# Harnessing the value of genomic data for evidence generation

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LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

# Overview

1. **Regulatory Overview**
   - EMA expert group for PGx
   - PGx-related regulatory steps in the past and future

2. **Reflection of PGx in the SmPCs – how far have we come?**
   - Where to find the information
   - important examples of PGx information labeled as a strong recommendation

3. **Challenges**
   - CYP3A4
   - Examples where PGx is currently reflected rather informatively in the SmPCs

4. **The Future: PGx and Big Data**
   - Value of large GWAS, proteome, and metabolome data for personalized treatment

5. **Current and future chances and challenges of PGx**

6. **Take-Home Messages**

# PGx stakeholder workshop September 2024

## Organizers

**Co-hosted by the European Commission (DG-RTD)**

**MWP ESEC members**

## Format

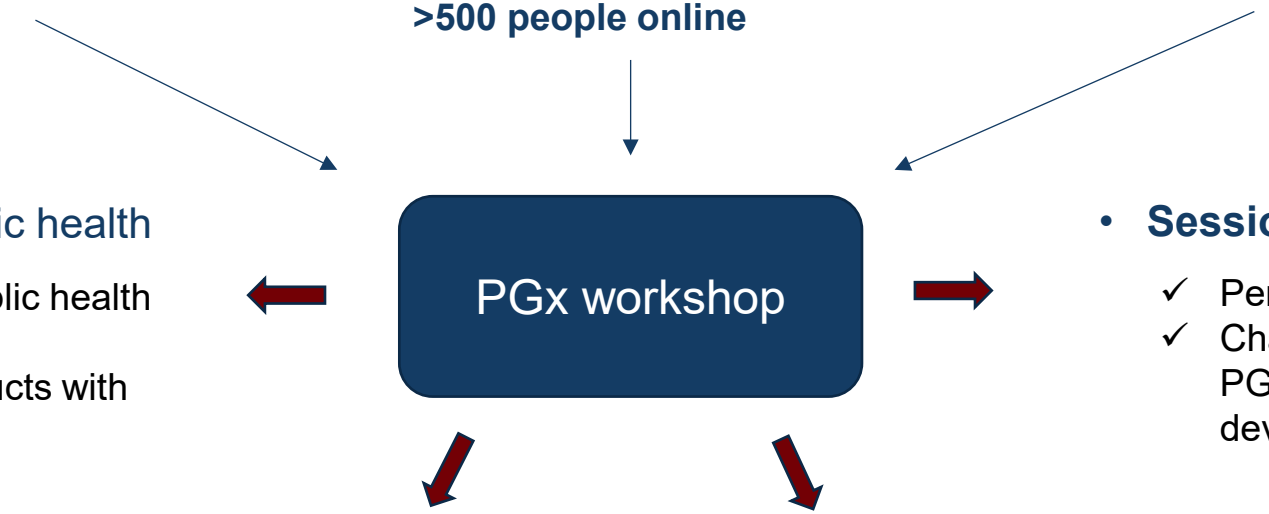
**Full-day hybrid workshop**

**60 in-person attendees**

**>500 people online**

## Material

**Available on the EMA homepage**




- **Session 1**: PGX and public health
  - ✓ Importance of PGx for public health
  - ✓ Regulatory perspectives
  - ✓ Centrally authorized products with PGx info in the SmPC

- **Session 2**: Clinical practice
  - ✓ Implementation of PGx in clinical practice
  - ✓ Country examples

- **Session 3**: Real World Data and Biobanks
  - ✓ Use of real-world data and biobanks in PGx research

- **Session 4**: Panel discussion
  - ✓ Perspectives from different stakeholders
  - ✓ Challenges and enablers for the use of PGx in healthcare and medicine development

# PGx SIA - Pharmacogenetics expert group within the EMA

EMA

**CHMP/CAT companion diagnostics (CDx) Expert Group**
- *questions regarding CDx*
- *Questions regarding assays*

**SAWP (scientific advice working party)**

**ONCWP / ESEC Oncology**
- *Anticancer Guideline*

**Innovation Task Force**

**former PGWP**

Methodology working party

ESEC

PGx SIA

European commission
In vitro diagnostics regulation

Medical Device Coordination Group (MDCG) Guideline Draft Groups:
- *Guideline on IVD*

EU Notified Body Groups
- *CDx SG* informal exchange with CDx Expert Group*

In vitro diagnostic Medical Devices (IVD) Working group
- *IVD subgroup on CDx*

*CDx SG = Subgroup of the European Notified Bodies created for informal exchange with CHMP/CAT CDx Expert Group

# History of and Upcoming Regulatory Steps in the Field of PGx

# Pharmacogenetic Information in the SmPCs

| Section | Title | Content Related to Pharmacogenetics |
|---|---|---|
| **4.1** | **Therapeutic Indications** | Indicates if pharmacogenetic testing is required for determining therapy eligibility (e.g., HER2 testing for trastuzumab). |
| **4.2** | **Posology and Method of Administration** | Provides information on dosing adjustments based on genetic variants affecting drug metabolism or efficacy (e.g., *TPMT* variants and azathioprine; *CYP2C9* variants and siponimod). |
| **4.3** | **Contraindications** | Lists any genetic conditions or polymorphisms that contraindicate drug use due to safety risks (siponimod and *CYP2C9*) |
| **4.4** | **Special Warnings and Precautions for Use** | Genetic variants that could increase adverse event risks, suggesting or requiring genetic testing (e.g. HLA variants, phenytoin, carbamazepine) |
| **4.5** | **Interaction with Other Medicinal Products** | Genetic variants that affect drug-drug interactions or response |
| **4.8** | **Undesirable Effects** | Highlights adverse reactions that may vary in frequency or severity based on genetic polymorphisms. |
| **5.1** | **Pharmacodynamic Properties** | Provides background on how genetic variants influence the drug's mechanism of action or efficacy |
| **5.2** | **Pharmacokinetic Properties** | Explains how genetic variants impact drug absorption, distribution, metabolism, and elimination |
| **5.3** | **Preclinical Safety Data** | May reference pharmacogenetic findings from preclinical studies |

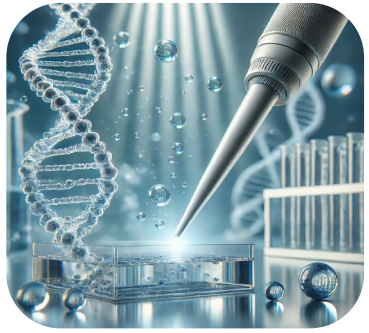
Clinical Relevance: Genetic testing information is usually included when specific variants considerably impact safety, efficacy, or dosing. This comprises especially (but not only):

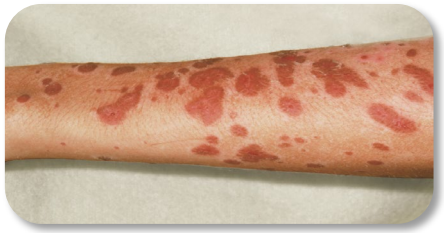
Sections 4.1 - 4.4:
Primary sections for information on mandatory or recommended genetic testing before or during treatment.

Sections 5.1 & 5.2:
Detailed pharmacogenetic insights on how genetic variants influence drug action and metabolism.

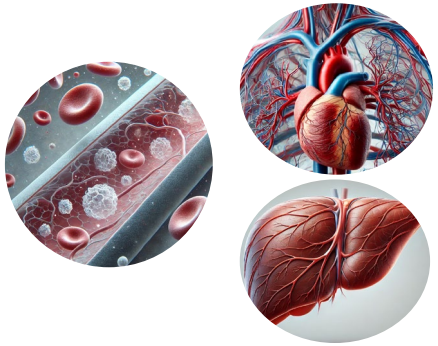
# Essential PGx Applications with Critical Clinical Impact

Companion Diagnostics (CDx)





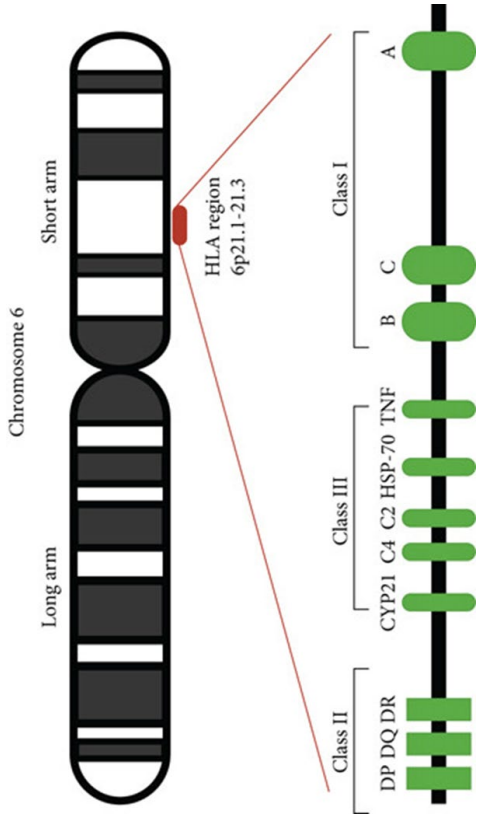
Hamilton et al. 2019, the Pharmaceutical Journal



| Drug | SmPC Section | Genotyping Requirement | Gene/Allele | Reason |
|---|---|---|---|---|
| **Ivacaftor** | 4.1 | strong | *CFTR* (several variants, e.g., *G551D*) | Confirm CFTR mutation responsive to ivacaftor |
| **Trastuzumab** | 4.1 | strong | HER2 overexpression | Confirm HER2 status for therapy suitability |
| **Gefitinib** | 4.1 | strong | EGFR-TK mutation status | Confirm activating mutations of EGFR-TK |
| **Maraviroc** | 4.1 | strong | CCR5-tropic HIV-1 | Confirm CCR5-tropic HIV-1, ineffective against others |
| **Abacavir** | 4.1 | strong | *HLA-B*5701* | Identify hypersensitivity risk |
| **Carbamazepine** | 4.2 | strong | *HLA-B*1502* | Identify risk of severe cutaneous adverse reactions in patients with Asian descent |
| **Sipominod** | 4.2 | strong | CYP2C9 poor metabolizer | Genotyping before start. Adjust dosing in case of reduced CYP2C9 activity |
| **Azathioprine & Mercaptopurine** | 4.2 | strong | *TPMT* (e.g., *TPMT*3A, *3C*) | Identify TPMT deficiency linked to myelotoxicity risk |
| **Capecitabine/ 5-Fluorouracil** | 4.3 | strong | *DPYD* (several variants) | Identify DPD deficiency linked to toxicity risk |

*List not exhaustive*

# HLA Genotyping recommendations in the SmPCs

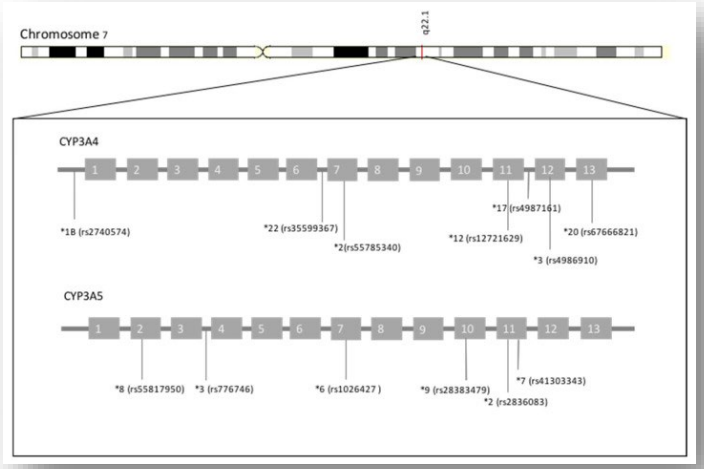



Medhasi et al. 2022, Journal of Immunology Research

| Drug | SmPC Section | Genotyping | Allele | Population |
|---|---|---|---|---|
| **Abacavir** | 4.1 | strong | *HLA-B*5701* | All |
| **Carbamazepine** | 4.2 | strong | *HLA-B*1502* | Asian (e.g., Han Chinese); |
| | 4.4 | Informs about association / no | *HLA-B*3101* | European and Japanese |
| **Allopurinol** | 4.4 | elective | *HLA-B*5801* | Asian |
| **Phenytoin** | 4.4 | caution | *HLA-B*1502* | Asian |
| **Oxcarbazepine** | 4.4 | caution | *HLA-B*1502* | Asian |
| **Lamotrigine** | 4.4 | caution | *HLA-B*1502* | Asian |
| **Flucloxacillin** | 4.8 | Informs about association / no | *HLA-B*5701* | All |

*"SmPC Section" refers to the section in the Summary of Product Characteristics where the genotyping recommendation is stated. List is not exhaustive*

# *CYP3A4 / CYP3A5* genetic variants




Saiz-Rodriguez M et al. 2020, Biomedicines

1

**Certain *CYP3A5* variants may be clinically relevant**
Influence Tacrolimus metabolism

2

**Currently limited Clinical Applicability of *CYP3A4* variants**
Only certain variants, like *CYP3A4*22*, currently show potential for influencing dosing guidance, for certain drugs while most *CYP3A4* alleles lack defined clinical relevance

3

**Complex Regulatory Mechanisms**
CYP3A4 activity is regulated by complex genetic and environmental factors, with overlapping metabolism involving CYP3A5, complicating allele-specific utility assessments

| *SNP* | rs Number | Functional Impact | Clinical Relevance | Allele Frequency |
|---|---|---|---|---|
| | | | ***CYP3A4*** | |
| *CYP3A4*22* | rs35599367 | Reduced enzyme activity | Influences drugs like statins and tacrolimus | White: ~5-8%<br>Asian: <1%<br>Black: <1% |
| | | | ***CYP3A5*** | |
| *CYP3A5*3* | rs776746 | Non-functional enzyme (loss of function) | Common in non-expressers; important for e.g. tacrolimus | White: ~80-90%<br>Asian: ~70-80%<br>Black: ~10-30% |
| *CYP3A5*6* | rs10264272 | Non-functional enzyme | Affects metabolism in individuals of African descent; impacts tacrolimus | White: <1%<br>Asian: Rare<br>Black: ~10-20% |
| *CYP3A5*7* | rs41303343 | Non-functional enzyme | Predominantly found in individuals of African descent, influencing drug metabolism | White: <1%<br>Asian: Rare<br>Black: ~5-10% |

4

**Measurement Challenges**
Distinguishing between CYP3A4 and CYP3A5 contributions is difficult due to shared substrate specificity

5

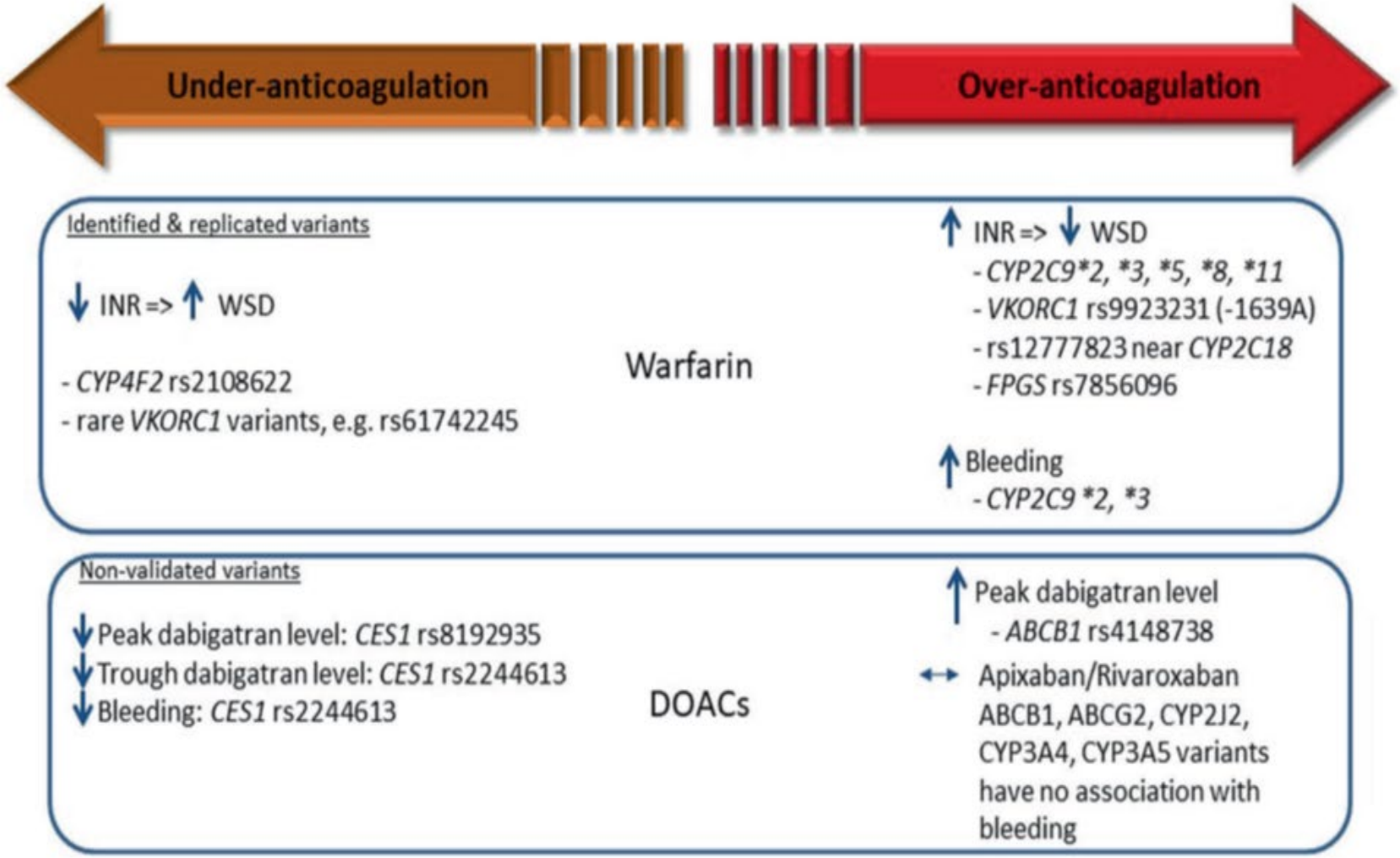
**Genotyping Difficulties**
The complex *CYP3A4* haplotype structure introduces uncertainties in the determination accuracy

6

**Rarity of Certain Alleles**
Low prevalence of some *CYP3A4* alleles limits the ability to fully characterize their effects in clinical settings

Pratt et al. 2023, The Journal of Molecular Diagnostics

# Optimized PGx as a basis for dosing recommendations in the future? Example anticoagulants (Warfarin and DOACs)




Cross et al. 2024, Pharmacogenomics J

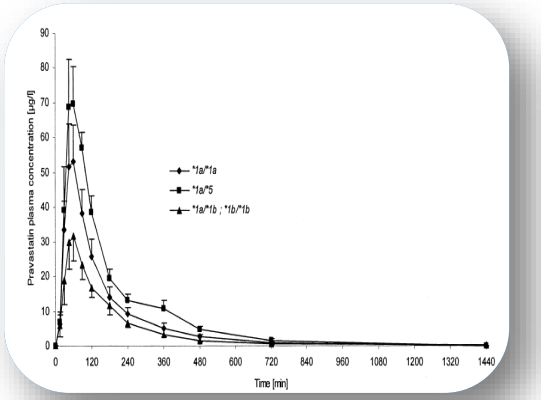
# Further optimized PGx as a basis for dosing recommendations in the future? Example statins – from small pilot studies to big data

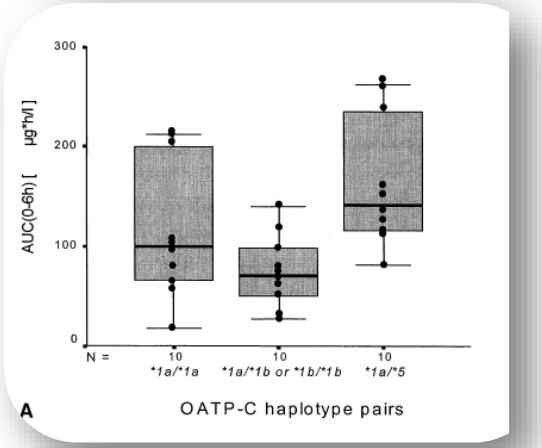
**Statins:**

Muscle symptoms in 1%-30% of statin users (mild to severe).

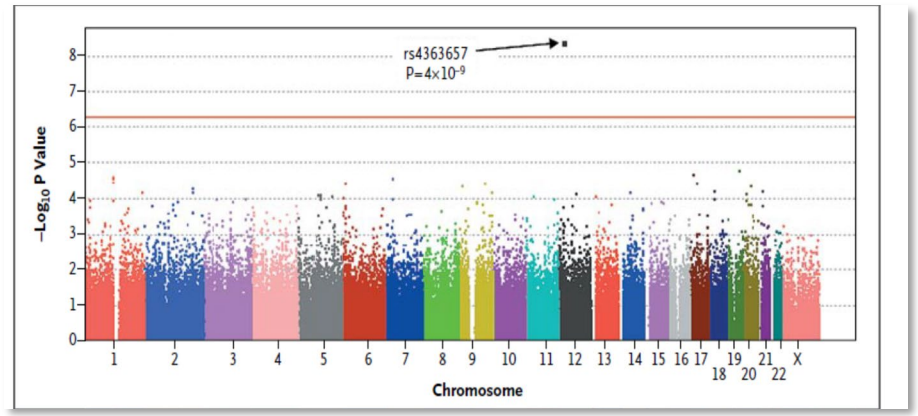
Severe myopathy: 0.1%

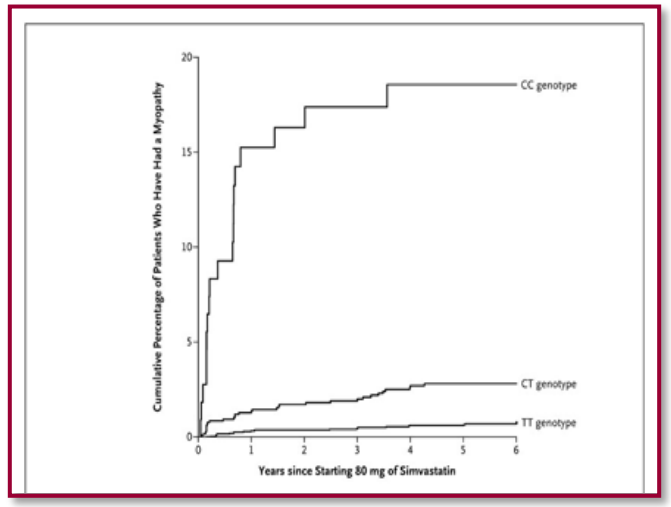
Rhabdomyolysis: <0.01%




Mwinyi et al. 2004, CPT



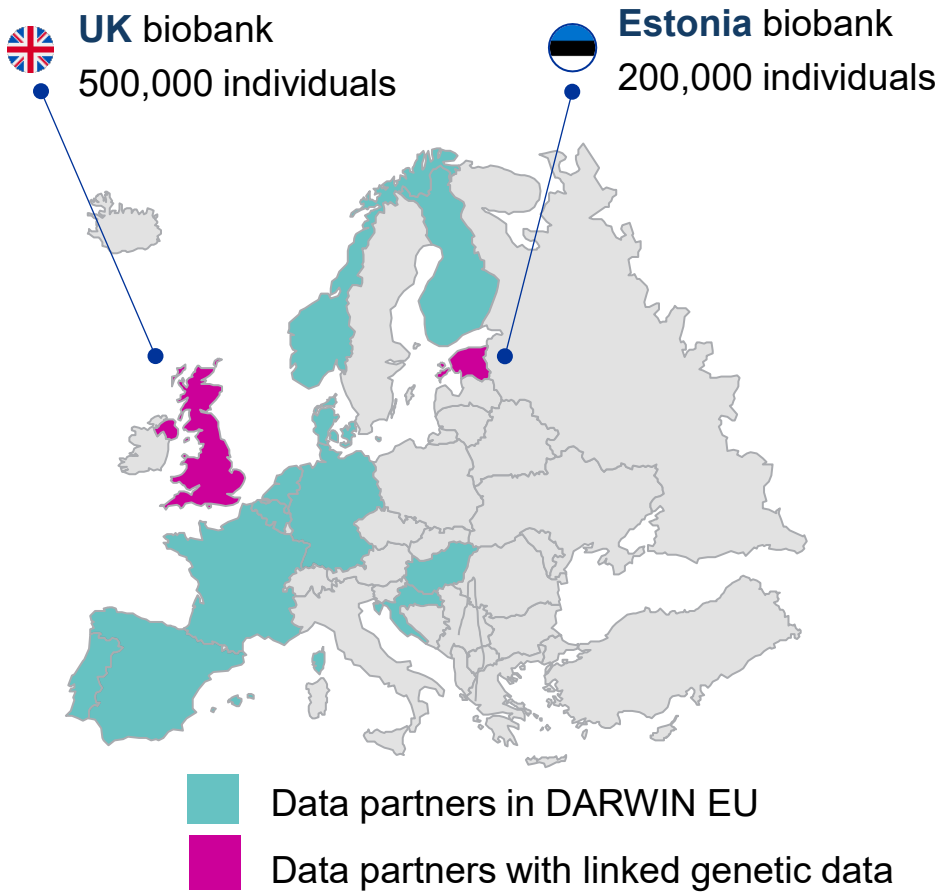

SEARCH Collaborative Group et al. 2008, NEJM

DARWIN EU

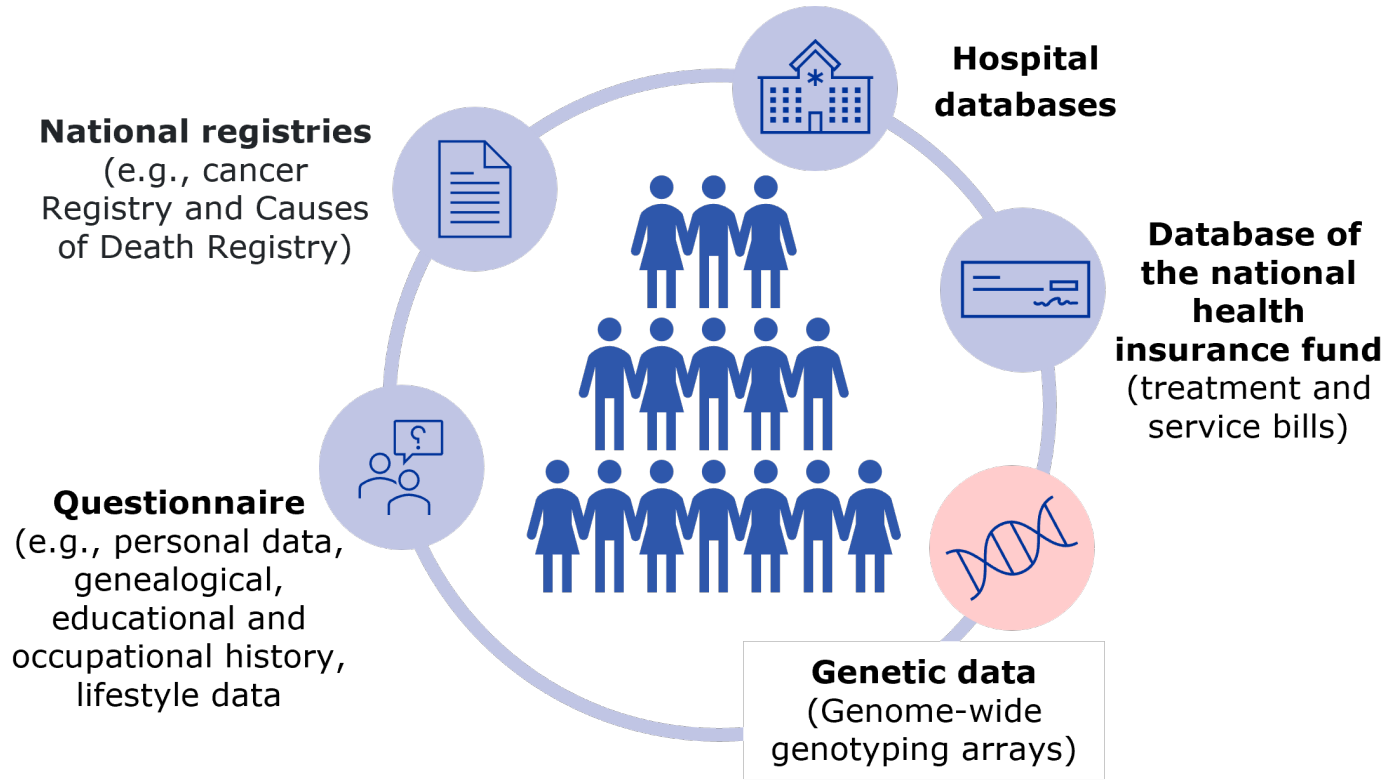
# Large Pharmacogenomics pilot study : Association between genetic polymorphisms of interest and risk of myopathy in statin users

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

DARWIN EU




## Access to genetic data linked to EHRs





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# DARWIN – statin study
# Context, objectives and timeline

DARWIN EU

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

## High-level aim of the pilot

- Contribute to increasing capability in understanding and leveraging pharmacogenomic evidence in regulatory decision-making
- Demonstrate capability of DARWIN EU to generate such evidence

## Rationale for the study

- Regulatory interest in exploring the role of OATP1B1 (*SLCO1B1* c.521CC) gene polymorphism in atorvastatin users with regards to risk of myopathy
- Ultimate aim to inform whether genetic testing may help predict risk of myopathy in users of atorvastatin and other selected statins, and whether dose adjustment may minimise this risk in carriers of the polymorphisms
- Other polymorphisms of interest include *ABCG2* (linked to rosuvastatin)

- **Primary objectives**
  - 1a - To estimate the risk of myopathy in new users of atorvastatin (any dose) according to genotype status
  - 1b - To estimate the risk of myopathy in new users of lower-dose atorvastatin according to genotype status
  - 1c - To estimate the risk of myopathy in new users of higher-dose atorvastatin according to genotype status
- **Secondary objectives**
  - 2a - To estimate the risk of myopathy in new users of simvastatin (separately for any dose, lower-dose and higher-dose) according to genotype status
  - 2b - To estimate the risk of myopathy in new users of rosuvastatin (separately for any dose, lower-dose and higher-dose) according to genotype status if feasible
  - 2c - To estimate the risk of myopathy in new users of fluvastatin (separately for any dose, lower-dose and higher-dose) according to genotype status if feasible
  - 2d - To estimate the risk of myopathy in new users of pravastatin (separately for any dose, lower-dose and higher-dose) according to genotype status if feasible

TIMELINE:

- Protocol to be published shortly in the HMA-EMA Catalogues of real-world data studies (final review ongoing)
- Findings expected in Q1 2025

# The Role of Big Data in Advancing Pharmacogenomics (PGx) – The use of Genome-Wide Data

## OPPORTUNITIES

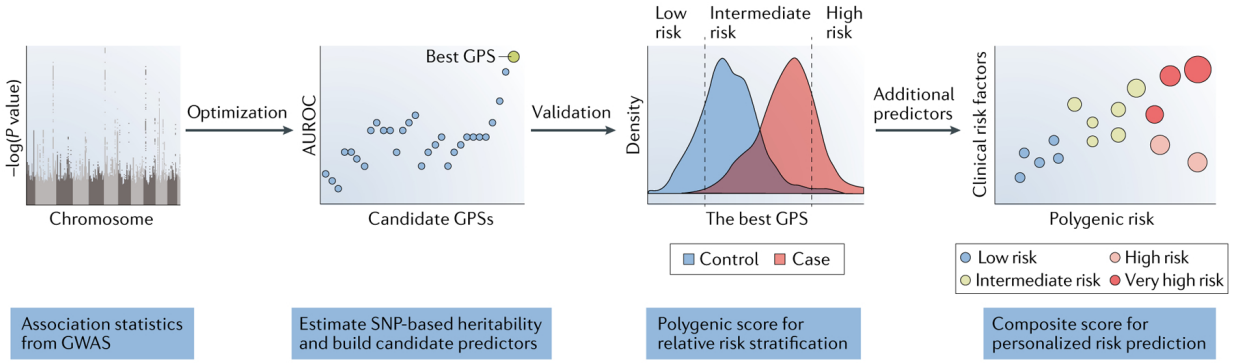
- **Identification of New Genetic Markers**:
  Genome-wide association studies (GWAS) enable the discovery of novel genetic variants linked to drug response and adverse effects.
- **Population-Specific Insights**:
  Large-scale genomic data help identify PGx markers across diverse populations, addressing ethnic variability in drug response.
- **Polygenic Risk Scores**:
  Combine multiple SNPs to predict individual risk for adverse reactions or drug efficacy, which may, in certain cases, enhance personalized treatment.
- **Genome-wide SNP enrichment analyses**
  Identify SNPs that influence gene expression (expression quantitative trait loci (eQTLs)), i.e. those enriched in regulatory regions, revealing functional links between genetic variation and phenotypic traits.

## Current State

- GWAS has identified some important PGx markers

Current Limitations:

- Impact of summary SNP effects not understood yet / needs to be to a stronger extent explored
- SNPs in non-coding areas and their impact on (long-distance) gene regulation not fully understood (eQTL signals)
- Adequate biobank data are missing
- Requires both validation and then also regulatory support




Liu et al. 2018, Nature Rev Nephrol

# Proteomics in personalized therapy

## METHODS

Mass Spectrometry (MS); Affinity-Based Methods (ELISA, Western Blot, or Protein Microarrays)

## APPLICATIONS

### Predicting Drug Response (biomarker-based patient stratification and therapy selection)

Identifies protein profiles and proteins linked to drug sensitivity or resistance

### Understanding Drug Action

Helps to understand drug action and side effects at the protein interaction level

### Novel Therapeutic Targets

Uncovers new proteins for developing tailored therapies

## OPPORTUNITIES

### Examples: Cancer Therapy, Neuropharmacology

Protein expression profiles in tumor cells

Protein expression in CFS (Alzheimer's disease, MS)

### Example: Drug Metabolism

Certain post-translational modifications of drug-metabolizing enzymes or transporters can affect their activity; dosing adjustments may be necessary

### Example: Inflammatory Diseases

Proteomic profiling can reveal e.g. specific kinases as potential drug targets

# Metabolomics in Personalized Therapy

### Biomarker Discovery

Metabolomics can identify metabolite biomarkers linked to drug response, providing insights into individual drug metabolism and potential resistance.

### Precision dosing

Measurement of levels of drug metabolites in blood or urine to determine if a patient is metabolizing the drug effectively, allowing for dose adjustments.

### Metabolic Phenotyping

Can group patients into metabolic phenotypes based on metabolite profiles, enabling precise dose adjustments for drugs with narrow therapeutic windows.

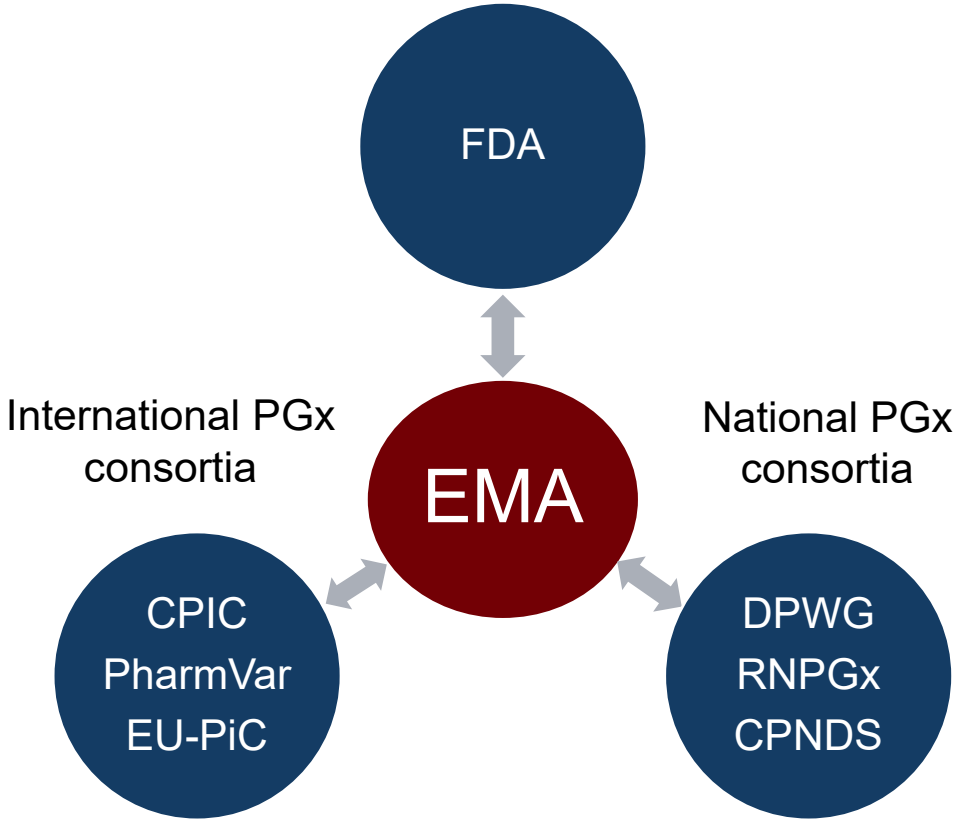
### Genetic and Environmental Influences

May help to clarify how genetic and environmental factors influence drug metabolism

Metabolomics data can provide valuable insights into drug metabolism profiling, prediction of drug interactions, and precision dosing.

# Current limitations of broad PGx applicability

| | |
|---|---|
| **Data Gaps** | Many older drugs lack adequate pharmacogenomic data for SmPC inclusion |
| **SmPC Updates** | Inconsistent updates for registered products with new pharmacogenomic findings |
| **New MAAs** | Comprehensive PGx data in new Marketing Authorization Applications better reflected than in older ones |
| **Currently very conservative approach** | Rather careful PGx implementation approach in SmPCs |
| **Global Inconsistency** | Lack of harmonization in PGx information across global regulatory agencies and consortia |
| **Ethnic Diversity** | Insufficient data on genetic polymorphisms across diverse ethnic groups |
| **PGx in psychopharmacology** | Still very limited information in SmPCs available regarding PGx guided dosing in psychiatry |



# Take home messages regarding regulatory needs in association with PGx

1

## Global Harmonization

Align pharmacogenomic guidelines and SmPC information across regions to ensure consistent application worldwide

2

## Education & Integration

Train healthcare professionals and promote the integration of pharmacogenomics into routine healthcare

3

## Ethnic-Specific Insights

Address genetic diversity across populations by considering polymorphisms specific to different ethnicities

4

## Robust Evidence

Conduct more cost-effectiveness studies and leverage real-world data to strengthen pharmacogenomic evidence

5

## Practical Relevance

Ensure pharmacogenomic information is sufficiently detailed in SmPCs and applicable in clinical practice

6

## Proactive Labeling approach

Update of older products and further in-depth evaluation of areas such as e.g., psychopharmacology and anticoagulative therapy

# Thank you very much!