CBG MEB | MEDICINES EVALUATION BOARD

Current state of the art in Pharmacogenomics - a regulatory perspective

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Content

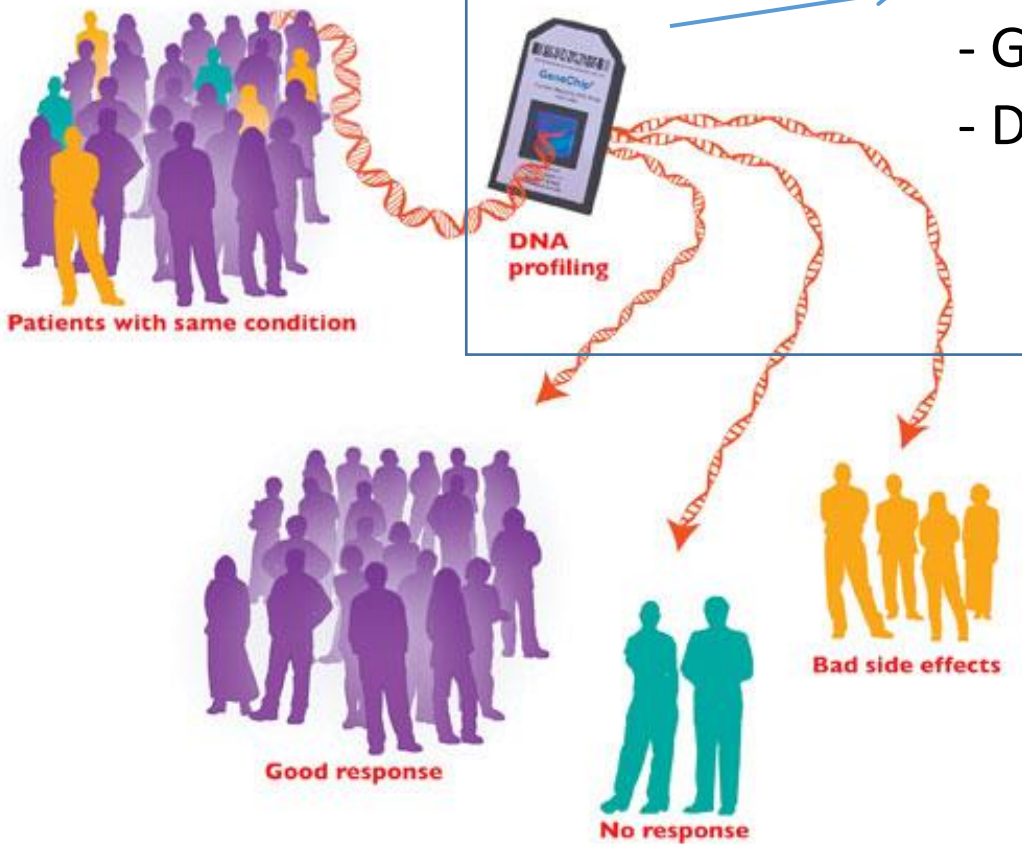
- History pharmacogenomics in regulation

  - Guidance

  - Application guidance

- Current situation and future

DNA profiling

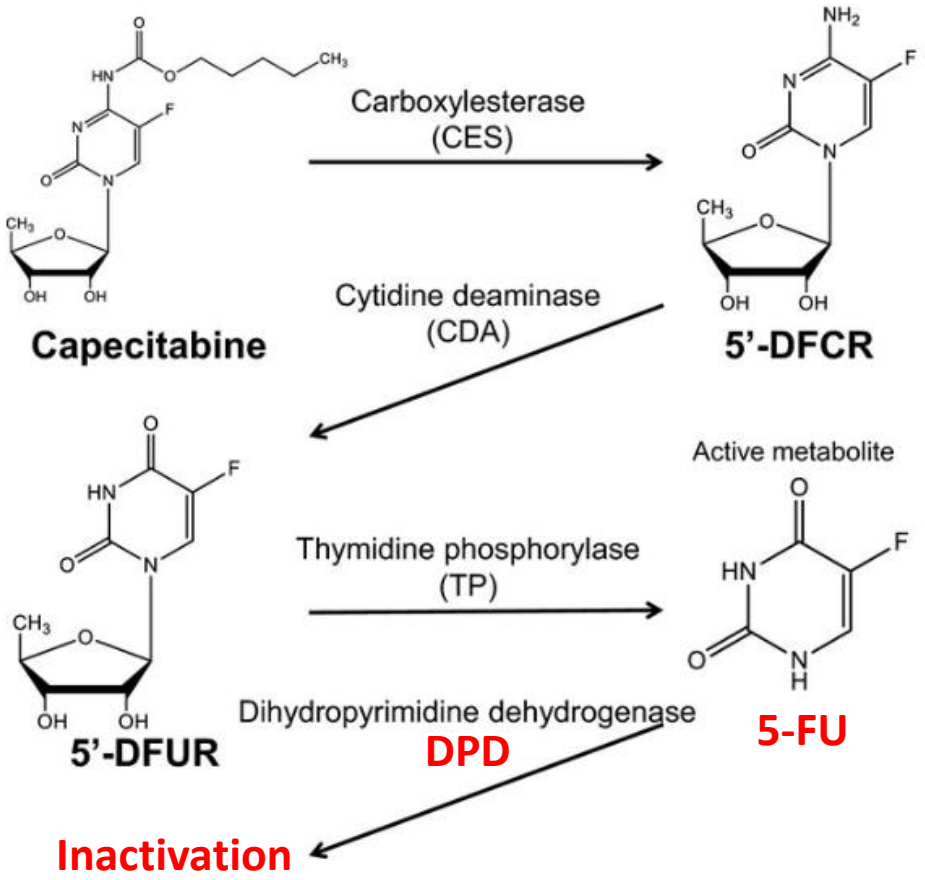


DNA profiling of:

- Germline DNA of patient
- DNA of disease (e.g. tumour)

History pharmacogenomics in regulation: PGx-PK

2001: capecitabin (Xeloda®)



SmPC section 4.3 contraindications:

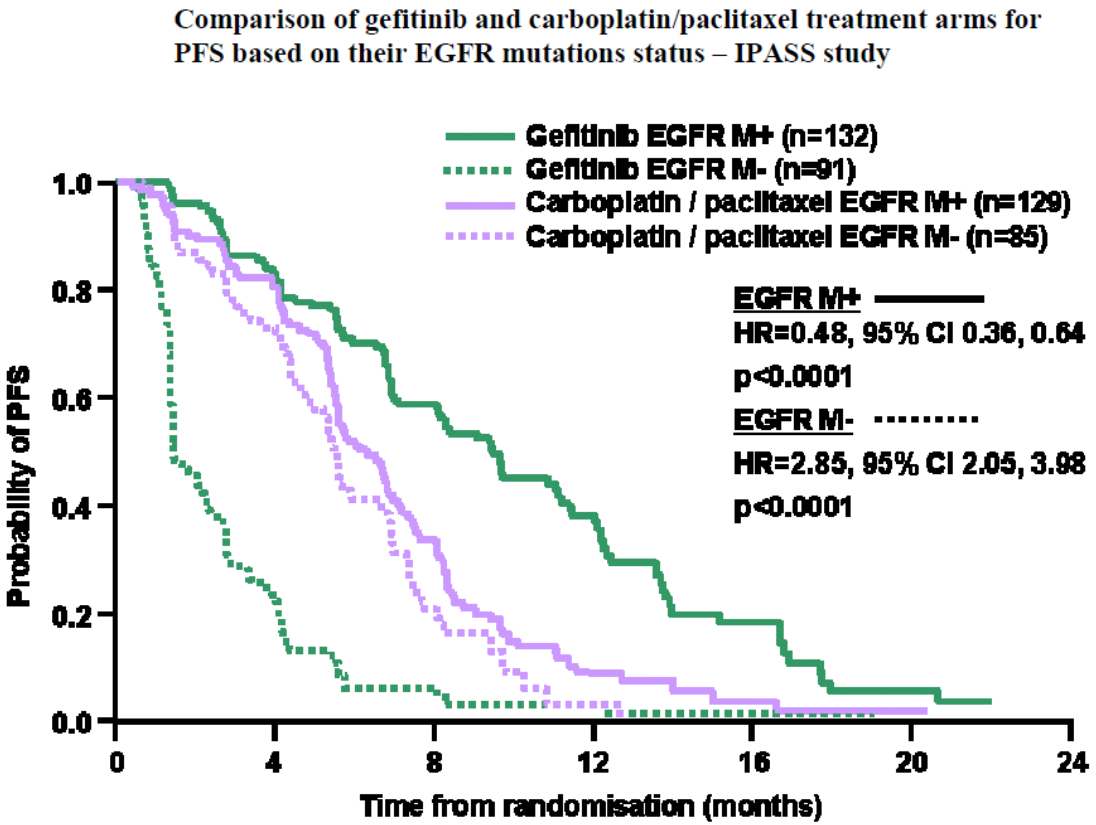
Known complete dihydropyrimidine dehydrogenase (DPD) deficiency (see section 4.4)

Since 2020: SmPC section 4.4 warnings:

Information and advice on partial DPD deficiencies

History pharmacogenomics in regulation: PGx-PD

2009: gefinitib (Iressa®)



SmPC section 4.1 indication:

IRESSA is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating mutations of EGFR-TK (see section 4.4).

History pharmacogenomics in regulation: idiosyncratic reactions

2008: abacavir (Ziagen®)

Registered in 1999

Idiosyncratic hypersensitivity reactions

Poorly understood nor manageable, until in 2007 the effect of a HLA polymorphisms was discovered, HLA-B*5701 allele.

Since 2008: SmPC section 4.1 indication:

…

***Before initiating treatment** with abacavir, **screening for carriage of the HLA-B*5701 allele should be performed** in any HIV-infected patient, irrespective of racial origin(see section 4.4). Abacavir should not be used in patients known to carry the HLA-B*5701 allele*

History pharmacogenomics in regulation

EMA aware of importance of PGx

Since 2005: EMA Pharmacogenomic Working Party PGWP (since 2023 via Methodology WP)

-Promoting investigation of PGx during drug development

-Promoting publication of PGx information in SmPC and EPAR

History pharmacogenomics in regulation

EMA PGx-related Guidelines:

2008 REFLECTION PAPER ON PHARMACOGENOMICS IN ONCOLOGY

2012 Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

2015 Guideline on key aspects for the use of pharmacogenomics in the pharmacovigilance of medicinal products

2018 Guideline on good pharmacogenomic practice

History pharmacogenomics in regulation

Intense global process:

The FDA provides guidance documents for industry, i.e., on pharmacogenomic data submissions and overview of pharmacogenomic biomarkers in drug labeling.

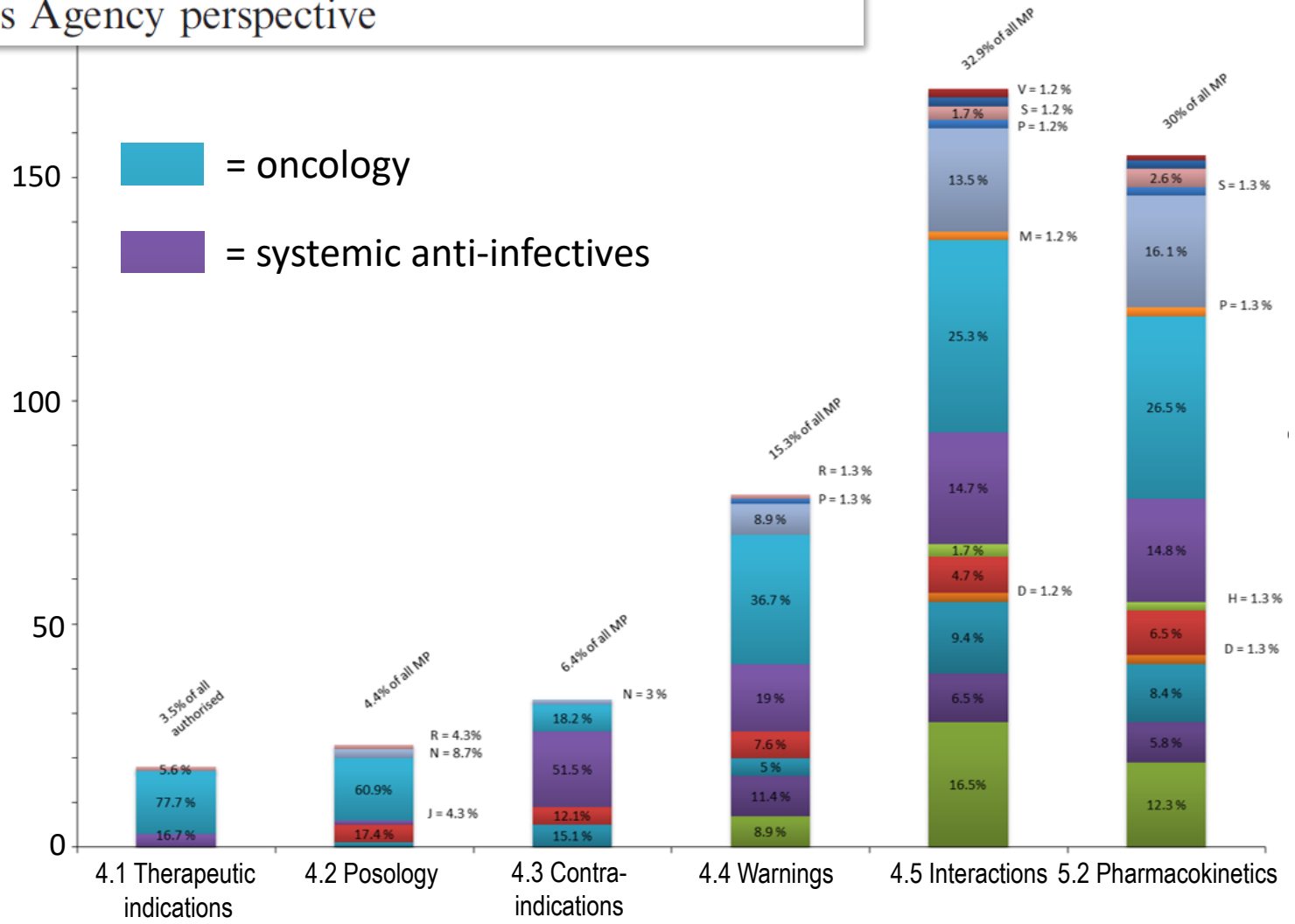
PMDA has issued guidance on the use of pharmacogenomics in drug development and post-marketing surveillance.

PGx data exchange and discussion with FDA and PMDA via PGWP

History pharmacogenomics in regulation: PGx information in EU SmPC

PERSPECTIVE

Pharmacogenomic information in drug labels: European Medicines Agency perspective



176 (**34%**) of all EMA authorised products (*1995-2014*) contain **PGx information in their label (SmPC)**

Ehmann et al, The Pharmacogenomics Journal (2015), 1–10
doi: 10.1038/tpj.2014.86

History pharmacogenomics in regulation: PGx-PK assessment

ARTICLE

Pharmacogenetic-Pharmacokinetic Interactions in Drug Marketing Authorization Applications via the European Medicines Agency Between 2014 and 2017

PK-related gene–drug interactions are addressed adequately in new EU Centralized Procedures, when it concerns non-CYP3A4 substrate drugs

=> For new medicinal products the EMA PGx-PK Guideline appears to be followed to a reasonable extent.

Maliepaard et al, Clinical Pharmacology & Therapeutics (2020) 338-349
doi:10.1002/cpt.1834

Current situation and future

Since 2012

-a number of new medicinal products registered with **PGx-PK** information in the SmPC (e.g. eliglustat (Cerdelga® 2D6), brexpiprazole (Rxulti® 2D6), mavacamten (Camzyos® 2C19)

-**PGx-PK** information added to SmPC to some already registered products (e.g. valproate (Plavix® CYP2C19), capecitabine (Xeloda® DPD)

-Numerous **oncological** products with specific **biomarkers/mutations**

Current situation and future

-Currently PGx received considerable attention during assessment of new MAAs

-in many cases –especially but not only for older already registered products- no adequate PGx data available to allow inclusion in SmPC

-SmPC of registered products is not always updated proactively. EMA takes a **risk-based approach** (e.g. carbamazepine and HLA*B 1502)

Current situation and future

Future

-attention to different genetic polymorphisms per ethnicity

-harmonization of PGx information in the label worldwide

-potential of real world data regarding PGx

-Connect to healthcare professionals aiming to drive the integration of pharmacogenomics into routine healthcare.

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