Translating genotype data of 44,000 biobank participants into clinical pharmacogenetic recommendations: challenges and solutions

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On behalf of all authors
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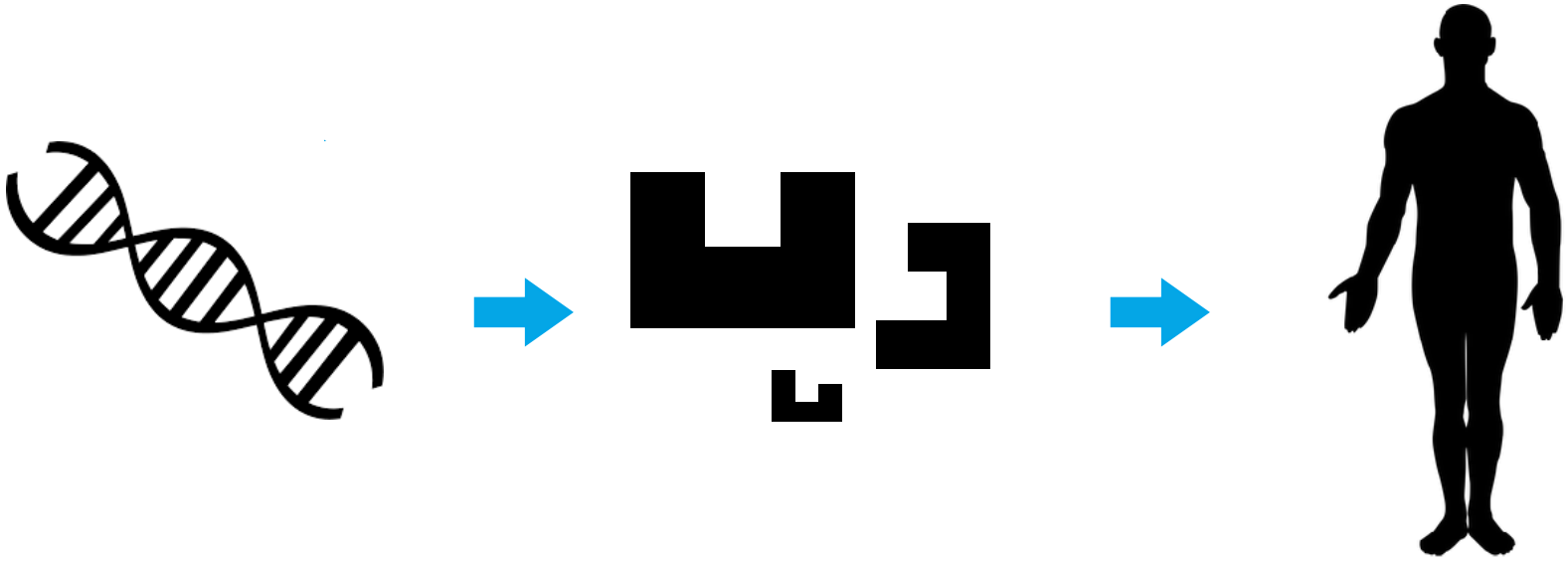
UNIVERSITY OF TARTU, ESTONIA

How we are built



DNA Proteins, enzymes Body

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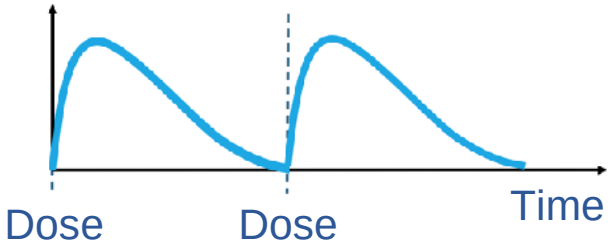
Inactive drug

Normal gene

Functional enzyme

Active drug

Drug concentration in blood



Pharmacogenetic phenotype

Normal

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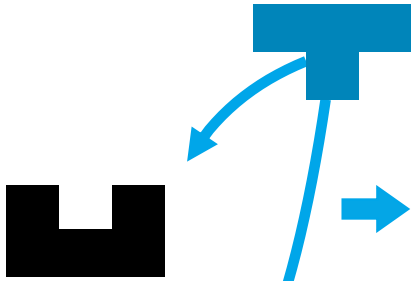
Inactive drug

Drug concentration in blood

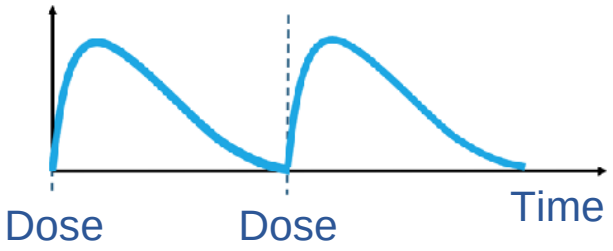
Pharmacogenetic phenotype

Normal gene



Functional enzyme

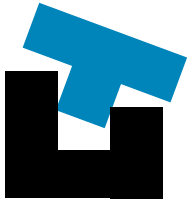
Active drug



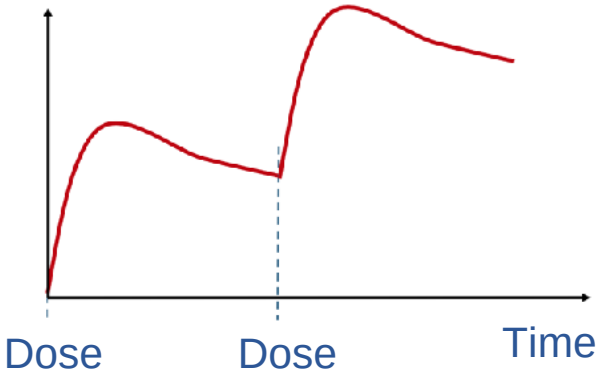
Normal

Gene with loss-of-function mutation

Non-functional enzyme



Inactive drug



Poor

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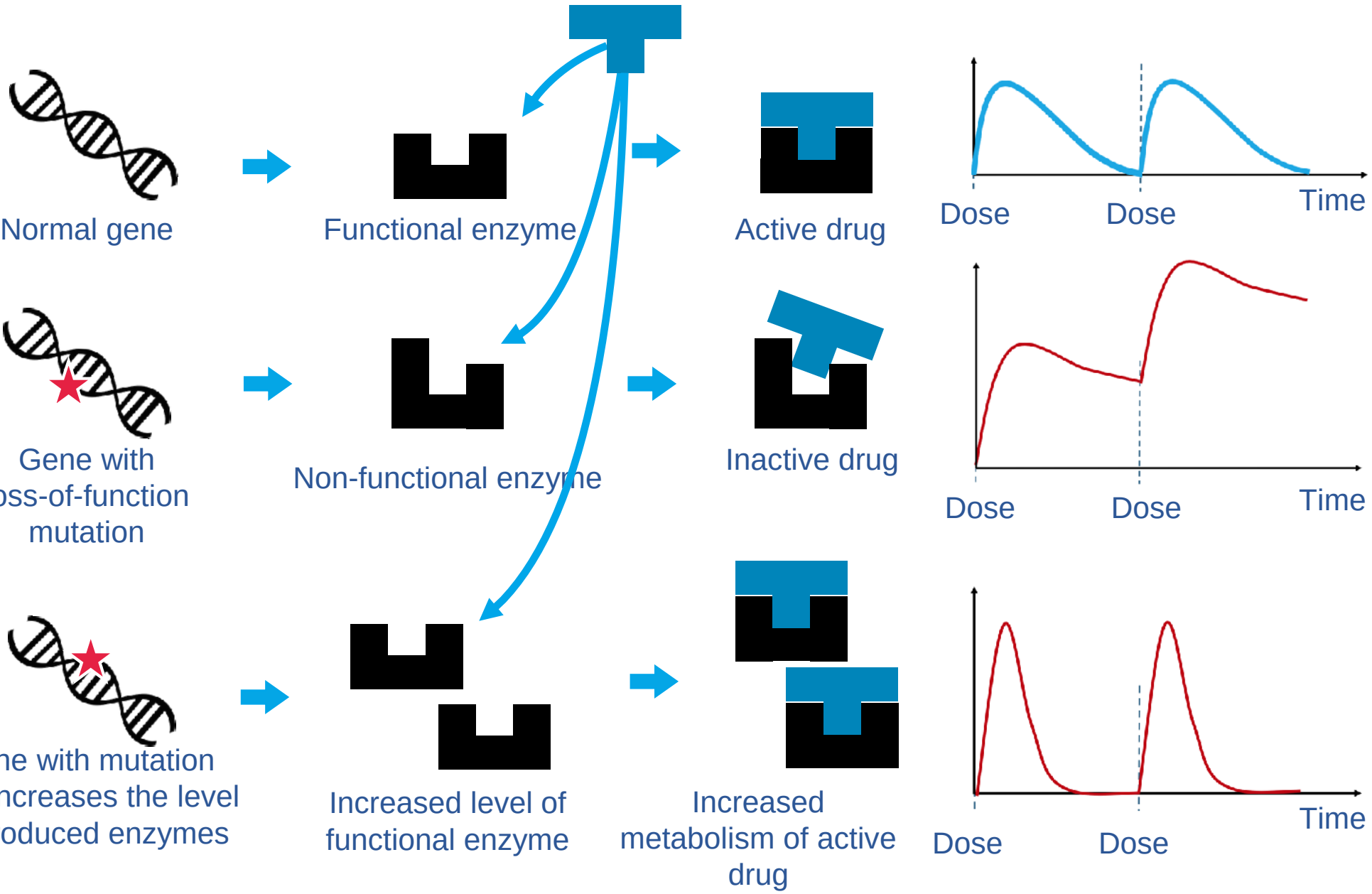

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Pharmacogenetic phenotype

Normal gene

Gene with loss-of-function mutation

Gene with mutation that increases the level of produced enzymes

Pharmaco-genetic knowledge

Normal

Poor

Rapid

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Pharmacogenetic phenotype

Pharmacogenetic recommendations

Normal gene

Gene with loss-of-function mutation

Gene with mutation that increases the level of produced enzymes

Pharmaco-genetic knowledge

Normal

Poor

Rapid

Information in drug leaflets

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11 pharmacogenomic genes of 44,000 biobank participants

Pharmaco-genetic knowledge

Normal

Poor

Rapid

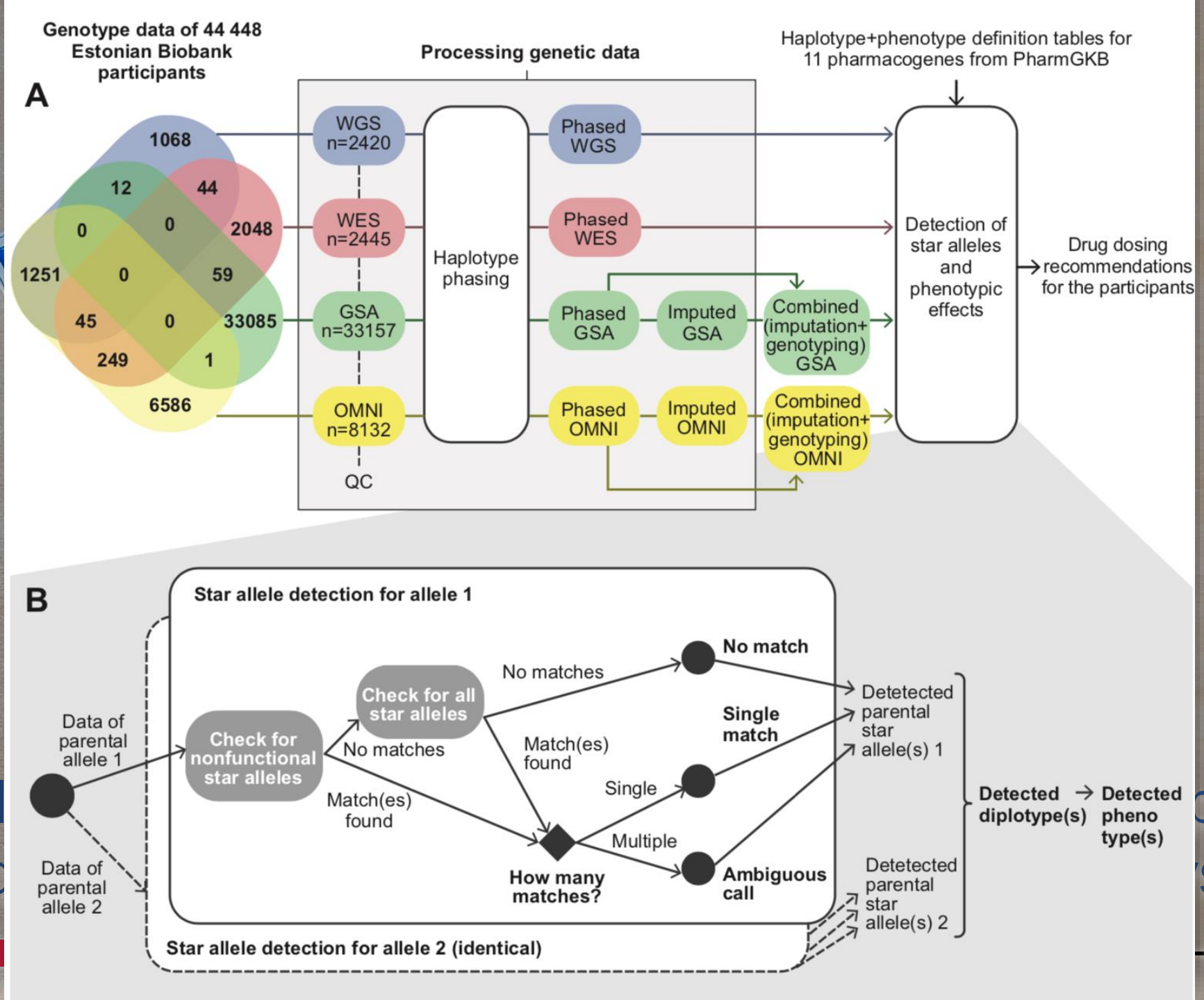
(and others)

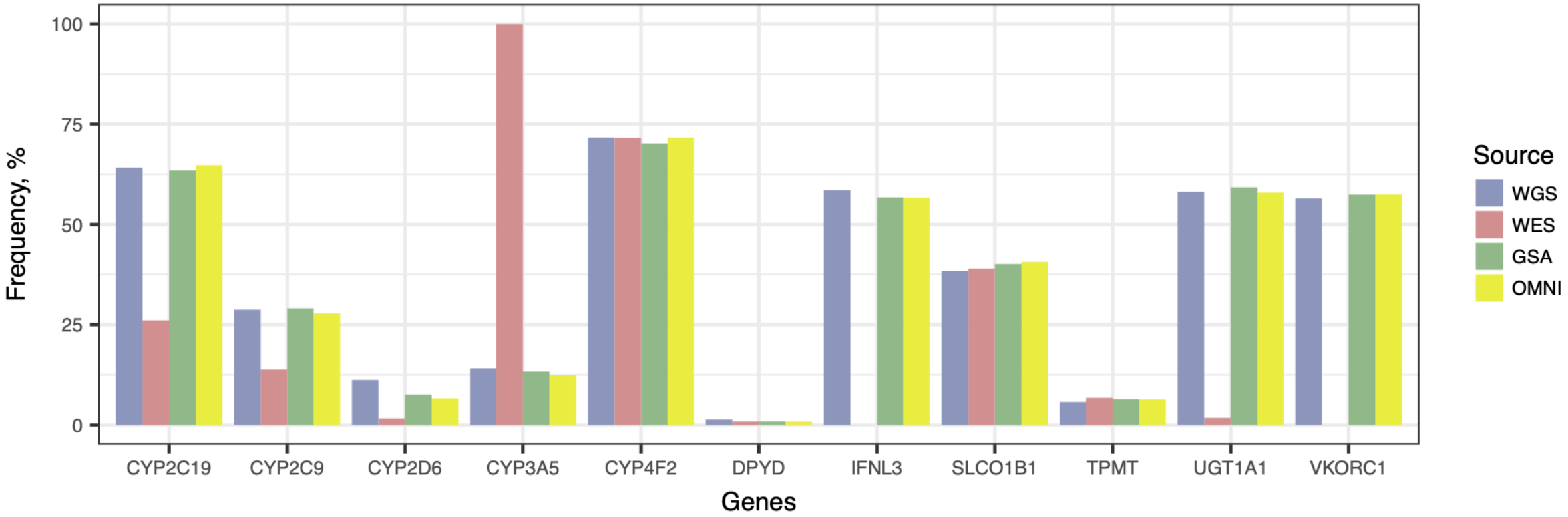
Predicted “phenotypes” for 11 genes for 44,000 participants of Estonian Biobank

Whole genome sequencing

Exome sequencing

Genotyping arrays


A
Genotype data of 44 448 Estonian Biobank participants
Processing genetic data
Haplotype+phenotype definition tables for 11 pharmacogenes from PharmGKB
1068
12
44
0
0
2048
1251
0
59
45
0
33085
249
1
6586
WGS n=2420
WES n=2445
GSA n=33157
OMNI n=8132
QC
Haplotype phasing
Phased WGS
Phased WES
Phased GSA
Imputed GSA
Combined (imputation+ genotyping) GSA
Phased OMNI
Imputed OMNI
Combined (imputation+ genotyping) OMNI
Detection of star alleles and phenotypic effects
Drug dosing recommendations for the participants
B
Star allele detection for allele 1
Data of parental allele 1
Data of parental allele 2
Check for nonfunctional star alleles
No matches
Check for all star alleles
No matches
No match
Match(es) found
Single match
Match(es) found
Single
Multiple
How many matches?
Ambiguous call
Detetected parental star allele(s) 1
Detetected parental star allele(s) 2
Detected diplotype(s) → Detected pheno type(s)
Star allele detection for allele 2 (identical)



Fraction of high risk phenotypic predictions by gene and method. High risk phenotypes are defined as those that differ from normal and unknown phenotypes and would require a different drug dosing or recommendation.

Genotyping arrays (with imputation)
are cost-effective alternatives
for pharmacogenetic testing

99.8%

of biobank participants
need a dosage adjustment
for at least one of the medications

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Feedback Report
for a biobank participant

Prepared: 17 May 2018

Jaana Tamm (F)

ID code: 47303115223

Data used for preparing the report

Age	65
Height	162 cm
Weight	87.3 kg
Waist circumference	95 cm
History of hypertension	Yes
History of myocardial infarction	No
Diagnosed diabetes	No

The preliminary data for your genetic information analysis were obtained via

- whole genome sequencing (WGS).

Important

The nature of this report is strictly scientific and it is above all designed to promote health literacy. It does not constitute medical advice or replace a consultation. The report takes into account personal health parameters and genetic information stored in the Estonian Biobank. It is based on scientific estimates that are as up-to-date as possible but may change in the future.

The genetic tests were conducted at the Core Facility of the Estonian Genome Centre.

The data about health risks and drug response presented in the report are estimates and not designed to be used as a standalone basis for making clinical decisions. The assessment of the results of the genetic analysis must also include other data, such as the results of clinical diagnostic tests, family history, health behaviour and environmental factors. Your doctor will be able to provide you with further recommendations based on their professional knowledge.

For more information about the report, please e-mail us at **egv.tagasiside@ut.ee** or call us on **+372 5154082**.

The content of this report is subject to a disclaimer and the provisions of the Personal Data Protection Act.

Response Issued (date and signature):

Report reseived (date and signature):

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Pharmacogenetics

Variations in genes that are necessary for drugs to take effect are one of the reasons why people have different reactions to medicines. Over the years, a number of genetic markers predictive of drug response have been identified. This test was used to determine the genetic markers of eight genes, which influence your response to 24 active substances used in medicines.

The following instructions can be given on the basis of the genetic variants tested:

Gene	Genotype	Assessment	Recommendations	Affected active substances
CYP2C19	*2/*17	Average drug metabolism	!	Escitalopram, citalopram, clopidogrel, sertaline, voriconazole, esomeprazole, lansoprazole, pantoprazole, omeprazole, clomipramine, amitriptyline
CYP2C9	*1/*1	Average drug metabolism	+	Phenytoin
CYP2C9; VKORC1	rs9923231 (GG)	Usual recommended dose	+	Warfarin
CYP3A5	*3/*3	Slow drug metabolism, Regular pattern	+	Tacrolimus
DPYD	*1/*1	Average drug metabolism	+	Capecitabine, fluoroacil
IFNL3	rs12979860 (TT)	Reduced drug efficacy	!	Peginterferon alpha-2b, ribavirin
SLCO1B1	rs4149056 (TT)	Average risk of myopathy	+	Simvastatin
TPMT	*1/*1	Average drug metabolism	+	Tioguanine, mercaptopurine, azathioprine

+ - Use a normal dose. ! - Use with caution; the dose may need to be adjusted. ! - Use with extreme caution; there is a risk of side effects.

Information for doctor

Gene	Genotype	Active substance	Influence of genotype	Recommendations
CYP2C19	*2/*17	Esomeprazole, lansoprazole, pantoprazole, omeprazole	Average drug metabolism.	Start treatment with normal dose.
CYP2C19	*2/*17	Escitalopram, citalopram	Slower than average drug metabolism	Start treatment with normal dose.
CYP2C19	*2/*17	Clomipramine, amitriptyline	Slower than average breakdown of tricyclic amines.	Start treatment with normal dose.
CYP2C19	*2/*17	Clopidogrel	Reduced inhibition of thrombocyte aggregation; increase in the residue of thrombocyte aggregation, resulting in an increased risk of cardiovascular side effects.	Start treatment with an alternative drug, e.g. those that contain prasugrel or ticagrelor as active substances.

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Next steps

- Align with MDR and IVDR regulations, obtain CE Marking
- GenMed project (2019-2022): Integrate pharmacogenetic recommendations to national online digital prescription system

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Thank you!

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