EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ENCePP Plenary meeting
12 November

Introduction to Pharmacogenomics

Presented by: Marisa Papaluca
Head of Scientific Support Office
European Medicines Agency

Pharmacogenomics - Definitions

ICH Definitions:

Pharmacogenomics (PGx) is defined as:

The study of variations of DNA and RNA characteristics as related to drug response.

Pharmacogenetics (PGt) is a subset of pharmacogenomics (PGx) and is defined as:

The study of variations in DNA sequence as related to drug response.

Pharmacogenomics can be defined as the technology that analyzes how the genetic makeup of an individual affects his/her response to drugs. As the word suggests, it combines the knowledge of pharmacology and of genomics. It is the technology that deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms (SNP) with a drug's efficacy or toxicity. By doing so, pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects.[3] Such approaches promise the advent of "personalized medicine"; in which drugs and drug combinations are optimized for each individual's unique genetic makeup.

Genetic variants and drug response

- Responses to virtually all drugs can vary between individuals
  - intrinsic factors (such as age, health and **genetics**) and/ or
  - extrinsic factors (such as diet, the use of concomitant drugs and adherence) that may affect drug PK and/or PD parameters

- Examples of genetic variants that influence drug response include:
  - single nucleotide polymorphisms (SNPs) = is a DNA sequence variation occurring when a single nucleotide — A, T, C or G — in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes in a human
  - insertions and deletions,
  - copy number variations

- Response to drugs depends on:
  - genes relevant to the drug's PK (**ADME)**,
  - genes that encode drug targets (intended or unintended) - and their associated pathways PD
  - Genes that influence disease susceptibility or progression
  - Genes that influence ADRs susceptibility

Pharmacogenomics variants and dose

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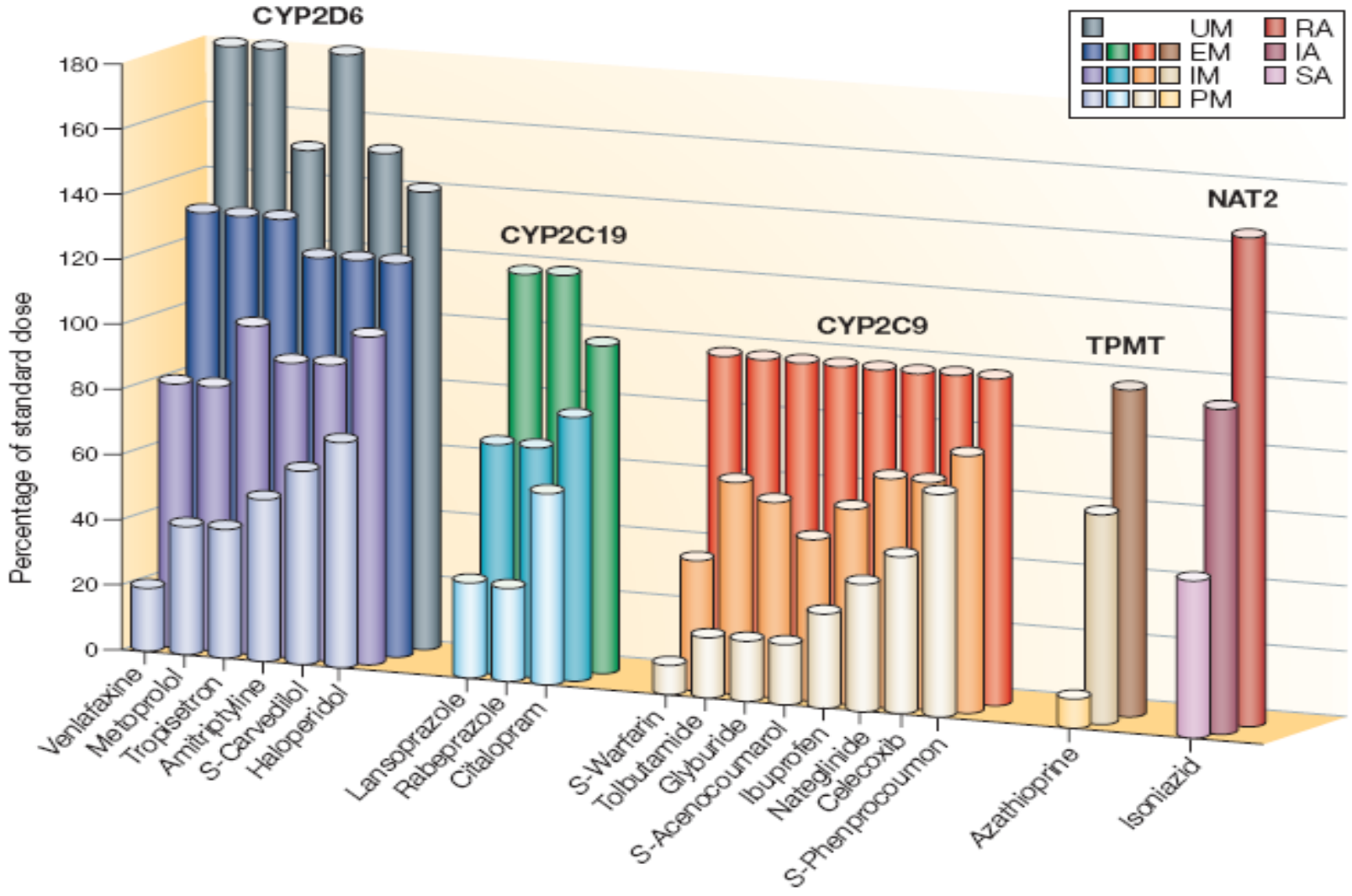

Stratified medicines

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Medicines in the centralised procedure with genomic biomarkers

Name	INN	Year	Marker	Objective	ATC
Ziagen	abacavir	1999	HLA-B*5701	Safety	J
Herceptin	trastuzumab	2000	HER2 receptor	Pts selection	L
Glivec[1]	imatinib	2001	c-kit	Pts selection	L
Trisenox[1]	Arsenic trioxide	2002	PML/RARα	Pts selection	L
Erbitux	cetuximab	2004	EGFR/K-Ras	Pts selection	L
Tarceva	erlotinib	2005	EGFR-	Pts selection	L
Sprycel[1]	dasatinib	2006	Ph+ chromosome BCR ABL fusion gene mutants	Pts selection	L
Celsentri	maraviroc	2007	CCR5 co-receptor	Pts selection	J
Tasigna[1]	nilotinib	2007	Ph+ chromosome	Pts selection	L
Vectibix	panitumumab	2007	K-Ras	Pts selection	L
Tyverb	lapatinib	2008	HER2	Pts selection	L
Iressa	gefitinib	2009	EGFR/K-Ras	Pts selection	L
Edurant	rilpivirine	2010	HIV – gen 1	Pts selection	J
Caprelsa	vandetanib	2011	RET mutation	Pts selection	L
Eviplera	emtric/rilpivir / tenofovir disoproxil	2011	HIV – gen 1	Pts selection	J
Victrelis	boceprevir	2011	HCV gen 1	Pts selection	J
Igemidi	gemcitabine elaidate	2012	Low hENT1 expression	Pts selection	L
Kalydeco	ivacatfor	2012	G551D mutation CFTR gene	Pts selection	R
Xalcori	crizotinib	2012	Anaplastic lymphoma kinase (ALK)-oncogenic variants	Pts selection	L
Zelboraf	vemurafenib	2012	BRAF V600 mutation	Pts selection	L
Zemaira	Human alpha1-proteinase inhibitor	2012	Alpha1 antitripsin mutation	Pts selection	R
Iclusig	ponatinib	2013	Ph+ chromosome BCR ABL fusion gene mutants	Pts selection	L
Bosulif	bosutinib monohydrate	2013	Ph+ chromosome BCR-ABL gene mutants T315I mutation	Pts selection	L

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Infectious disease

Oncology

Respiratory

products

Pharmacogenomics and outcomes

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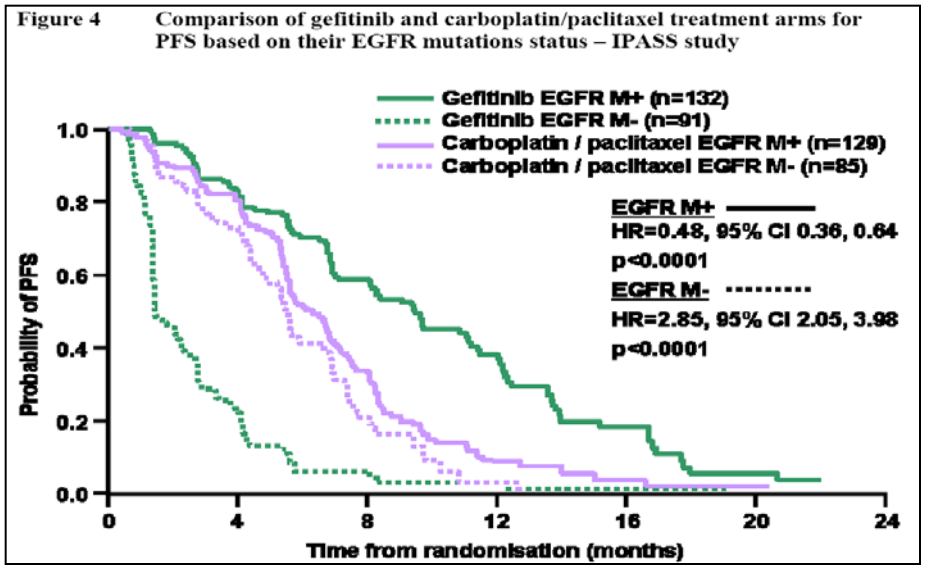

Table 2 | **Examples of genes affecting PK, PD or disease susceptibility or progression**

Area involved	Treatment or disease	Gene involved
ADME (PK)	Clopidogrel	*CYP2C19* variants[14–16]
	Simvastatin	*SLCO1B1* variants[13,32]
PD	Vemurafenib	*BRAF* variants (for example, BRAF-V600E)[47]
	Cetuximab and panitumumab	*KRAS* variants (for example, wild-type KRAS)[48]
Disease susceptibility or progression	HIV	*CCR5* variants (that is, CCR5-Δ32)[49]
	Rheumatoid arthritis	*HLA-DRB1* and *HLA-DRB4* variants[50]

ADME, absorption, distribution, metabolism and excretion; *CCR5*, chemokine (C-C motif) receptor 5; *CYP2C19*, cytochrome P450, family 2, subfamily C, polypeptide 19; *HLA-DRB*, major histocompatibility complex, class II, DR beta; PD, pharmacodynamics, PK, pharmacokinetics; *SLCO1B1*, solute carrier organic anion transporter family, member 1B1.

Pharmacogenomics variants and ADRs

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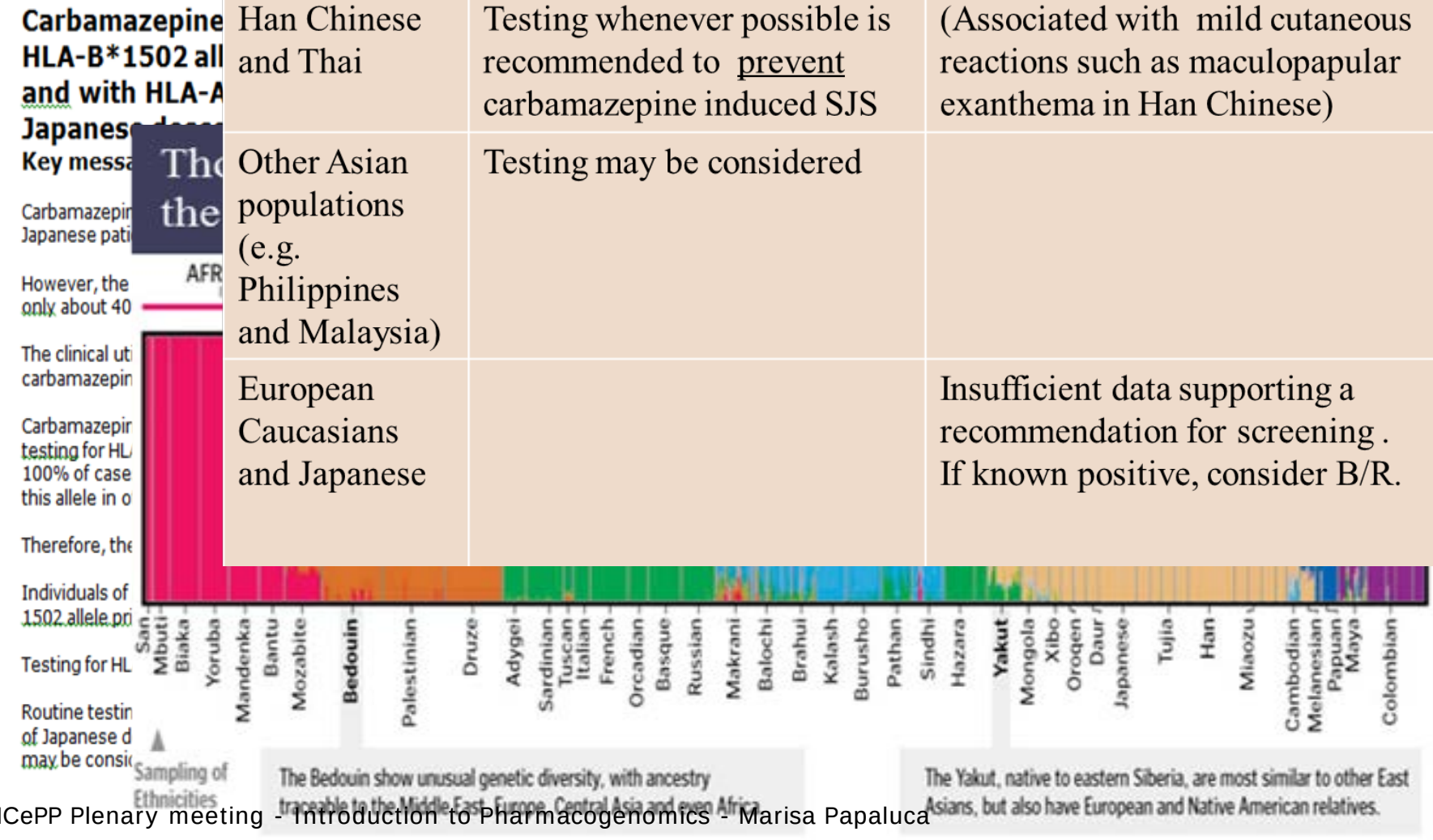
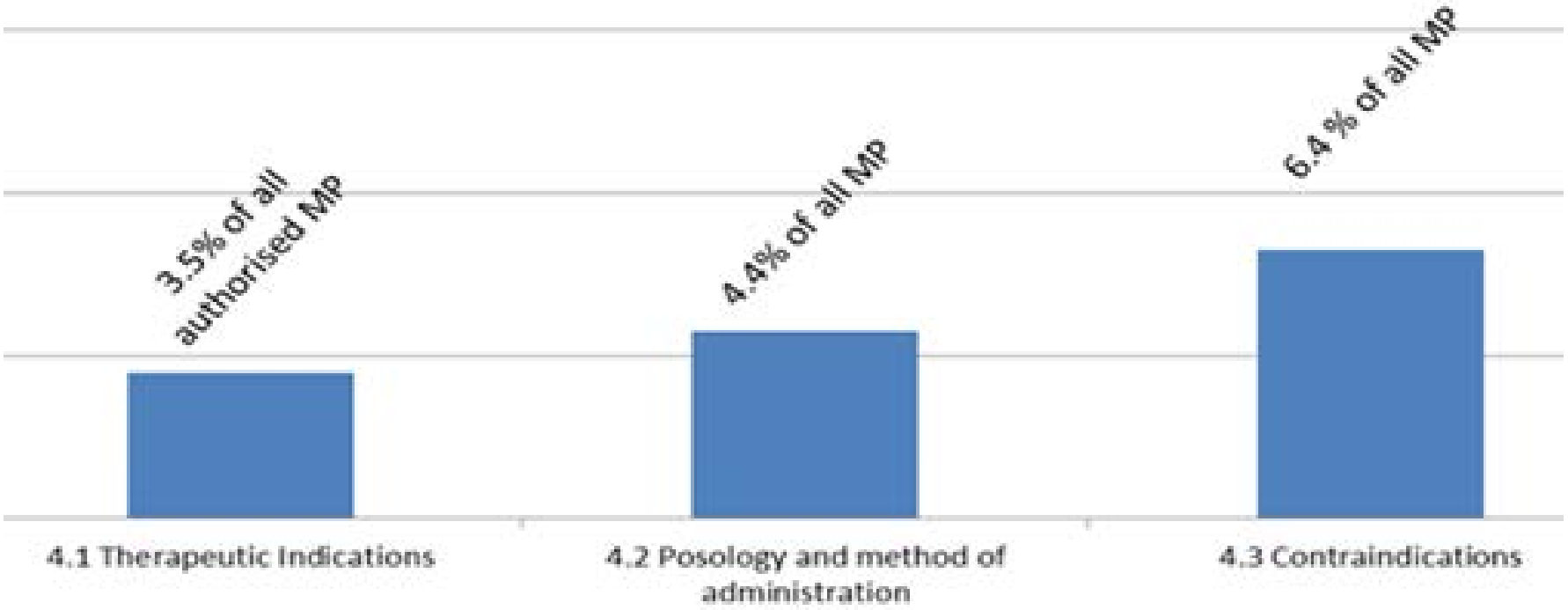
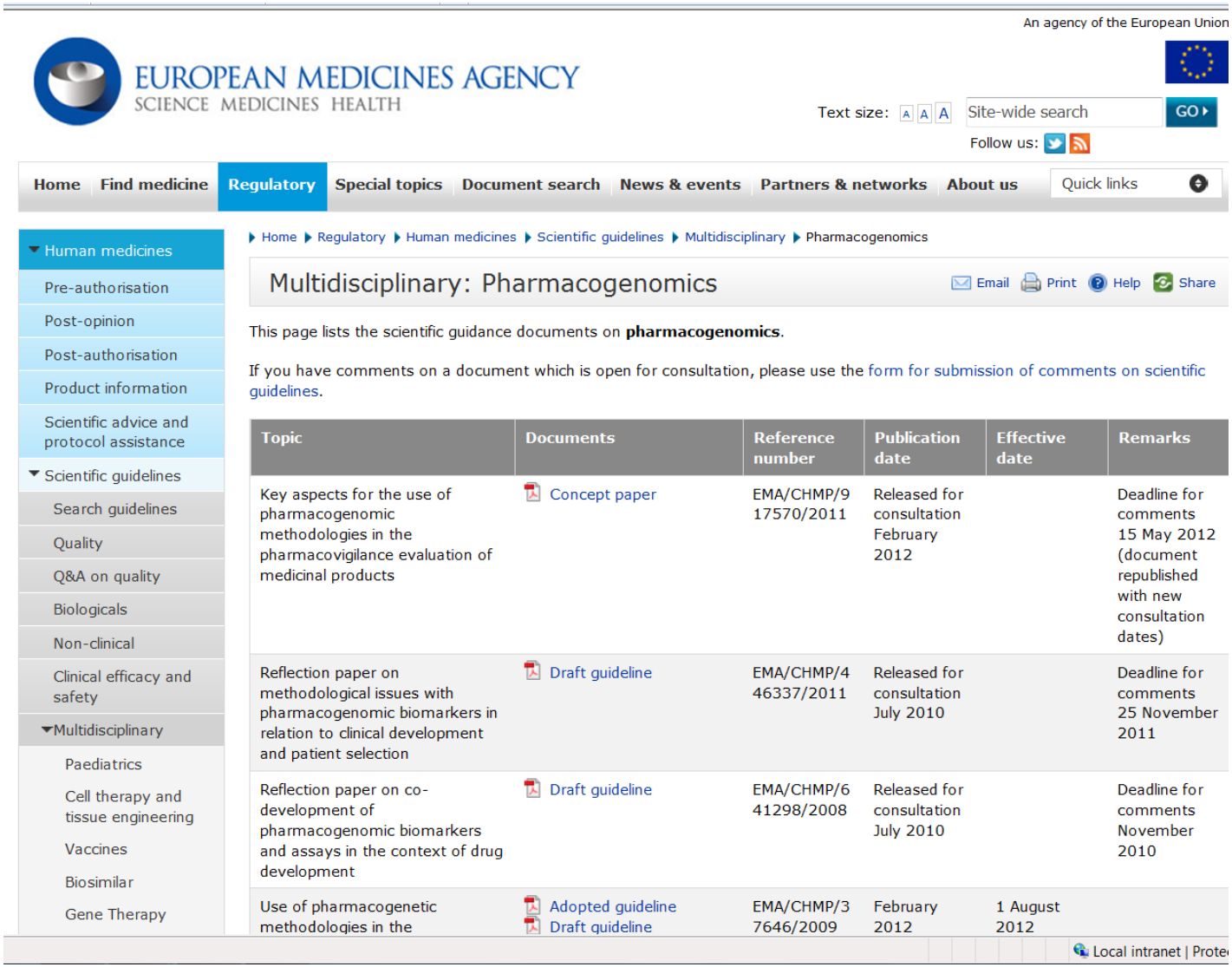
Population example	HLA-B*1502 SJS/TEN	HLA-A*3101 cutaneous hypersensitivity ADRs
Han Chinese and Thai	Testing whenever possible is recommended to prevent carbamazepine induced SJS	(Associated with mild cutaneous reactions such as maculopapular exanthema in Han Chinese)
Other Asian populations (e.g. Philippines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



Pharmacogenomics and SmPC





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Multidisciplinary: Pharmacogenomics

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This page lists the scientific guidance documents on **pharmacogenomics**.

If you have comments on a document which is open for consultation, please use the form for submission of comments on scientific guidelines.

Topic	Documents	Reference number	Publication date	Effective date	Remarks
Key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products	Concept paper	EMA/CHMP/917570/2011	Released for consultation February 2012		Deadline for comments 15 May 2012 (document republished with new consultation dates)
Reflection paper on methodological issues with pharmacogenomic biomarkers in relation to clinical development and patient selection	Draft guideline	EMA/CHMP/446337/2011	Released for consultation July 2010		Deadline for comments 25 November 2011
Reflection paper on co-development of pharmacogenomic biomarkers and assays in the context of drug development	Draft guideline	EMA/CHMP/641298/2008	Released for consultation July 2010		Deadline for comments November 2010
Use of pharmacogenetic methodologies in the	Adopted guideline Draft guideline	EMA/CHMP/37646/2009	February 2012	1 August 2012	

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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

Perspectives

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

Marc Maliepaard[1,7], Charity Nofziger[2,7], Marisa Papaluca[3], Issam Zineh[4], Yoshiaki Uyama[6], Krishna Prasad[5], Christian Grimstein[4], Michael Pacanowski[4], Falk Ehmann[3], Silvia Dossena[2] & Markus Paulmichl[2] About the authors

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Pharmacogenetics, one of the cornerstones of personalized medicine, has the potential to change the way in which health care is offered by stratifying patients into various pretreatment categories, such as likely responders, likely non-responders or likely to experience adverse drug reactions. In order to advance drug development and regulatory science, regulatory agencies globally have promulgated guidelines on pharmacogenetics for nearly a decade. The aim of this article is to provide an overview of new guidelines for the implementation of pharmacogenetics in drug development from a multiregional regulatory perspective — encompassing Europe, the United States and Japan — with an emphasis on clinical pharmacokinetics.

EMA guidance on Pharmacogenomics in drug development

Factors describing when pharmacogenetics studies are required

- If **in vitro and/or clinical (in vivo)** studies indicate that a known functionally polymorphic enzyme or drug transporter is:
  - likely to be important in the **metabolism and elimination of the drug**.
  - likely to represent an **important factor** in the **formation, elimination or distribution** of a pharmacologically active or **toxic metabolite**.

- if clinical studies indicate that differences in (PK) properties cannot be explained by other intrinsic or extrinsic factors and are likely to influence the efficacy or safety of the drug.

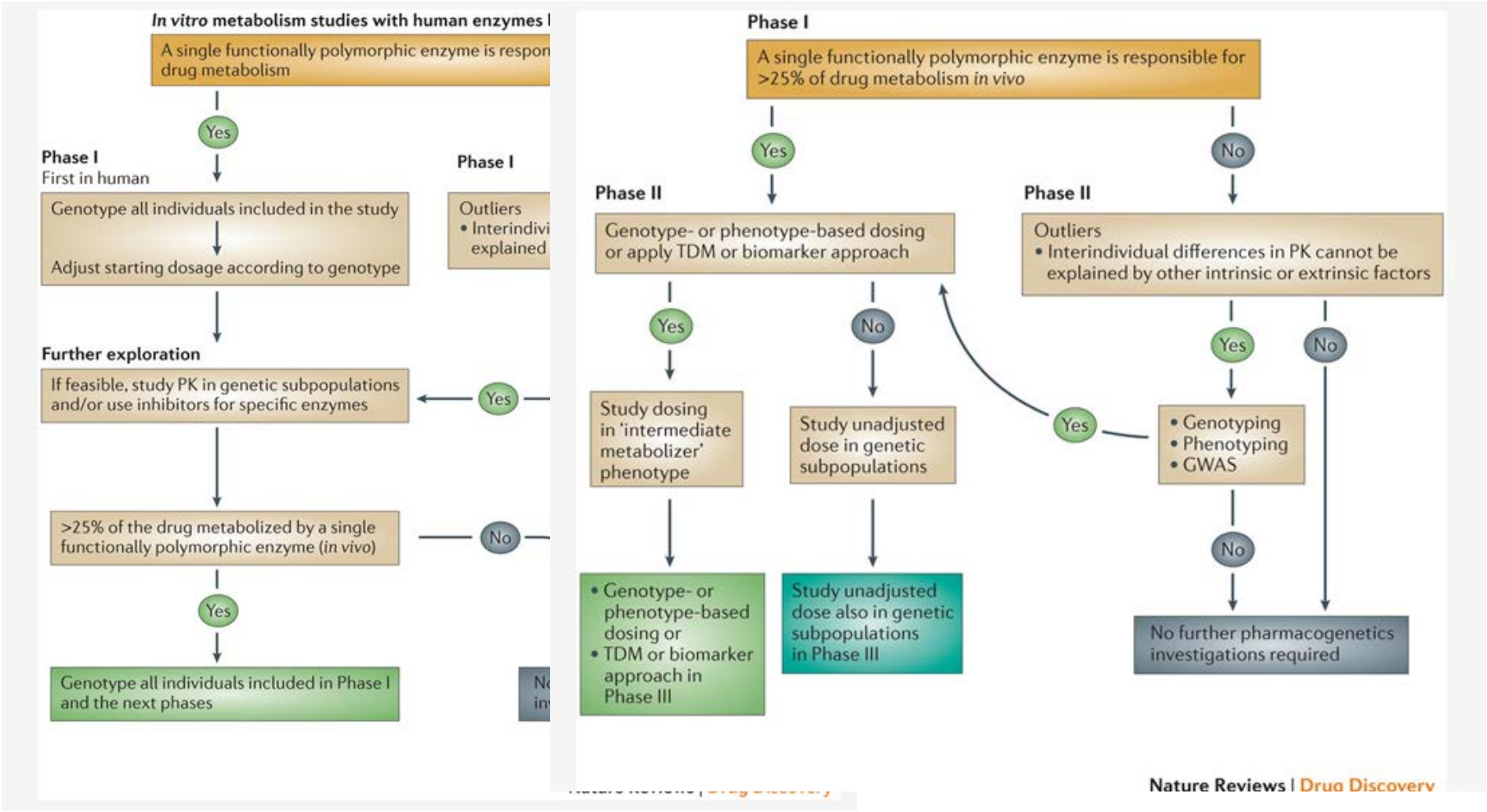
Factors describing when pharmacogenetics studies are recommended

- If the available in vitro data indicate that a polymorphic enzyme or drug transporter contributes to the PK properties of the active substance, but that the **quantitative role is relatively low based on the in vitro data**.

- Or if there is **high interindividual PK variability**, or there are **PK outliers** with higher

- Or if **major PK differences between ethnic groups**

EMA guidance on Pharmacogenomics in drug development



EMA guidance on Pharmacogenomics in drug development

Factors describing when pharmacogenetics studies are considered in Phase III studies

- If **difference in dosage is likely to be clinically relevant** (genotype- or phenotype-based dosing regimen was developed in Phase I / II)
- If **difference in exposure is likely to be clinically relevant**, but owing to the available marketed formulations it is **not possible to adjust the doses** → Patients tested positive for a specific genotype or phenotype (at risk) should then be **excluded from trials**.
- If preliminary studies suggest that a **marked difference in drug exposure related to polymorphic enzymes** lacks **clinical relevance**, phase III trial should confirm that genotype has no impact on treatment.

EMA guidance on Pharmacogenomics in Pharmacovigilance

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15 December 2011
EMA/CHMP/917570/2011
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products

Agreed by Pharmacogenomics Working Party	December 2011
Adoption by CHMP for release for consultation	15 December 2011
Start of public consultation	15 February 2012
End of consultation (deadline for comments)	15 May 2012

Comments should be provided using this template. The completed comments form should be sent to PGWPSecretariat@ema.europa.eu

Keywords	*Pharmacogenomics, Pharmacovigilance, Biomarkers, genomic variations*

Problem statement

- 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.

- Guidance is needed for the evaluation of genomic influences during Pharmacovigilance activities in order to inform and improve clinical use of specific treatments.

Key areas discussed

1. More systematic consideration of pharmacogenomics, with application of relevant biomarkers in safety specification of the RMP for targeted therapies

2. Medicines including in the Product Information special recommendations for subpopulations with genetic polymorphisms

3. Early consideration on when, post authorisation genomic data may need to be monitored or collected
   - to confirm appropriate dose and co-medications
   - to provide advice based on identified genomic biomarkers

Key areas discussed

3. 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.

4. Consideration of level and type of evidence

- for identification of signals, and
- how to report to the competent authorities (e.g. in RMP updates, PSURs – published studies etc).

5. Impact of genomic-based risk minimisation measures on Product Information

The guidance should ensure that recommendations are clear and read across existing CHMP/PGWP guidelines and Pharmacovigilance Guidelines

EMA guidance on pharmacogenomics in pharmacovigilance

Guideline on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products

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Thanks for your attention

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