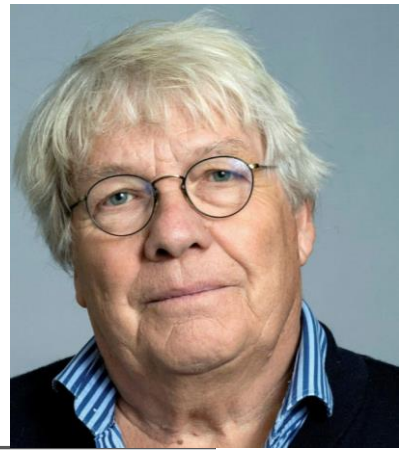
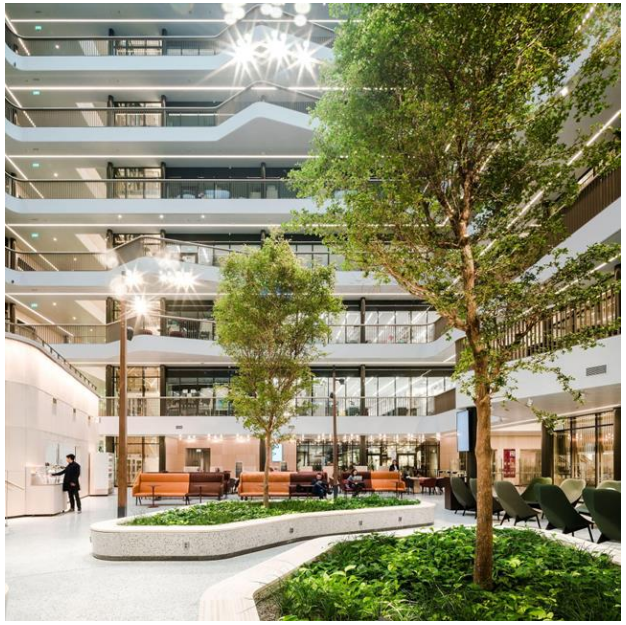
Pharmacogenomics, an update





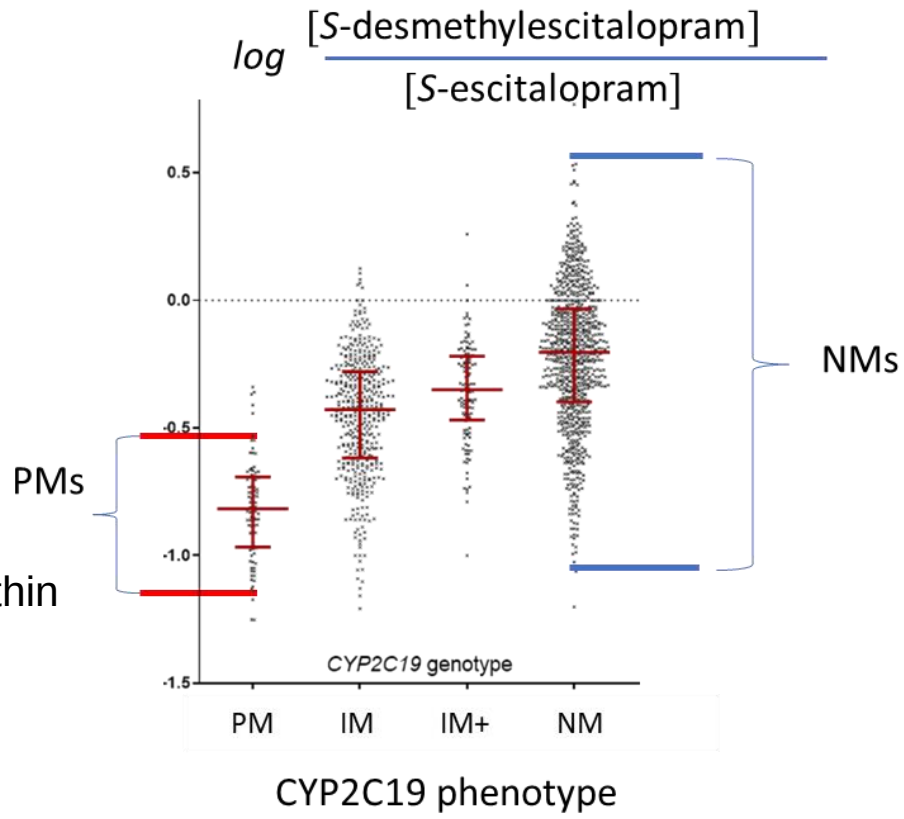
Magnus Ingelman-Sundberg, PhD, BSc.Med, Professor
Department of Physiology and Pharmacology,
Karolinska Institutet, Stockholm, Sweden

CoI: Co-founder and co-owner of HepaPredict AB

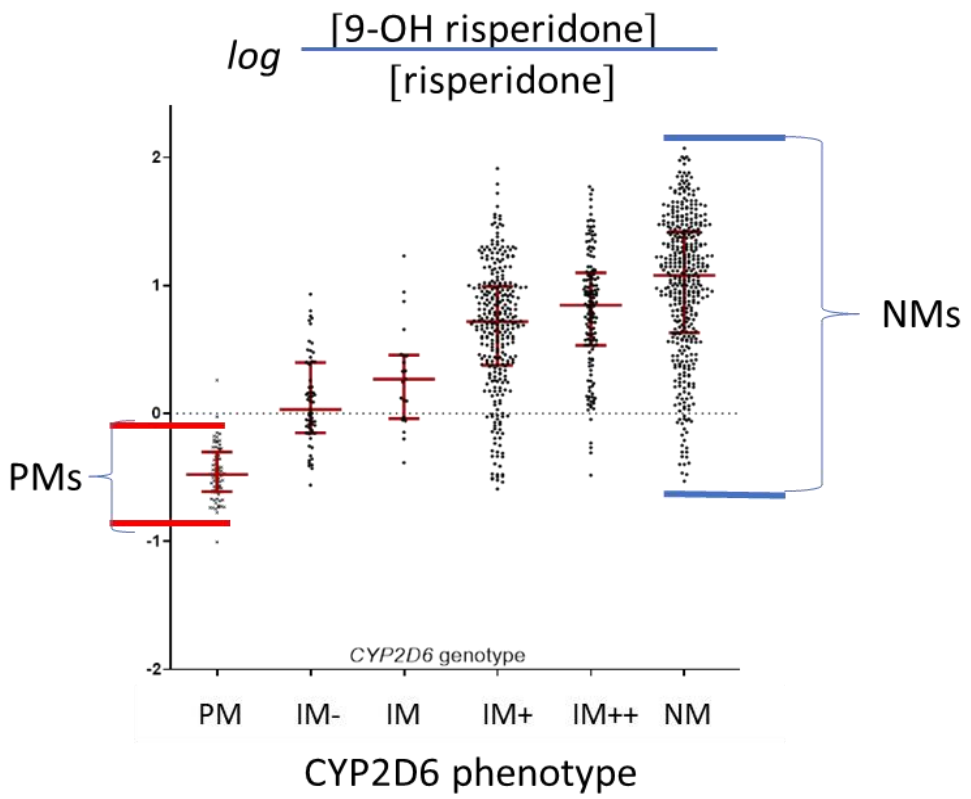
Prospective randomized clinical trials in pharmacogenomics: Focus on pharmacogenomic background and design

The interindividual variation in pharmacokinetics of escitalopram and risperidone among defined phenotypes is very large

PM= poor metaboliser
IM = intermediate metaboliser
NM= normal metaboliser



Jukic et al. *Am J Psychiatry* 2018

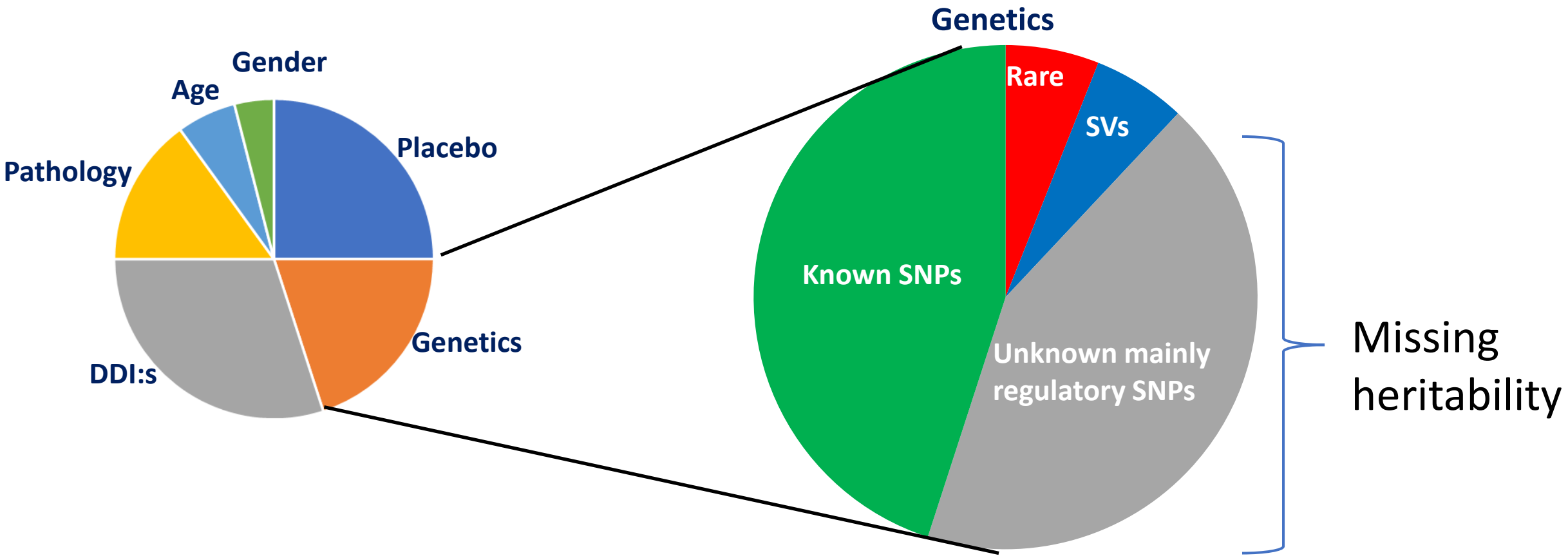


Jukic et al. *Lancet Psychiatry, 2019*

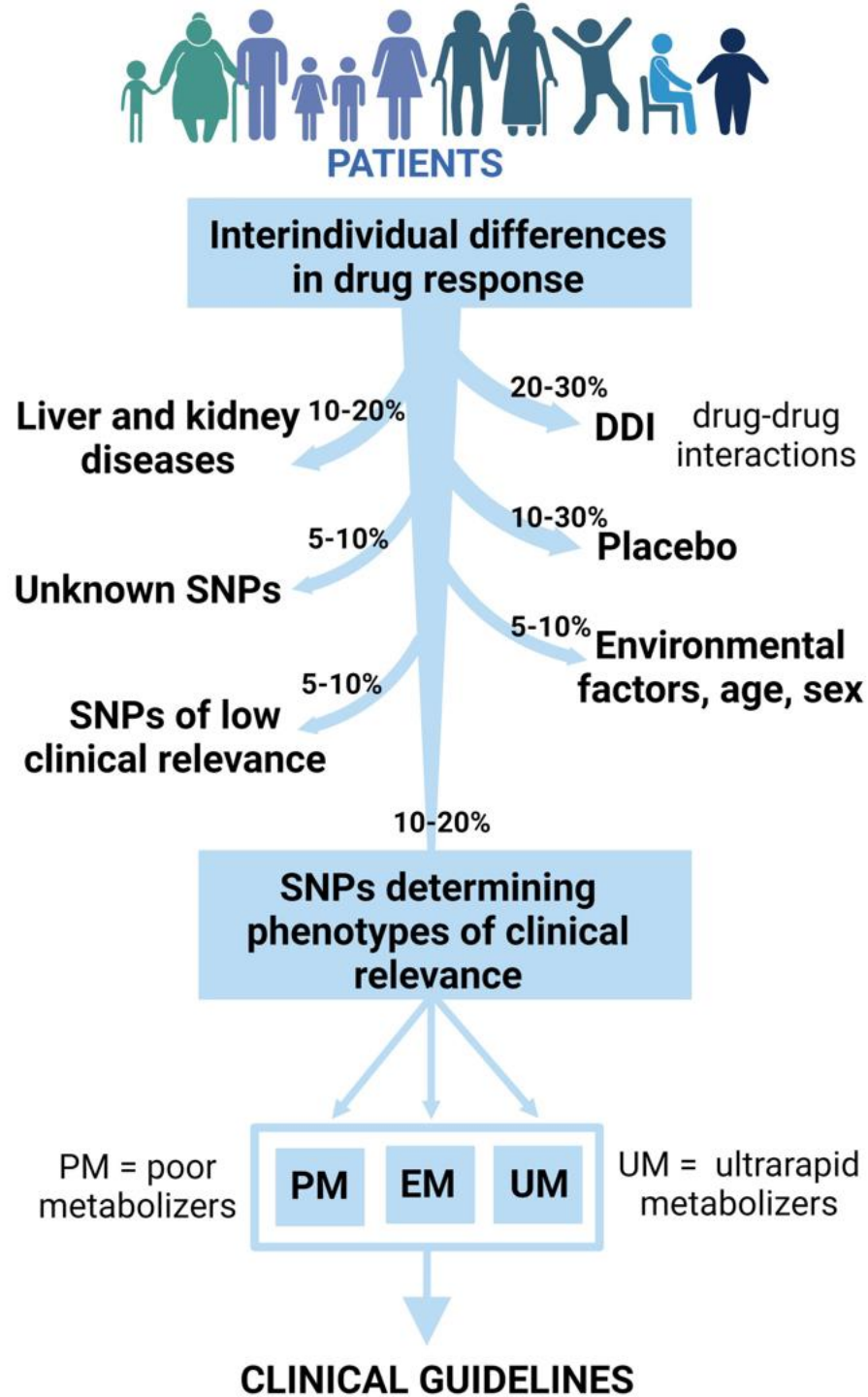
Causes for the large spread within each phenotype include:

i) drug-drug interactions
ii) bad compliance
iii) unknown genetic variants not analysed
iv) liver and kidney pathologies
v) contribution of other enzymes

Estimated importance of different factors for interindividual variability in drug metabolism and response (%)



SV - structural variants


PATIENTS
Interindividual differences in drug response
Liver and kidney diseases
10-20%
20-30%
DDI
drug-drug interactions
5-10%
Unknown SNPs
10-30%
Placebo
5-10%
SNPs of low clinical relevance
5-10%
Environmental factors, age, sex
10-20%
SNPs determining phenotypes of clinical relevance
PM = poor metabolizers
PM
EM
UM
UM = ultrarapid metabolizers
CLINICAL GUIDELINES

The missing heritability for height has been solved !

Table 1 Summary of results from within-ancestry and trans-ancestry GWAS meta-analyses

Cohort ancestry or ethnic group	Number of studies	Max *n* (mean *n*)	Number of GWS COJO SNPs (P_{GWAS} <5×10^{-8})	Number of GWS loci (35 kb)	Cumulative length of non-overlapping GWS loci in Mb (% of genome)
European (EUR)	173	4,080,687 (3,612,229)	9,863 (8,382)	6,386	552.5 (18.4%)
East Asian (EAS)	56	472,730 (320,570)	918 (807)	821	60.5 (2.0%)
Hispanic (HIS)	11	455,180 (431,645)	1,511 (1,195)	1,373	101.0 (3.3%)
African (AFR)	29	293,593 (222,981)	453 (404)	412	30.4 (1.0%)
South Asian (SAS)	12	77,890 (59,420)	69 (65)	66	4.7 (0.2%)
Trans-ancestry meta-analysis ($META_{FE}$)	281	5,314,291* (4,611,160)	12,111 (9,920)	7,209	647.5 (21.6%)

GWAS of 5.4 million individuals of diverse ancestries revealed that 12,111 independent SNPs are significantly associated with height and account for nearly all of the common SNP-based heritability. These SNPs are clustered within 7,209 non-overlapping genomic segments with a mean size of around 90 kb, covering about 21% of the genome.

Yengo et al., *Nature* 2022 Oct; 610:704-712.

Clinical trials in pharmacogenomics, 19 studies 2012-2020

Most common drug-gene pairs in these studies

- CYP2D6-codeine
- CYP2D6- SSRIs or TCAs
- CYP2C19- clopidogrel
- CYP2C19- SSRIs or TCAs
- CYP3A5- tacrolimus
- TMPT- thiopurines
- DPYD- fluoropyrimidines
- SLCO1B1- simvastatin
- CYP2C9/VKORC1- warfarin
- HLA-B-abacavir
- HLA-B- carbamazepine
- CYP2D6- tramadol
- CYP2D6- tamoxifen
- HLA-B- allopurinol

These 8 genes have been among the most relevant in the RCTs in pharmacogenomics when using germline gDNA; *CYP2C19* and *CYP2D6* dominate

Luczak T, et al., *Pharmacogenomics.* 2021;22:345-364

Top ranked gene drug pairs for pharmacogenomic predictions made by FDA & DPWG

Drug	Gene	Phenotypes	FDA	DPWG
Amifampridine	NAT2	PMs	YES	NO
Atomoxetine	CYP2D6	PMs	YES	NO
Azathioprine	TPMT and/or NUDT15	IMs or PMs	YES	YES
Capecitabine	DPYD	IMs or PMs	YES	YES
Carbamazepine	HLA-B	*15:02 allele positive	YES	NO
Celecoxib	CYP2C9	PMs or *3 carriers	YES	NO
Clopidogrel	CYP2C19	IMs or PMs	YES	YES
Fluorouracil	DPYD	IMs or PMs	YES	YES
Irinotecan	UGT1A1	IMs or PMs	YES	YES
Mercaptopurine	TPMT and/or NUDT15	IMs or PMs	YES	YES
Siponimod	CYP2C9	IMs or PMs	YES	YES
Thioguanine	TPMT and/or NUDT15	IMs or PMs	YES	YES
Mavacamten	CYP2C19	IMs or PMs	YES	NO
Simvastatin	SLCO1B1	521 TC or 521 CC	YES	YES

Current problems of pharmacogenomic guidelines

Of 54 drugs with actionable gene–drug interactions according to CPIC and DPWG guidelines, only 50% of the corresponding SmPCs or drug labelling contained actionable pharmacogenomic information.

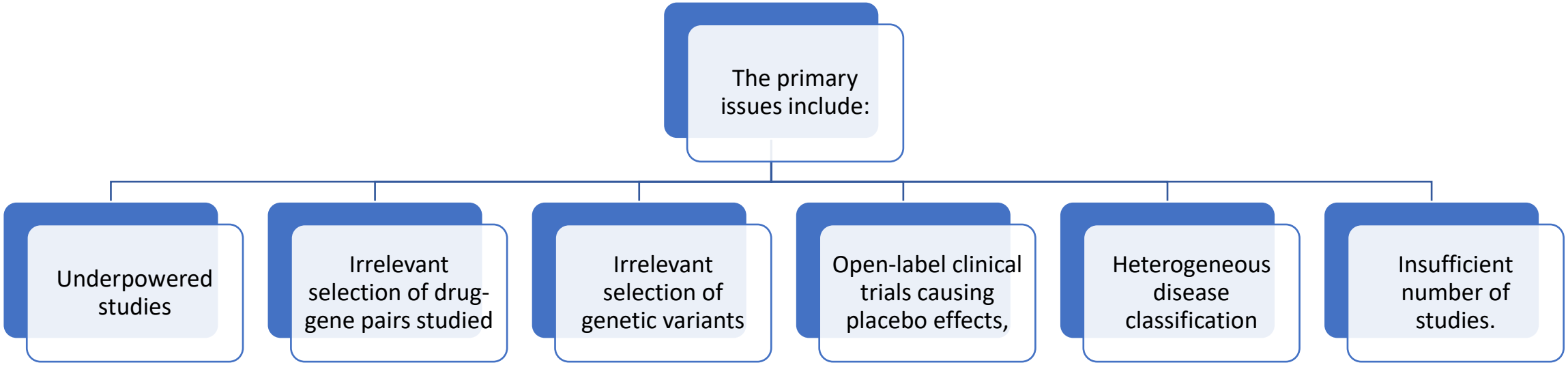
Concordant FDA, EMA/FM, CPIC, and DPWG recommendations were found for only 10 (18%) of these 54 drugs.

Some guidelines cover pharmacogenomic variations of limited clinical importance

Shekhani, R. et al. *Clin Pharmacol Ther*.107:1240-1255 (2020).
Ingelman-Sundberg M *Clin Pharmacol Ther.* 2024 Aug 5. doi: 10.1002/cpt.3403

Heterogenous pharmacogenomic classifications

This inconsistency in classification of pharmacogenomic biomarkers is largely attributed to the weak scientific and clinical foundations of many published studies.

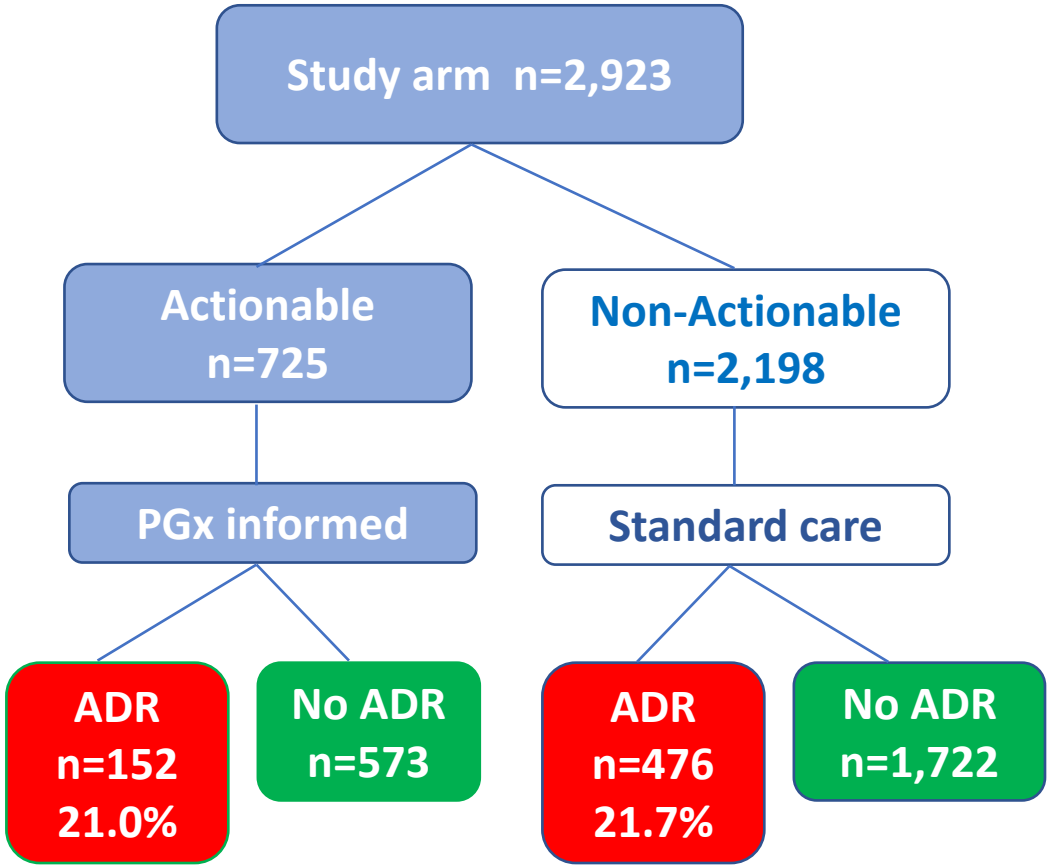


Meta-analyses in this area are often performed but not homogeneous enough, e.g. in terms of

- Drug concentrations,
- Drug selection,
- Timing of treatment
- Initial pathophysiological definition.

Role of placebo: A closer look at the study arm in the U-Pgx prepare study

6944 patients were enrolled and assigned to receive genotype-guided drug treatment (STUDY ARM) n=3342) or standard care (n=3602). 12 different pharmacogenes were analysed and the effect of genotyping monitored



Overall patients in the study arm had 28 % less ADRs than those in the study group.

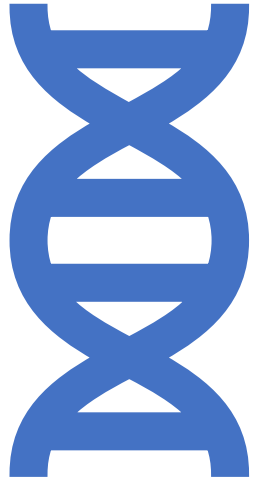
However, in the study group ***both*** patients on standard drug care and PGx informed drug treatment had 28 % less ADRs

Curtis *Lancet* 2023 Jun 3;401(10391):1850-1851
Rogers A, et al., *Lancet*. 2023 Jun 3;401(10391):1850.
Peñas-LLedó & LLerena. *Lancet*. 2023 Feb 4;401(10374):320-321
Swen et al., *Lancet*. Feb 4 2023 401:347-356.
Damkier & Andersen *Basic Clin Pharmacol Toxicol*. 2023 Oct;133(4):397-399

Firm phenotype-genotype relationships are required.

Phenotype – pharmacogenomic aspects:

- Focus on pharmacokinetics, the main endpoint of interest for the polymorphic action in pharmacogenomics.
- Focus on specific gene-drug pairs
- Biobanks - Today too disperse phenotypes relatively far from the genetic variable gene influence containing limited true PK data
- Useful biobank information: dose, time, actionable genes, liver/kidney pathology, co-medications
- Clinically preferred - > 10 000 patients fully gDNA sequenced receiving one drug in a putative interesting gene-drug pair



Why is pharmacogenomics not used much in the clinics?

Shekhani, R. et al. *Clin Pharmacol Ther*.107:1240-1255 (2020).

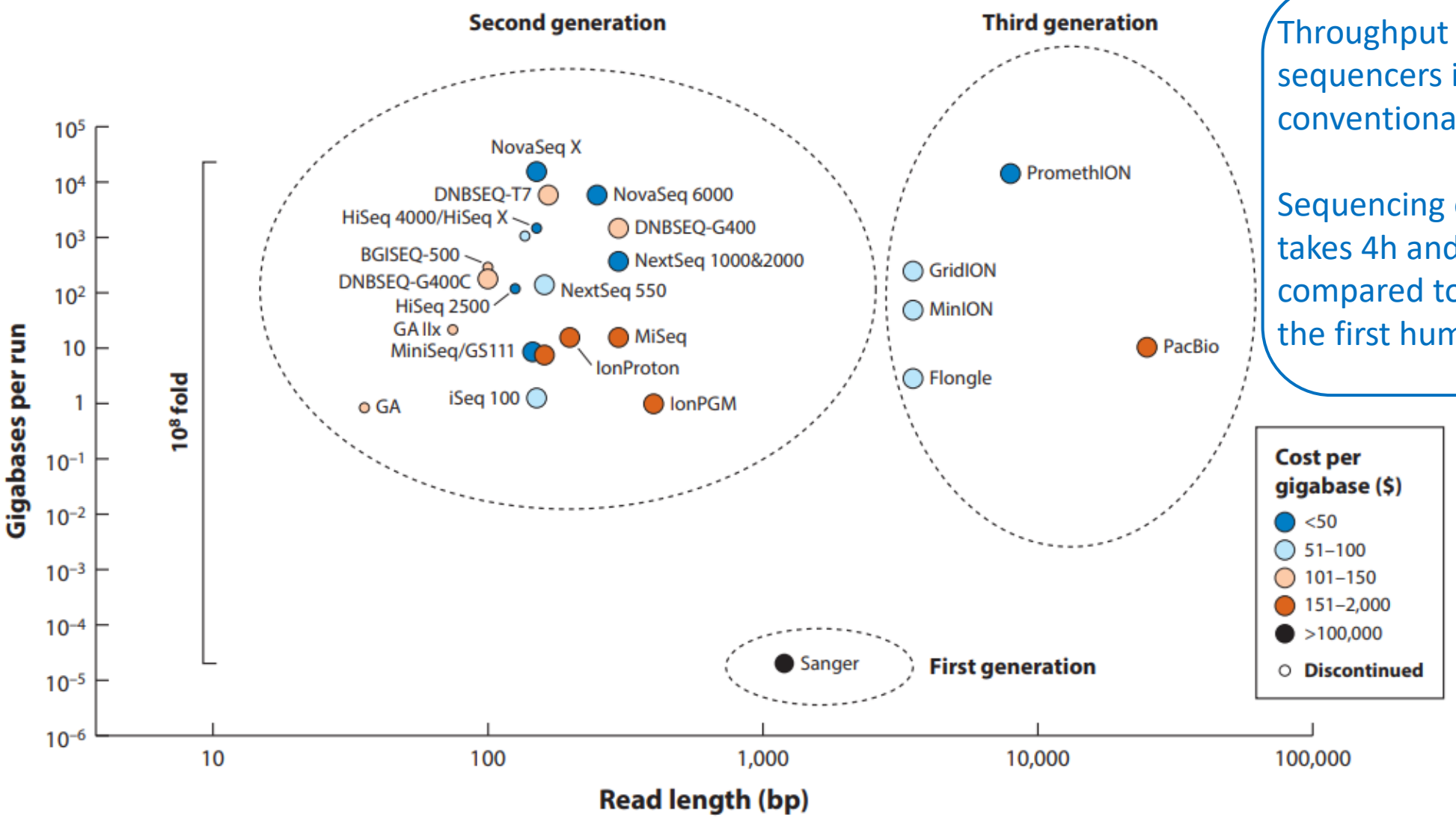
Ingelman-Sundberg M *Clin Pharmacol Ther.* 2024 Aug 5. doi: 10.1002/cpt.3403

Key issues relevant to the limited use of pharmacogenomic markers in routine clinical work include:

- Lack of evidence of clinical benefit
- Limited awareness and training of clinicians
- Complexity and interpretation of pharmacogenomic information
- Time pressure for clinicians
- Availability and cost of pharmacogenomic tests
- limited implementation of pharmacogenomic data in electronic health records (EHR)

In the future

Development of commonly used sequencing technologies. Sequencers and their read lengths, throughputs, and costs per gigabase



Throughput of the best next-generation sequencers is > 108 times higher than for conventional Sanger sequencing.

Sequencing of a human genome now takes 4h and costs around $500 USD compared to 13 years and $3 billion for the first human draft genome

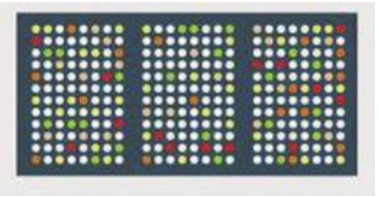
Lauschke, Zhou & ingelman-Sundberg *Annu. Rev. Pharmacol. Toxicol.* 2024. 64:2.1–2.19

Better pharmacogenomic predictions for the future

Patients
n> 100,000

Drug
phenotyping

NGS/Long Read WGS/
Imputed GWAS analyses



AI based analyses
genotype - phenotype

Gene variant
functionality scores

Clinical pharmacogenomics

To think of regarding RCTs in pharmacogenomics

- Closed labels required but difficult to achieve in a clinical setting; Blinding for at least the patients.
- In a normal patient population, the extent of functionally variant genes is usually very small with the exception for *CYP2D6* and *CYP2C19*.
- For appropriate comparison the number of patients with actionable and non-actionable genes should be similar in size.
- The bias factors i) diet, ii) co-medications, iii) liver and kidney status would be controlled for.

To think of regarding RCTs in pharmacogenomics (….cont)

- For many polymorphic genes we do have knowledge of only 50 % of clinically relevant genetic variants.
- Placebo effects are always evident and must be coped with.
- Grade 2 ADRs can not be considered.
- Firm endpoints must be there including assay for drug pharmacokinetics/blood levels.
- Only analyse gene-drug pairs where effects of genetic variants have been described.
- The extent of functional effect of various genetic variants must be considered
- Consider only gene drug pairs where the drug is an efficient substrate for the corresonsing enzyme

Acknowledgements

- Sander van Riet
- Åsa Nordling
- Marin Jukic
- Inger Johansson
- Espen Molden

Vetenskapsrådet

erc Advanced Grant

erc European Research Council Established by the European Commission PROOF OF CONCEPT