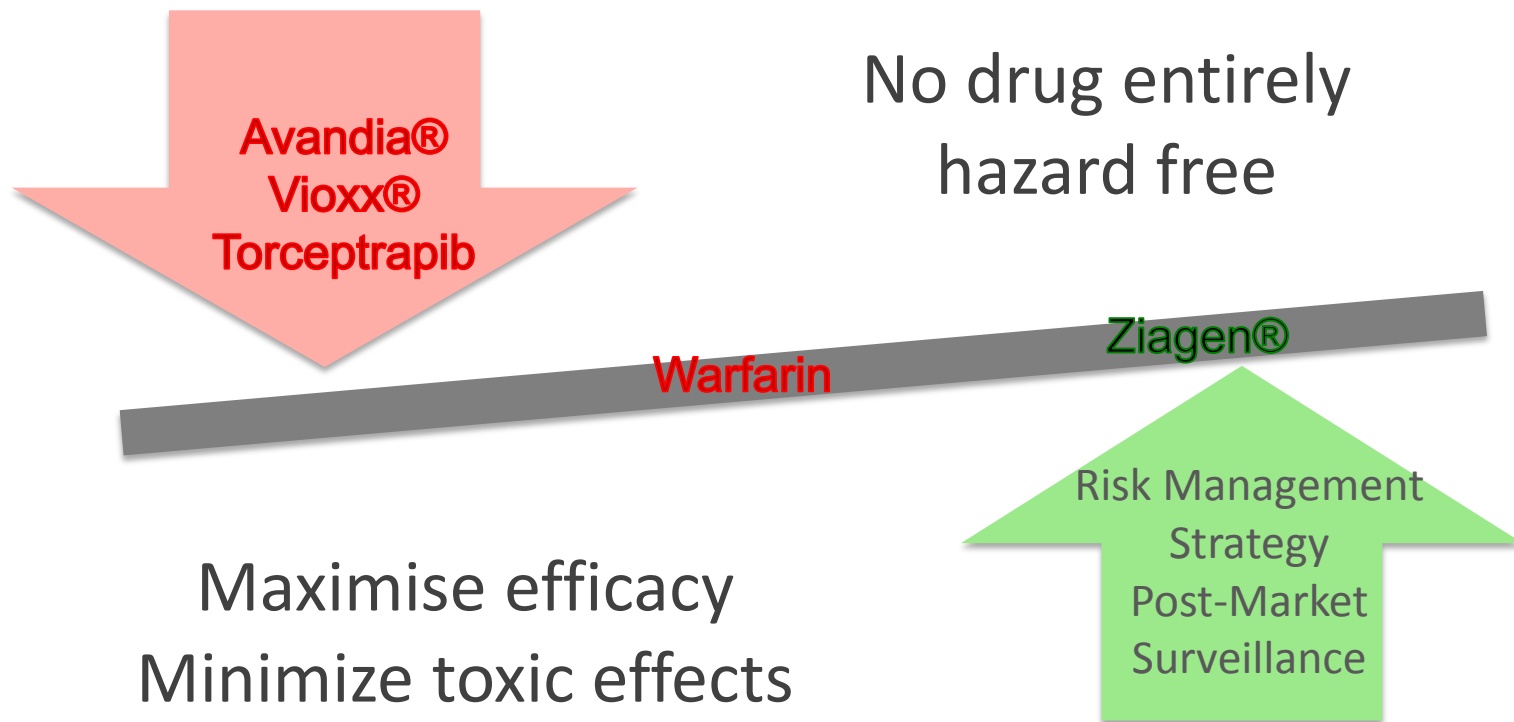
# The Challenge and the Opportunity .. *Variability*

- People do not respond to medicines the same way
  - Adverse events, dose, efficacy
  - Often difficult to predict
- By 2020 most medicines paid for on the basis of results<sup>1</sup>



<sup>1</sup>PwC Pharma 2020: Challenging business models, which path will you take?

# Adverse Effects of Drugs – the pressing need for biomarkers



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# ---and stem the growing number of drug withdrawals

Drug substance ( Brand name )	Year action taken	Major safety concerns	Licence Holder
Dilevalol (Unicard)	1990	Hepatotoxicity	Schering – Plough Limited
Metipranolol (Glauline eye drops 0.6%)	1990	Uveitis	Chauvin Pharmaceuticals
Triazolam (Halcion)	1991	Psychiatric reactions	Upjohn
Terodiline (Micturin)	1991	Arrhythmias	Pharmacia
Temafloxacin (Teflox)	1992	Multi-system toxicity	Abbott Labs
Flosequinan (Manoplax)	1993	Excess mortality	Boots
Remoxipride (Roxiam)	1994	Aplastic anaemia	Astra
Naftidrofuryl Oxalate Injection (Praxilene)	1995	Cardiotoxicity	Lipha
Pemoline (Volital)	1997	Hepatotoxicity	Various companies
Troglitazone (Romazin)	1997	Hepatotoxicity	Glaxo Wellcome
Sertindole (Serdolect)	1998*	Arrhythmias	Lundbeck A/S
Tolcapone (Tasmar)	1998	Hepatotoxicity	Roche
Fenfluramine (Ponderax)	1998	Cardiac valvular disease	Servier
Dexfenfluramine (Adifax)	1998	Cardiac valvular disease	Servier
Mibefradil (Posicor)	1998	Drug interactions	Roche
Trovafloxacin (Trovan)	1999	Hepatotoxicity	Pfizer
Grepafloxacin (Raxar)	1999	QT prolongation	Glaxo Wellcome
Pulmonary surfactant (Alec)	2000	Increased mortality	Britannia Pharmaceuticals Ltd
Cisapride (Prepulsid, Alimix)	2000	Disorders of heart rhythm	Janssen-Cilag
Droperidol (Droleptan)	2001	Disorders of heart rhythm	Janssen-Cilag
Cerivastatin (Lipobay)	2001	Rhabdomyolysis	Bayer
Rofecoxib (Vioxx)	2004	Risk of thrombotic events	Merck Sharp & Dohme
Valdecoxib (Bextra)	2005	Serious skin reactions	Pfizer
Co-proxamol (paracetamol + dextropropoxyphene)	2005	Risks of overdose and misuse	various

# GSK share price sank on Avandia news

Source: Deloitte



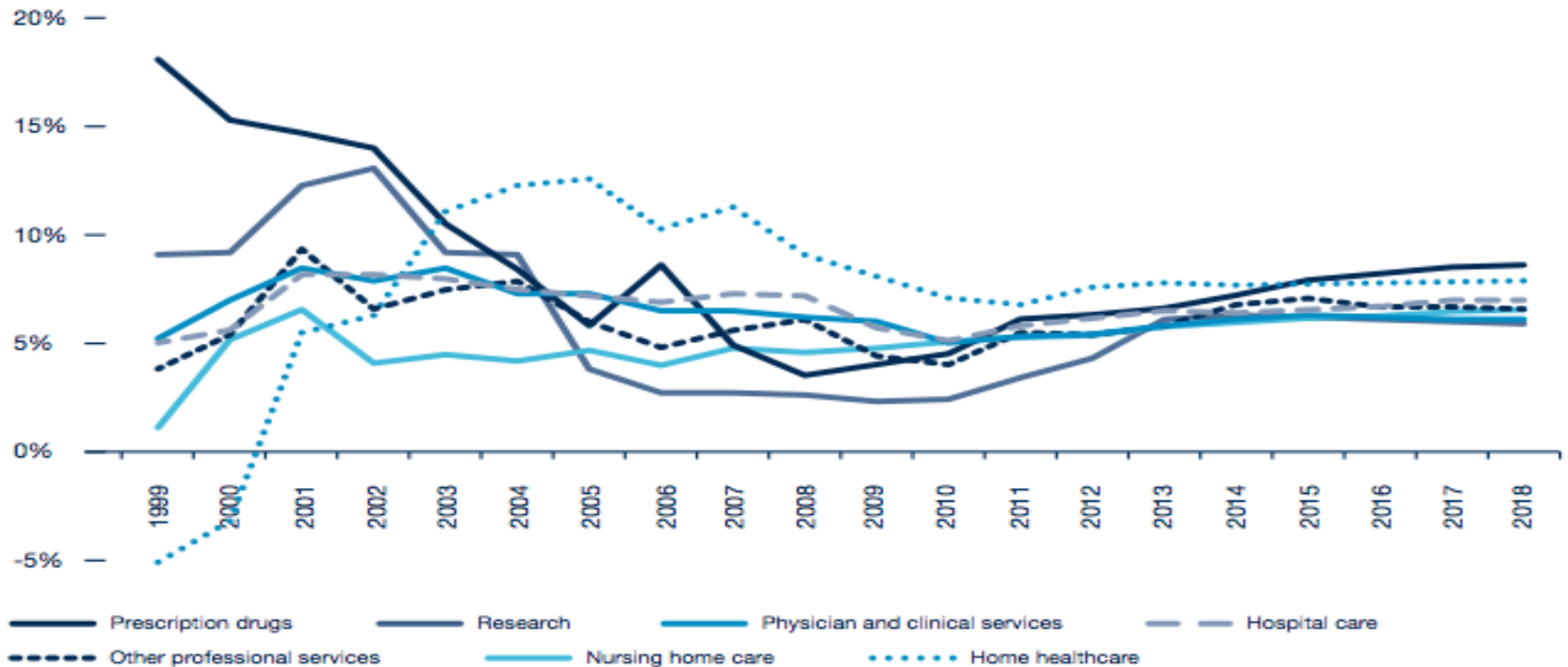
May 2008

June 2008

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# Prescription drug costs continue to rise

Figure 12: Growth in national health expenditures - cost per capita (1999-2018)



Note: Values for 2008 through 2018 are projections.  
Sources: Centers for Medicare and Medicaid Services, US Census Bureau

Ref.: Behind the numbers: Medical cost trends for 2010. PricewaterhouseCoopers

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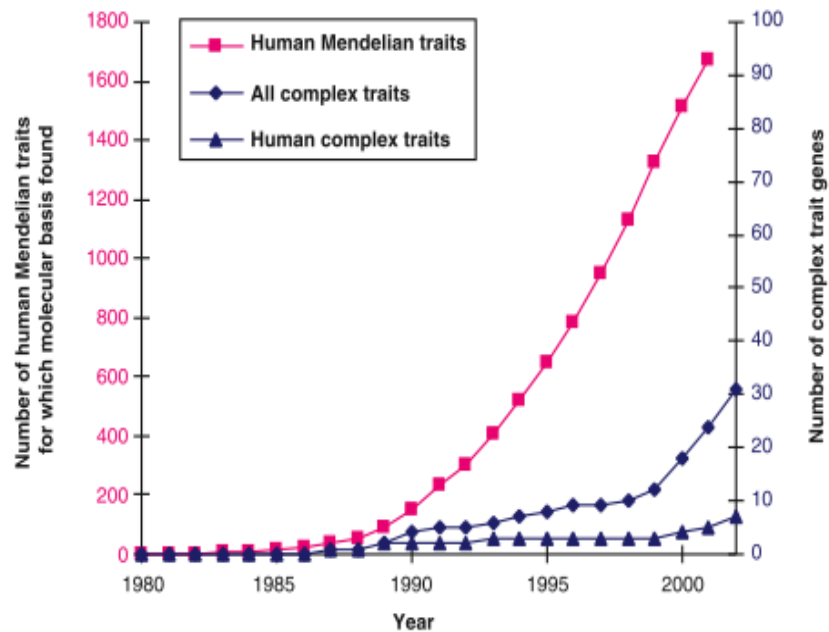


# Exponential increase in genetic information

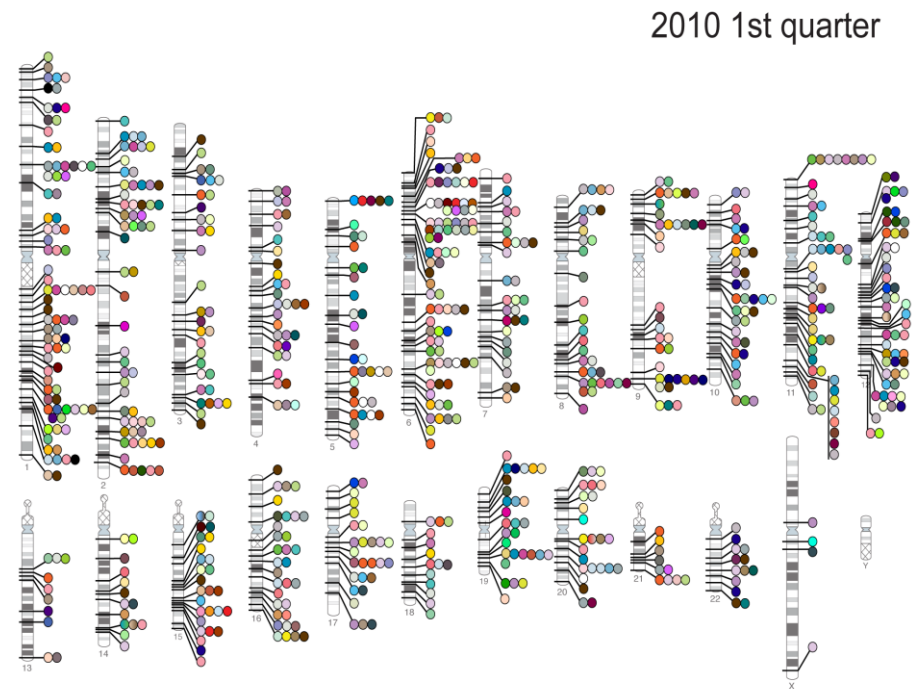
– new windows on disease pathophysiology and individual variability

**2002:** ~10 known complex disease genes

**2010:** >500 replicated associations

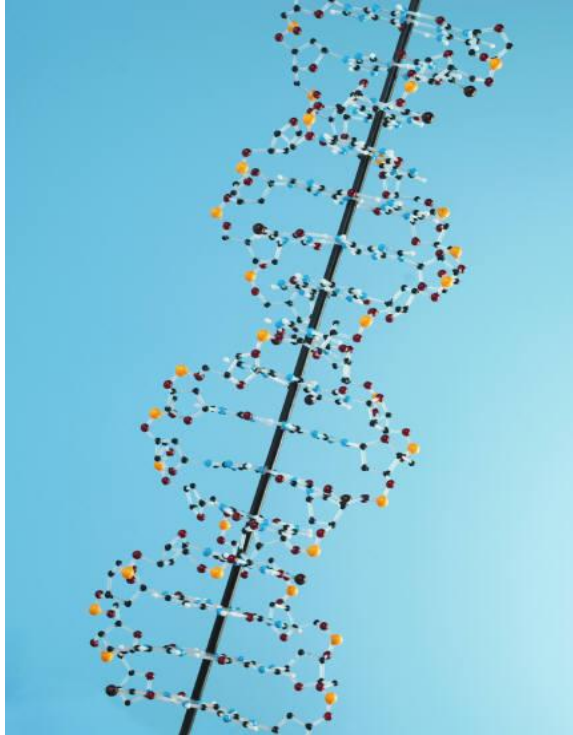


Finding genes that underlie complex traits  
Anne M. Glazer *et al.* Science (2002) 298: 2345

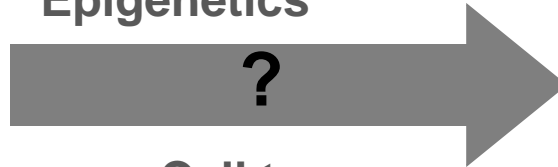


Published Genome-Wide Associations through 3/2010,  
779 published GWA at  $p \leq 5 \times 10^{-8}$  for 148 traits

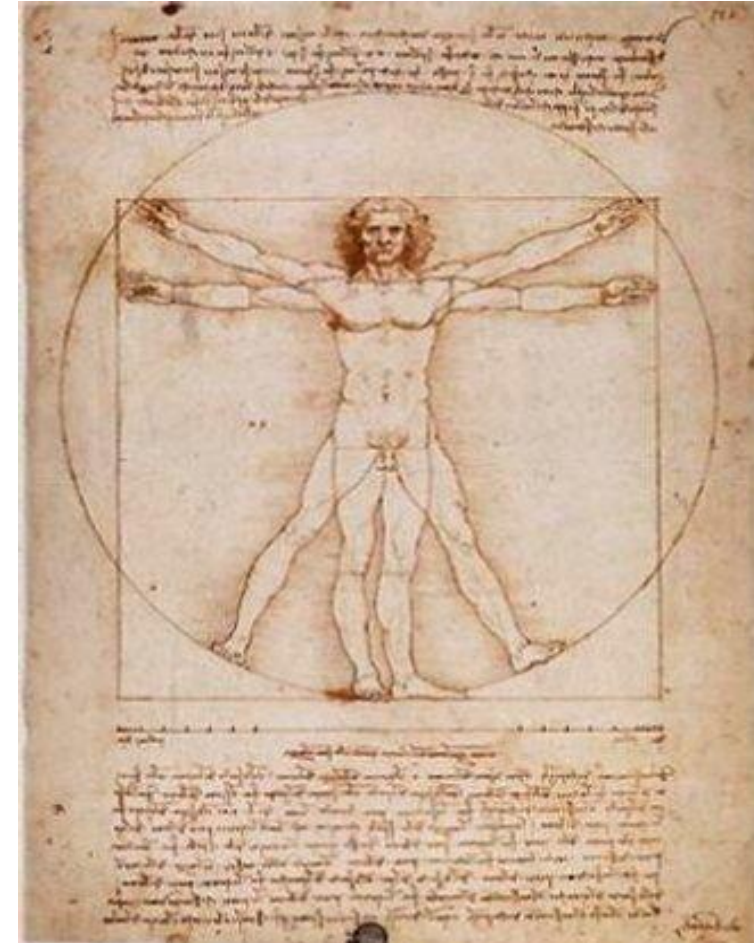
# Genome variation and biological complexity



SNPs  
Insertions  
Deletions  
Rearrangements  
Copy number variation  
Micro RNAs  
Chromosomal structure  
Epigenetics



Cell types  
Tissues  
Organs  
Systems  
Age  
Gender  
Biochemical milieu  
Environment

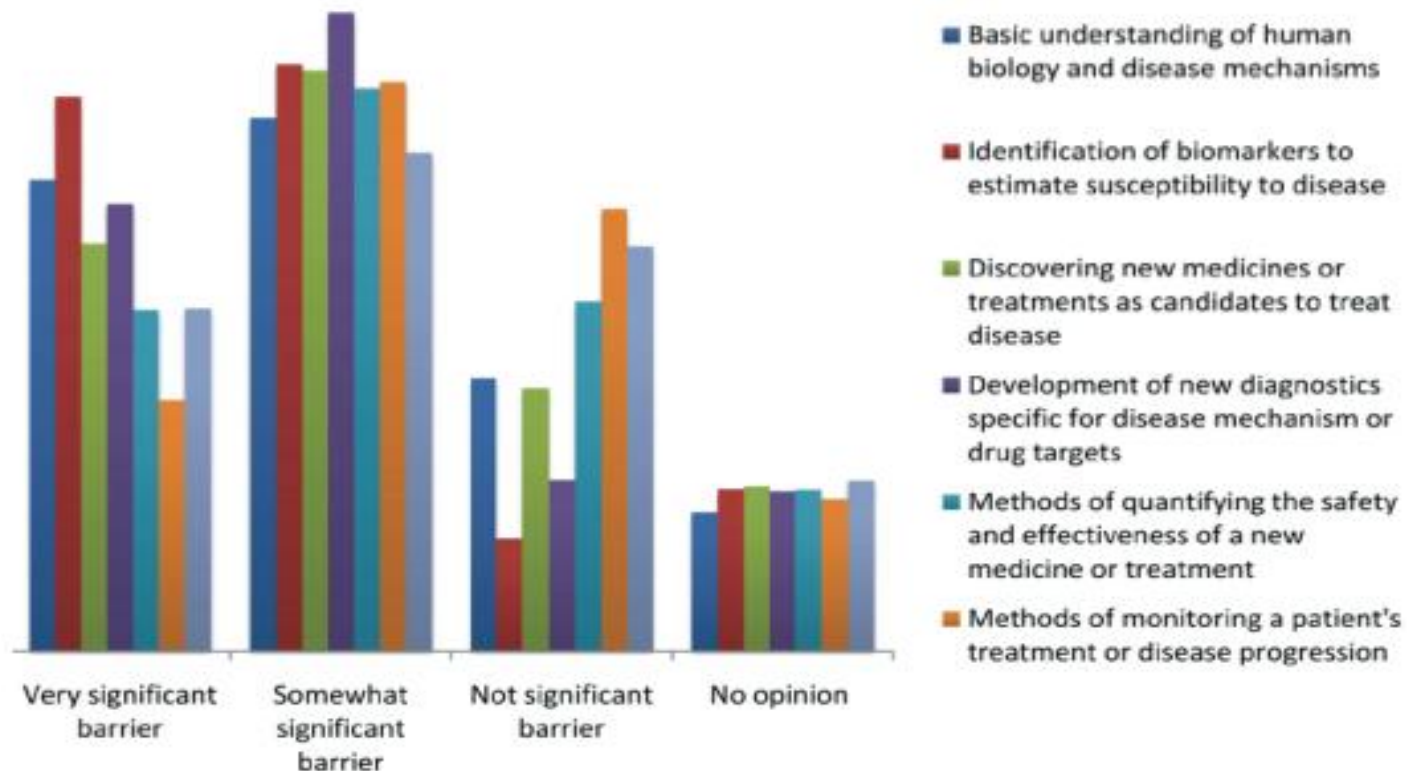


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# Key Scientific Barrier – identifying the appropriate biomarkers

From: Health for all, care for all  
ScienceBusiness & Karolinska  
Institute survey 2010

## Distribution of perceived scientific barriers



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# Area of active interest for Pharma

*We demand that every product in our pipeline has a biomarker... (to) increase magnitude of treatment effects*

Dave Brennan, CEO AstraZeneca

BioCentury 1<sup>st</sup> Feb 2010

# Industry signs up

- **Medco** launches Plavix, Effient comparative effectiveness study examining role of genetics - October 2009
  - ‘With Plavix going generic in 2011 financial savings may be found’  
[www.medcohealth.com](http://www.medcohealth.com)
- **Qiagen & Pfizer** agreement to develop gene-based diagnostic for brain cancer – February 2010
  - PF-04948568 is Phase II trials for glioblastoma multiforme
- **AstraZeneca** to boost personalised healthcare efforts
  - ‘we demand that every product in our pipeline has a biomarker... (to) increase magnitude of treatment effects’ BioCentury February 1 2010
- **Eli Lilly** is embracing personalised medicine
  - ‘(potential) to identify unpromising drugs early in R&D’
  - Could lead to ‘smaller, accelerated clinical trials’
  - ‘relatively large share of a more segmented pie’, ‘repeat prescribing and patient compliance’

The new science of personalized medicine: Translating the promise into practice, PwC 2009

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# Medco Health Solutions - Warfarin genetic testing decreases hospitalisation rate

16 March 2010

## News Alert

**Medco, Mayo Clinic study reveals using a simple genetic test reduces hospitalization rates by nearly a third for patients on widely prescribed blood thinner**

*-- First study to show gene tests improve clinical outcomes in 'real world' settings*

*-- Research presented at American College of Cardiology annual meeting finds incorporating pharmacogenomics substantially reduces risks associated with the blood thinner warfarin*

**ATLANTA, March 16, 2010** – Hospitalization rates for heart patients taking warfarin, the world's most-prescribed blood thinner, dropped by approximately 30 percent when genetic information was available to doctors prescribing the drug, researchers from Medco Health Solutions, Inc.-- in association with the Medco Research Institute™ -- and Mayo Clinic announced today. Results of the first nationwide prospective study examining outcomes when incorporating genetic testing into the management of warfarin as part of the usual care of patients were presented today at the American College of Cardiology's 59<sup>th</sup> annual scientific session and will be published in the Journal of the American College of Cardiology.

<http://www.medcohealth.com/>



# Warfarin label change to reflect PGx information

22 January 2010

- Table of recommended doses depending on CYP2C9 and VKORC1 genotype
- Increased warfarin sensitivity (□ risk of overdose at “standard” dose)

Table 5: Range of Expected Therapeutic Warfarin Doses Based on CYP2C9 and VKORC1 Genotypes<sup>†</sup>

VKORC1	CYP2C9					
	*1/*1	*1/*2	*1/*3	*2/*2	*2/*3	*3/*3
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

<sup>†</sup>Ranges are derived from multiple published clinical studies. Other clinical factors (e.g., age, race, body weight, sex, concomitant medications, and comorbidities) are generally accounted for along with genotype in the ranges expressed in the Table. VKORC1 –1639 G→A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. Patients with CYP2C9 \*1/\*3, \*2/\*2, \*2/\*3 and \*3/\*3 may require more prolonged time (>2 to 4 weeks) to achieve maximum INR effect for a given dosage regimen.

# Regulators leading the way in integrating new science into decision making

FDA: pharmacogenetics safety data in drug labels

Drug Name	Genetic Biomarker	Label Update	Specific Risk	Type of Evidence
Clopidogrel	CYP2C19	Nov 2009	Reduced efficacy	Retrospective
Panitumumab/ Cetuximab	KRAS	July 2009	Absence of benefit	Retrospective
Carbamazepine	HLA- B*15:02	Dec 2007	Steven-Johnson syndrome/ toxic epidermal necrolysis	Retrospective
Abacavir	HLA-B*57:01	July 2008	Hypersensitivity reaction	Prospective
Warfarin	CYP2C9, VKORC1	Aug 2007, Jan 2010	Over-anticoagulation	Retrospective, Prospective
Irinotecan	UGT1A1	Aug 2006	Neutropenia	Retrospective
6- Mercaptopurine	TPMT	July 2004	Myelosuppression	Retrospective

# OPINION

## Voluntary exploratory data submissions to the US FDA and the EMA: experience and impact

Nature Reviews Drug Discovery 2010; 439: 435 - 445

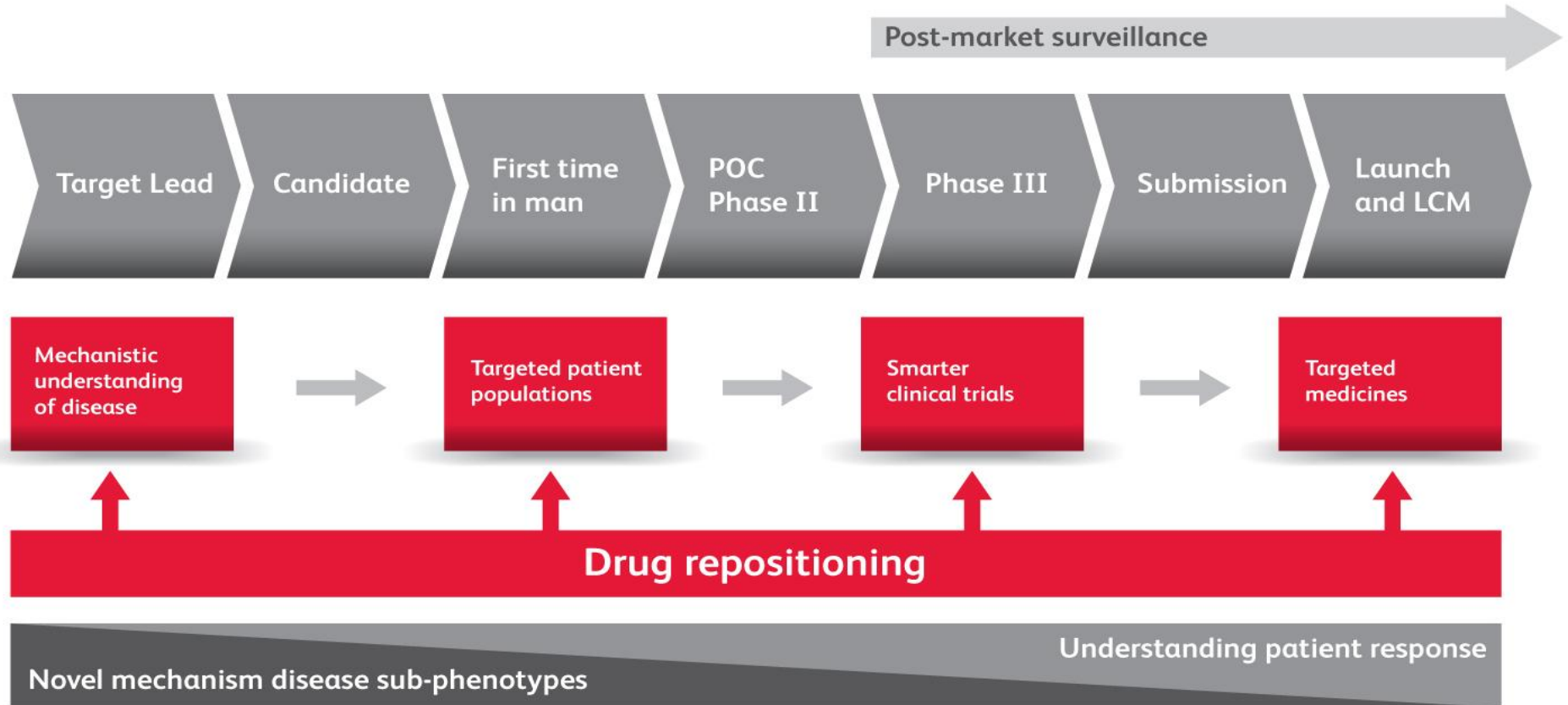
Company	Drug	Biomarker	Type of Evidence
Wyeth	Temsirolimus	<ul style="list-style-type: none"><li>- Renal cell carcinoma biomarkers</li><li>- Exploratory biomarkers: transcriptional signatures</li></ul>	Retrospective
Roche	Capecetabine	<ul style="list-style-type: none"><li>- Drug safety hypothesis &amp; overall strategy and process to biomarker research</li></ul>	Prospective
Eli Lilly	Prasugrel	<ul style="list-style-type: none"><li>- Genotype-derived drug-metabolising phenotype</li><li>- Pharmacogenetic section in NDA</li><li>- "Specific genetic questions evolved during clinical development"</li></ul>	Retrospective
AstraZeneca	Ximelagatran	<ul style="list-style-type: none"><li>- Mechanism underlying ALT elevations</li><li>- Proteomic and metabolomic biomarkers</li></ul>	Retrospective, Prospective
Novartis	Renal transplant	<ul style="list-style-type: none"><li>- Renal allograft biomarkers</li><li>- Transcriptomics in kidney tissue samples</li></ul>	Prospective

# Topics



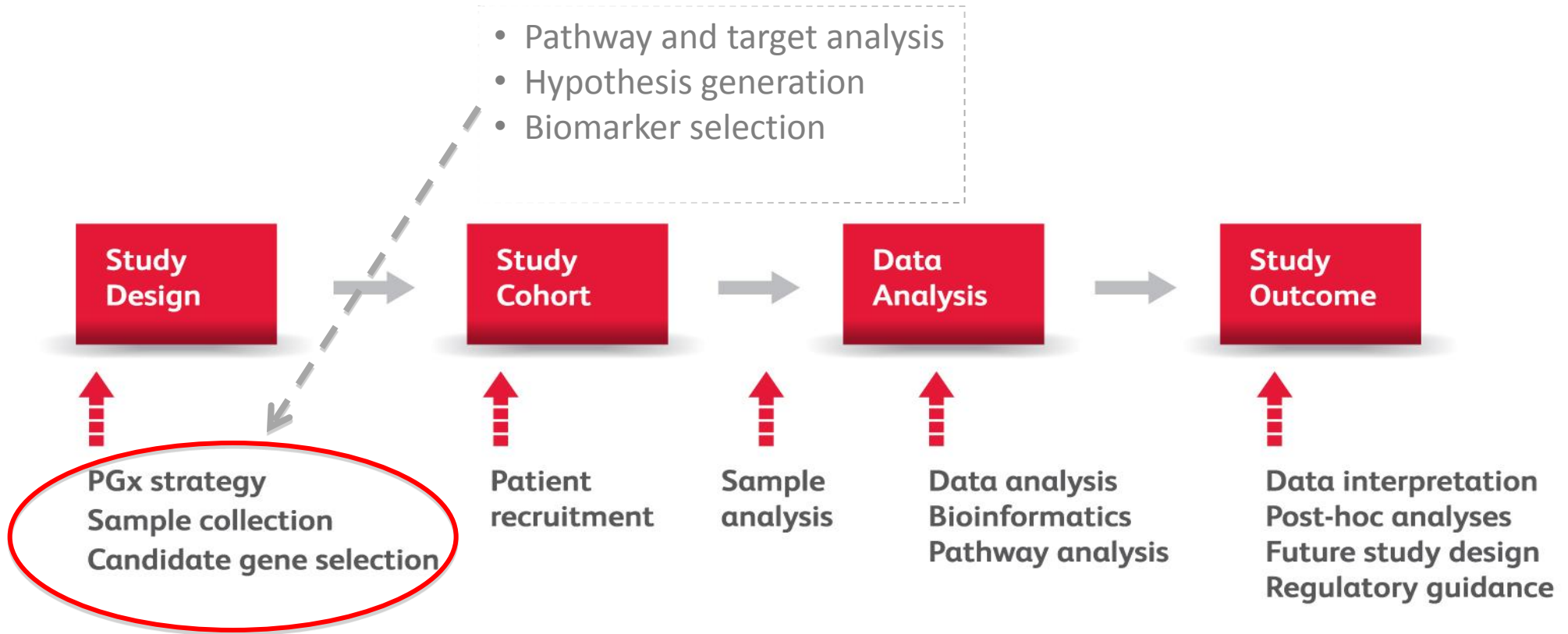
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# Opportunities from harnessing emerging science – genetics, expression profiling, biomarkers



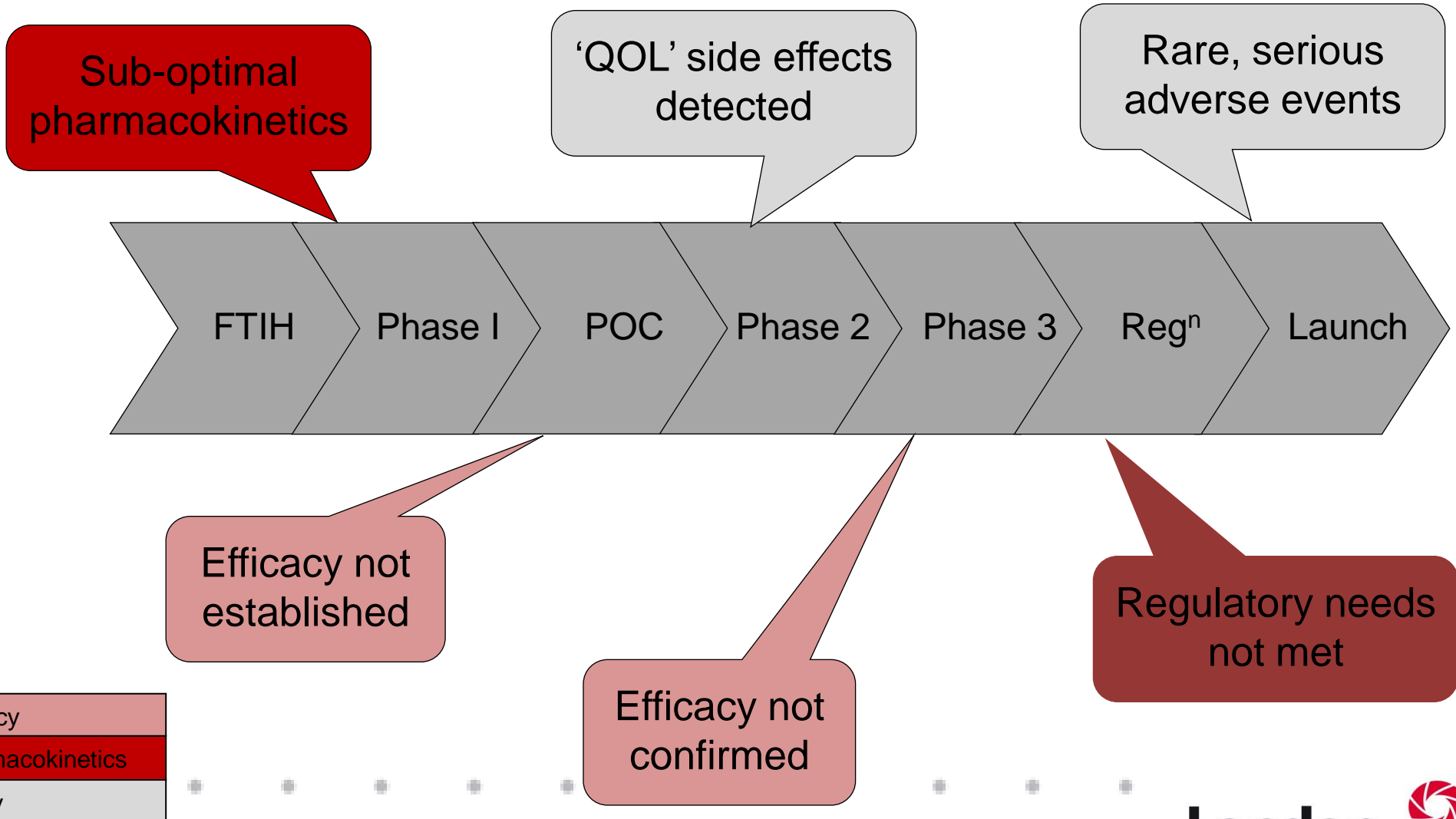
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# Pharmacogenetic plan deliverables



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# Pharmacogenetics - answering questions across the pipeline



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**No samples**

**No science**

# EMA: Pharmacogenetic Working Party

## New guidance / reflection papers

Guidelines / Reflection Papers	Timelines
Guideline on the use of PG and in PK studies	Release for consultation 3Q09 Finalisation 2010
Reflection paper on co-development of PG biomarkers a test platforms	Release for consultation 3Q09 Finalisation 2010
Reflection paper on statistical and methodological issues associated with PG biomarkers	Release for consultation 4Q09 Finalisation 2010
Reflection paper on genomics and personalised medicines	Release for consultation 4Q09 Finalisation 2010



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

22 April 2010  
EMA/CHMP/37646/2009  
Committee for Medicinal Products for Human Use (CHMP)

## Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

### Draft

Draft Agreed by Pharmacogenomics Working Party and EWP- PK	March 2010
Adoption by CHMP for release for consultation	22 April 2010
End of consultation (deadline for comments)	31 October 2010

This guideline replaces the Reflection Paper on the use of Pharmacogenetics in the Pharmacokinetic Evaluation of Medicinal Products (EMEA/128517/2006)

Comments should be provided using this [template](#). The completed comments form should be sent to [PGWPSecretariat@ema.europa.eu](mailto:PGWPSecretariat@ema.europa.eu)

Keywords	<i>Pharmacogenetics, pharmacokinetics, clinical development</i>
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# Collected samples to answer emerging clinical findings

- “A **retrospective** analysis in order to implement emerging data may be acceptable provided all the following conditions are met:
  - Plausible biological **hypothesis** exists
  - Post-hoc analysis is pre-specified in **the statistical analysis plan**
  - The data collected allow the characterisation of the **phenotype**
  - **Sample size** sufficient to draw conclusions
  - DNA is available for a **large proportion** of patients
  - The assay has an acceptable **performance**”

Ref: Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products : Draft  
22 April 2010 EMA/CHMP/37646/2009

# Using pharmacogenetics in pharmacokinetic studies – *prospective Vs retrospective*

Ref: Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products : Draft 22 April 2010 EMA/CHMP/37646/2009

- “Studies of PGx effects on PK are recommended if any of the following conditions are met:
  - Available data indicate only **partial contribution** of a polymorphic enzyme or transporter to the PK of the active substances but the quantitative role is unknown, *or*
  - There is high inter-individual **PK variability** or there are PK outliers with markedly higher . Lower exposure of the active substance or metabolites, which give rise to **clinical efficacy and safety concerns** based on the existing knowledge
  - Safety concerns are observed which may be related to genetic differences in system or target organ exposure, *or*
  - Major difference in PK are observed in different **ethnic groups**”

# Three questions regulators often ask (themselves / sponsors)\*

Bruno FLAMION Chair, Scientific Advice Working Party (SAWP), CHMP-EMA  
FDA/DIA 5th Workshop in a Series on Pharmacogenomics Generating and Weighing Evidence in Drug  
Development and Regulatory Decision Making. February 2-4, 2010

- Are the retrospective findings consistent?
  - Statistical approach consistent?
- Is there a need for confirmatory (possibly prospective) PGx data?
  - What is the level of evidence needed to stratify or exclude patients in a pivotal (PIII or adaptive P II/III) trial?
- What will be in the impact of the proposed PGx testing in clinical practice (for the patient's benefit)?
  - The clinical utility?

# Rimonabant: obituary for a wonder drug

Comment. Lancet 2010; 376: 485

## Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial



*Eric J Topol, Marie-Germaine Bousser, Keith A A Fox, Mark A Creager, Jean-Pierre Despres, J Donald Easton, Christian W Hamm, Giles Montalescot, P Gabriel Steg, Thomas A Pearson, Eric Cohen, Christophe Gaudin, Bernard Job, Judith H Murphy, Deepak L Bhatt, for The CRESCENDO Investigators\**

### Summary

**Background** Blockade of the endocannabinoid receptor reduces obesity and improves metabolic abnormalities such as triglycerides, HDL cholesterol, and fasting blood glucose. We assessed whether rimonabant would improve major vascular event-free survival.

Lancet 2010; 376: 517-23

See [Comment](#) page 489

\*The webappendix lists the

with ximelagatran. As with this trial, knowledge about the appropriate clinical criteria for inclusion, with use of genomic data indicating high risk of side-effects at the time of study entry, could have pre-empted or at least reduced the serious psychiatric side-effects. For example, a study<sup>14</sup> showed that single nucleotide variants in a tyrosine kinase receptor gene (*NTRK2*) involved in neurotrophic signalling were associated with more than four-fold increased risk of suicide. Furthermore, the clinical benefit of endocannabinoid-1 blockade could have been manifest in patients with a particular gene variant in the endocannabinoid-1 or related pathways.

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# Topics

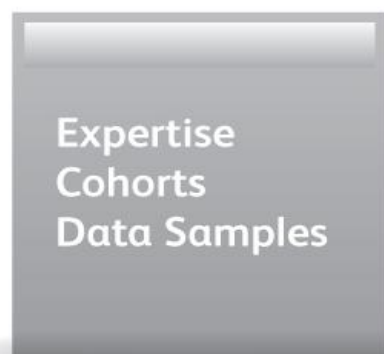


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Partners



Company  
Collaborators

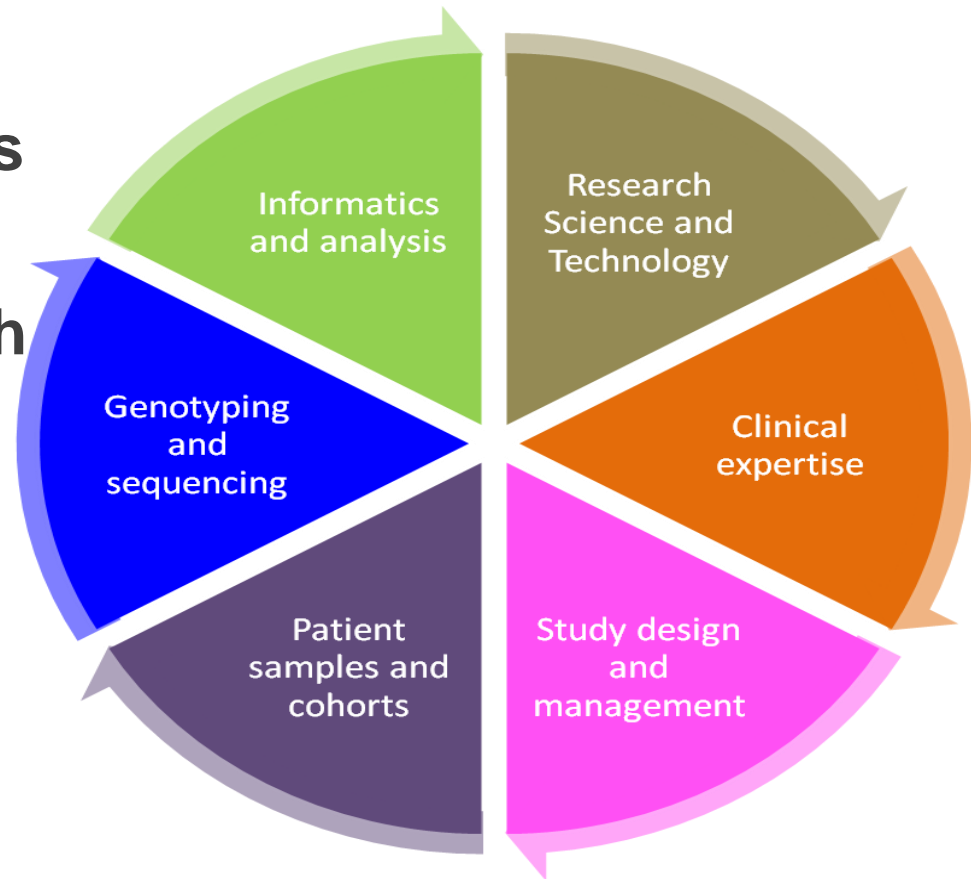


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# Comprehensive support for pharmacogenetic and biomarker studies

- **3,000 academic groups**
- **£650m annual research spend**
- **3 universities in world top 25**



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