Patients Organisations
Working Party

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SCIENCE MEDICINES HEALTH

Why biomarkers in clinical drug development and use

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Scientific Committees Regulatory Science Strategy

Outline

- Why biomarkers
- Biomarkers and medicines development
- Biomarkers in clinical use
- The future with biomarkers

Why biomarkers?

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Individual's response to medicines is variable and complex

- **Intrinsic factors** (e.g. age, health status, genetics)
- **Extrinsic factors** (such as diet, the use of concomitant drugs, exposure to sunshine etc.)
- **Interplay of factors 1, 2 + characteristics of the medicine**

Why Biomarkers

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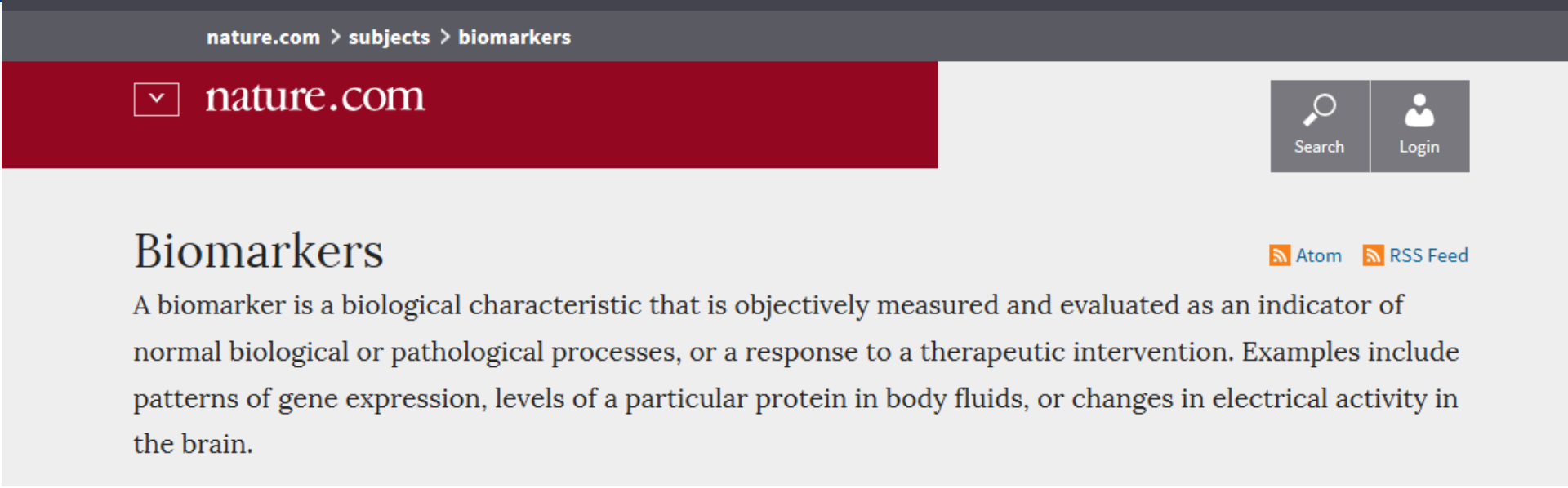

A growing variety of BMs, most often panels of them, measured with *modern technologies* allowing all of us

- to *augment precision in the judgment* necessary for selecting the medicine and course of action appropriate for each person
- to *better understand health, risk factors and mechanisms of diseases*

Why Biomarkers

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Biomarkers (BM) augment understanding and precision for medicines development and use

- Individual's susceptibility to disease, clinical onset and progression
- Individual's susceptibility to Adverse Drugs Reactions (influenced by genes*)
- Individual's mechanisms for drug's **A**bsorption, **D**istribution, **M**etabolism (transformation) and **E**limination in the body (**ADME**–**P**harmaco **K**inetic - PK) (influenced by genes*).
- Individual's disease characteristics and medicines' mode of action**:** Medicines bind /interact with various components in the body called *targets* and from this interaction *pathways* are activated: this is about the Mechanism of Action of the medicine and its **P**harmaco **D**ynamics (PD influenced by genes*)

*Genes influence depends on a number of characteristics and include**:** penetrance, alleles status, epigenetic (including influence of other drugs/environment) …

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BMs and drug response: ADME

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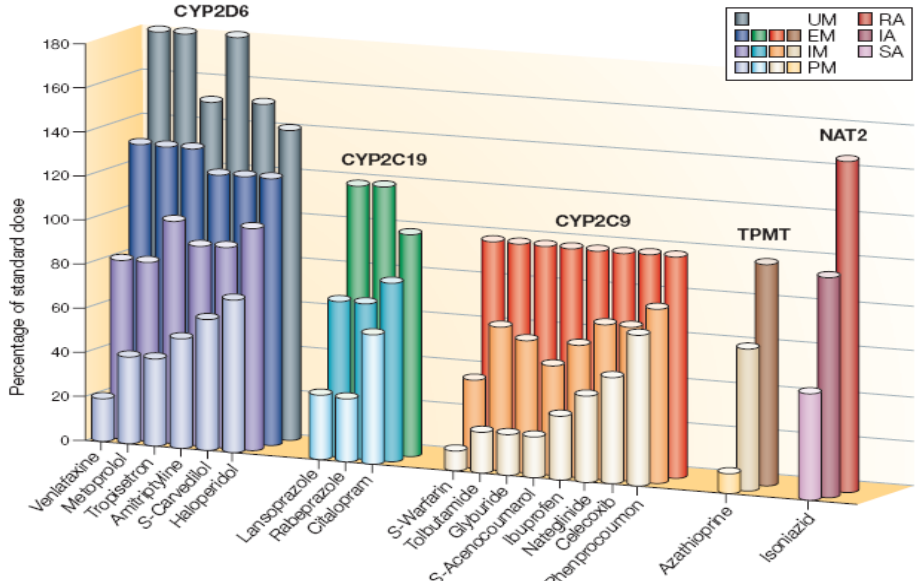
- **30–50% of all clinically used drugs** are metabolised by functionally polymorphic enzymes (phase I and phase II)

- plasma levels of some drugs at the same dosage can vary **5-20-fold** among individuals by e.g. excessive prodrug activation



→ **Guidelines on genomics BM in drug development (phase I-III)**

BM sampling and testing : global requirements

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ICH harmonisation for better health

- **ICH E18: Genomic sampling and management of genomic data in clinical trials and other studies**

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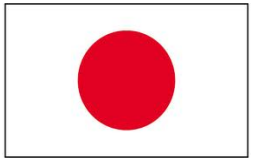
12 December 2011
EMA/CHMP/37646/2009
Committee for Medicinal Products for Human Use (CHMP)

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



Guidance for Industry

Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling

Issue	Regulatory agency		
	European Medicines Agency	Pharmaceutical and Medical Devices Agency, Japan	US Food and Drug Administration
Development phases covered in guideline or guidance	Preclinical and clinical development (Phases I–IV; focusing on PK)	Clinical development (Phases I–IV)	Early clinical development (Phases I and II)
Banking of DNA samples	Highly recommended	Encouraged*	Strongly encouraged
Genomic testing	Required‡	Recommended	Recommended
In vitro cut-off values§	>50%	None	None
In vivo cut-off values§	>25%	None	None

*Does not apply to category A (see main text for more details). ‡Is a firm requirement only when *in vitro* (>50%) or *in vivo* (>25%) cut-off values are met. §For when pharmacogenetics-related testing is required in pharmacokinetics (PK) studies.

Nature Reviews Drug Discovery 12, 103-115 (February 2013) | doi:10.1038/nrd3931
Opinion: Pharmacogenetics in the evaluation of new drugs: a multiregional regulatory perspective

BM and clinical trials

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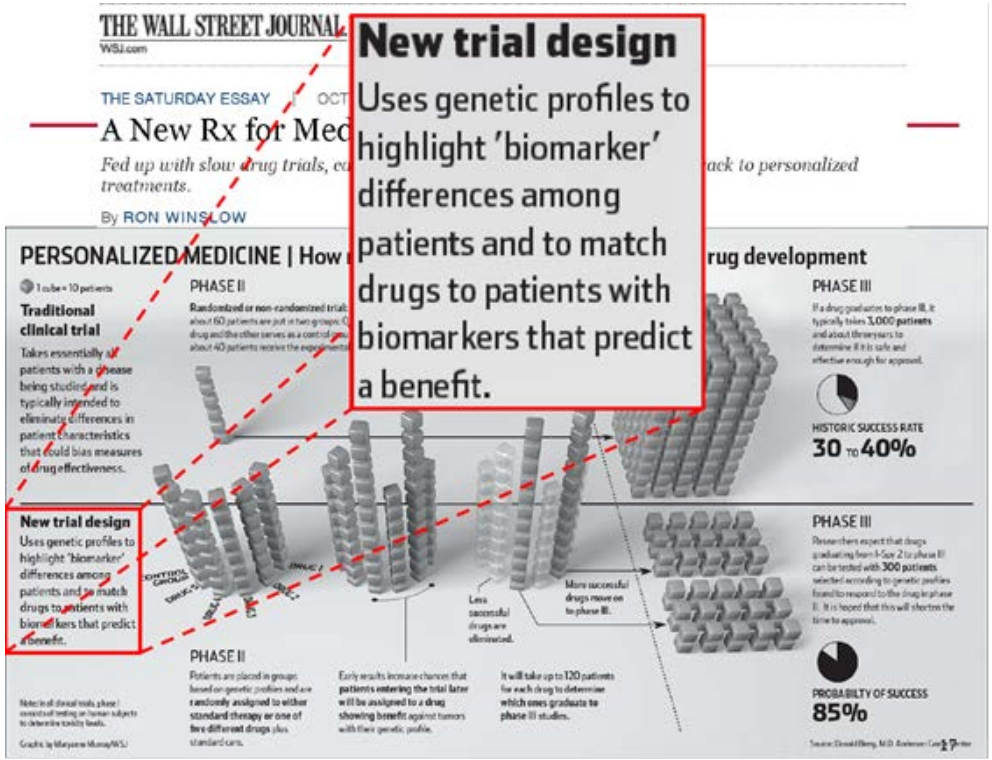

Biomarkers: more to come

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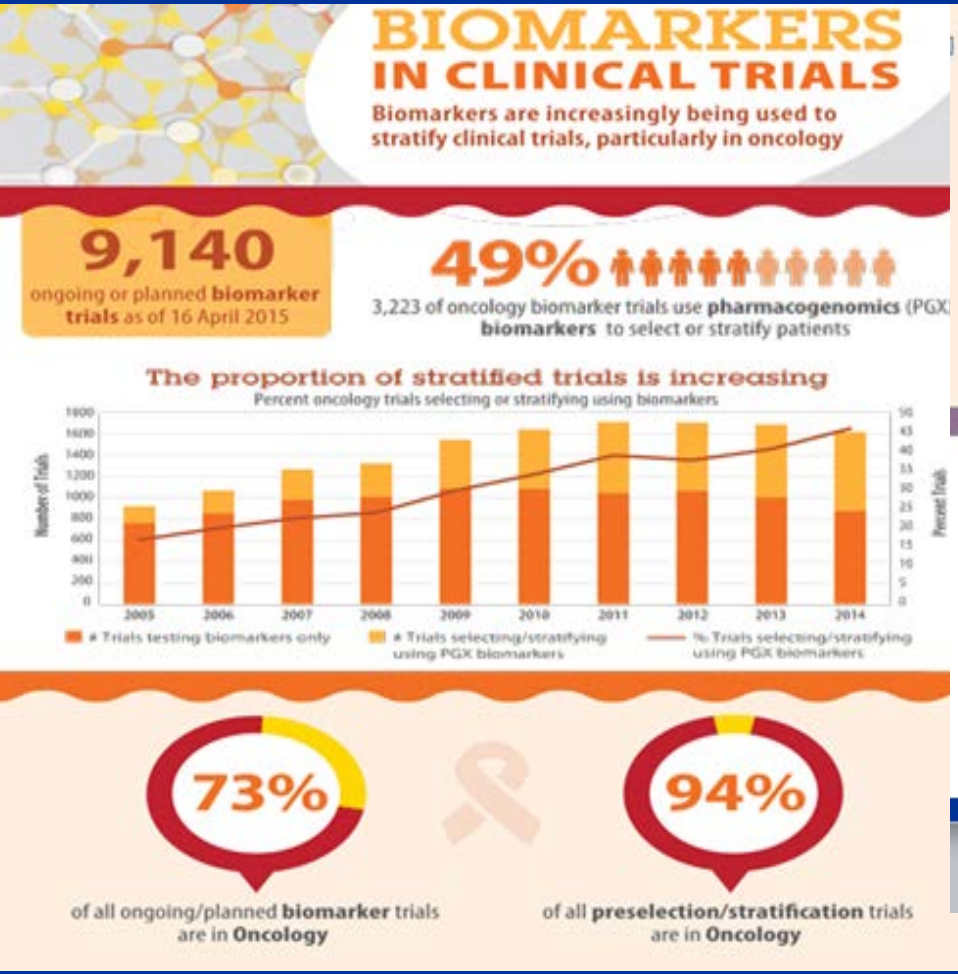

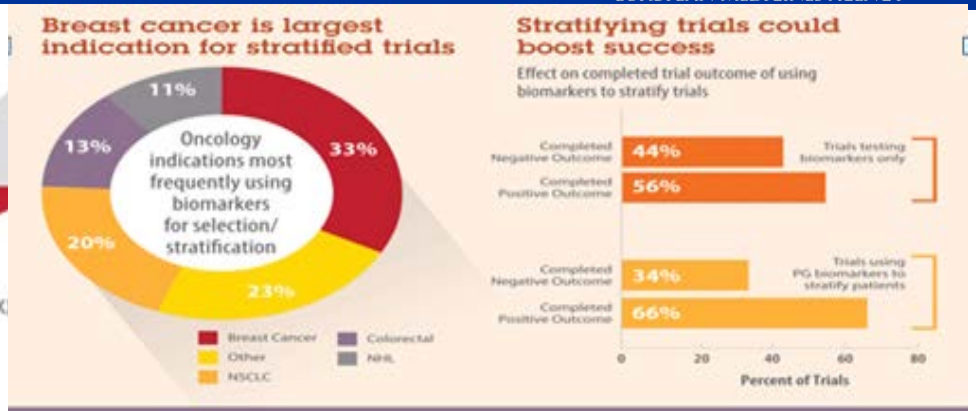

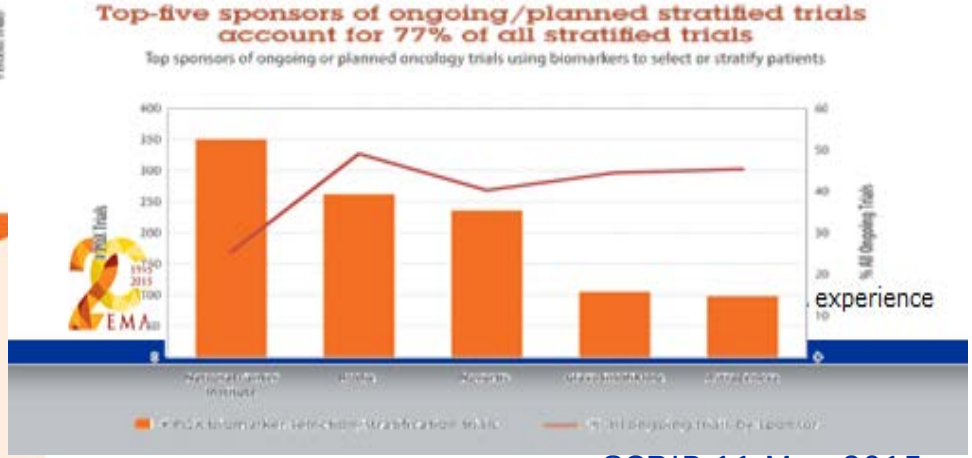

SCRIP 11 May 2015

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BM driven medicines on the increase

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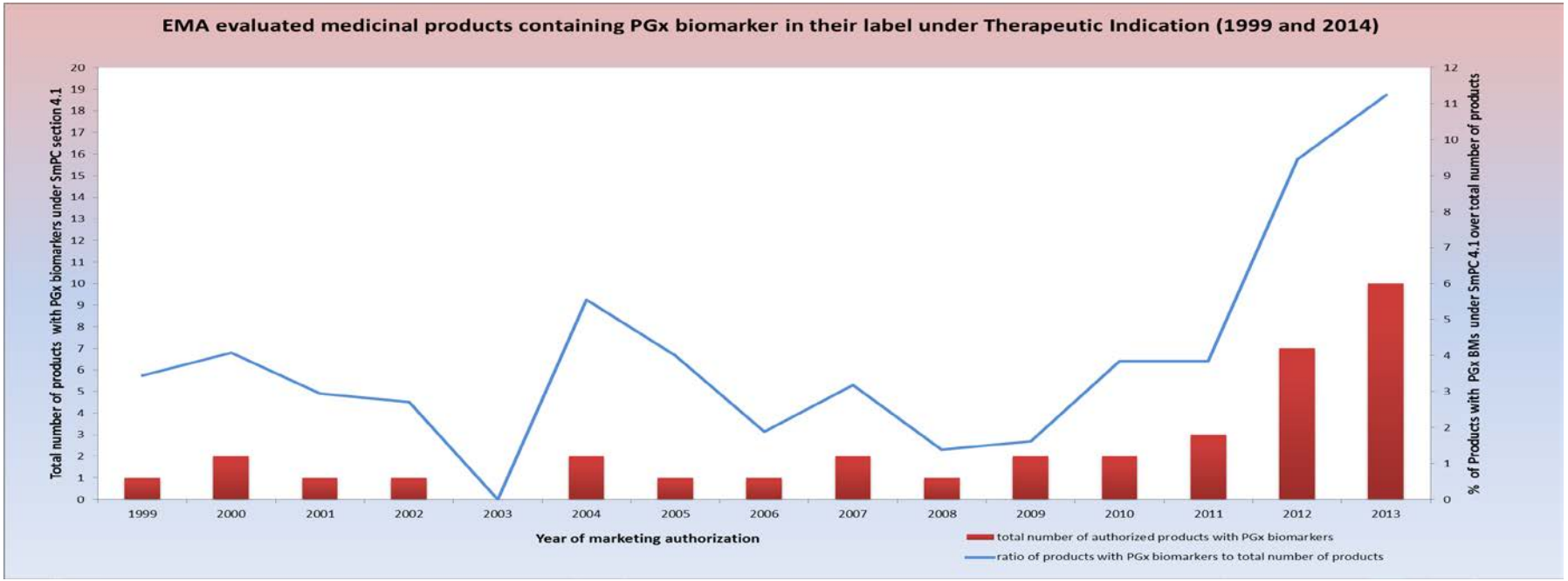
Figure 2: Number of medicinal products and ratio of medicinal products containing a genomic biomarker (gene) in their product label under "Therapeutic Indication" per year.



The number of pharmacogenomic biomarker in EU product label have been steady between 1999 and 2010 and since then gradually increasing in recent years. Initially, they have been intended for information only, progressing into becoming one of the important determinant for selection of patients likely to benefit from treatment and "more" individualised dose selection. Biomarker information may also be included in the labelling in case of negative selection (i.e., if the biomarker is used to select a population unlikely to respond) or in case of uncertainty about the value of the biomarker but where a negative selection is suspected, e.g. vandetanib.

Pharmacogenomic information in drug labels: European Medicines Agency perspective
The Pharmacogenomics Journal (2015), 1 – 10

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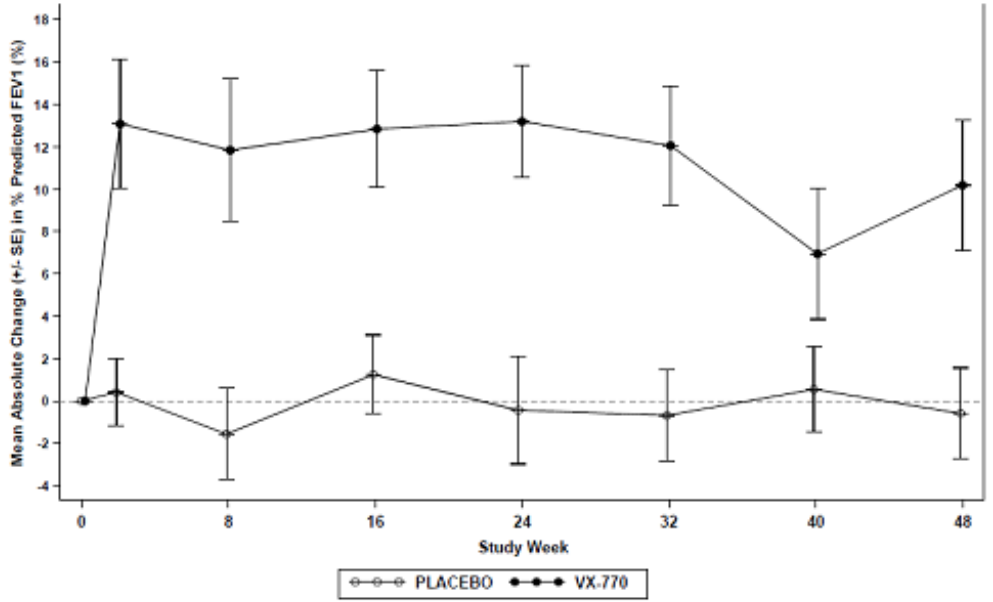
Cystic Fibrosis with G551D-CFTR mutation

Figure 11 Mean Absolute Change From Baseline in Percent Predicted FEV1 by Treatment in study 103
Full Analysis Set



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BBC news

Health

Cystic fibrosis drug offers hope to patients

By James Gallagher Health editor, BBC News website

17 May 2015

From the section Health

BMs in clinical use: pharmacovigilance

- The occurrence of **rare but serious ADRs or lack of efficacy / effectiveness** have often been **identified late** in drug development phase or long after drug approval

- **Limited information** available on the **utilisation of a genomic biomarker** during follow up (**post marketing**) or on the **effect of labelling** with genomic information.

- Guidelines have been adopted for the evaluation of **genomic influences during Pharmacovigilance activities** in order to inform and improve clinical use of specific treatments.

Collection and storage of genomic material (e.g. DNA or other)

- during clinical trials and
- up on the occurrence of serious ADRs, lack of effectiveness post authorisation or unexpected worsening of the condition

BMs in clinical use: pharmacovigilance

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Carbamazepine
HLA-B*1502 all
and with HLA-A
Japanese desce
Key message

Carbamazepine-induced s
Japanese patients are ass

However, the evidence to
only about 40% of patien

The clinical utility of testi
carbamazepine is not pro

Carbamazepine-induced S
testing for HLA-B*1502 a
100% of cases could be a
this allele in other Asian p

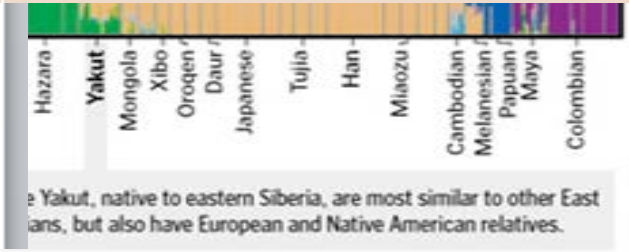
Therefore, the recommer

Population example	HLA-B*1502 SJS/TEN	HLA-A*3101 cutaneous hypersensitivity ADRs
Han Chinese and Thai	Testing whenever possible is recommended to prevent carbamazepine induced SJS	(Associated with mild cutaneous reactions such as maculopapular exanthema in Han Chinese)
Other Asian populations (e.g. Philippines and Malaysia)	Testing may be considered	
European Caucasians and Japanese		Insufficient data supporting a recommendation for screening . If known positive, consider B/R.

Individuals of Han Chinese and Thai origin should, whenever possible, be tested for HLAB* 1502 allele prior to treatment with carbamazepine.

Testing for HLA-B*1502 allele in other Asian populations at genetic risk may be considered.

Routine testing for HLA-A*3101 allele is not recommended. If European Caucasians or patients of Japanese descent are known to be positive for HLA-A*3101 allele, the use of carbamazepine may be considered if the benefits are thought to exceed the risks.



e Yakut, native to eastern Siberia, are most similar to other East
ians, but also have European and Native American relatives.

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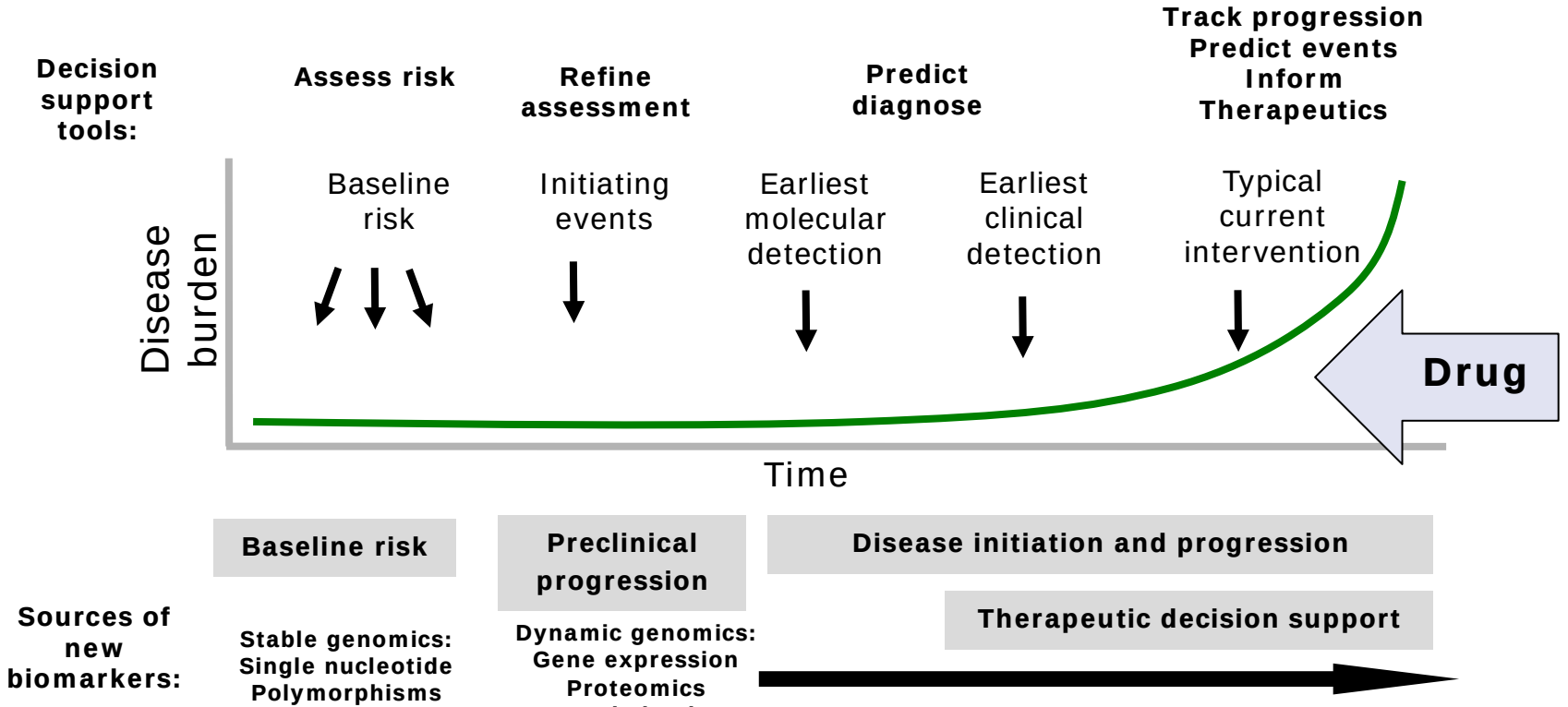
Biomarkers potential



Source: "Personalized Medicine: Current and Future Perspectives," Patricia Deverka, MD, Duke University, Institute for Genome Sciences and Policy; and Rick J. Carlson, JD, University of Washington

Take away messages

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- Biomarkers are measured with *modern technologies* (e.g. genomics, digital tools): useful to better develop medicines and personalise care *adding precision to the clinical judgment* about which medicines an individual may either benefit from and how (e.g. dose) or should avoid
- BM are measurements that may be *requested by the regulatory authorities or proposed by sponsors* for medicines in clinical development and use
- The potential of data generated on biomarkers is well *beyond the medicines* themselves: personalised, participatory, preventive, predictive and *patient centred health care*
- The BM samples and data:
  - *contributions from patients groups with* discussion and participation in *shaping the informed consent principles* a key document with statements on the reason for taking samples/ measurements, the planned and future use of the samples and data, the measure for data privacy protection, the description of interactions and communication on both expected and unexpected findings
  - *Yourself*: Have your interpreted results with you for the future (https://www.pharmgkb.org/): clinically relevant
  - *Yourself*: Know in which biobank/database your "sample" is and for how long : help the system to evolve

Thanks for your attention and questions

Further information

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