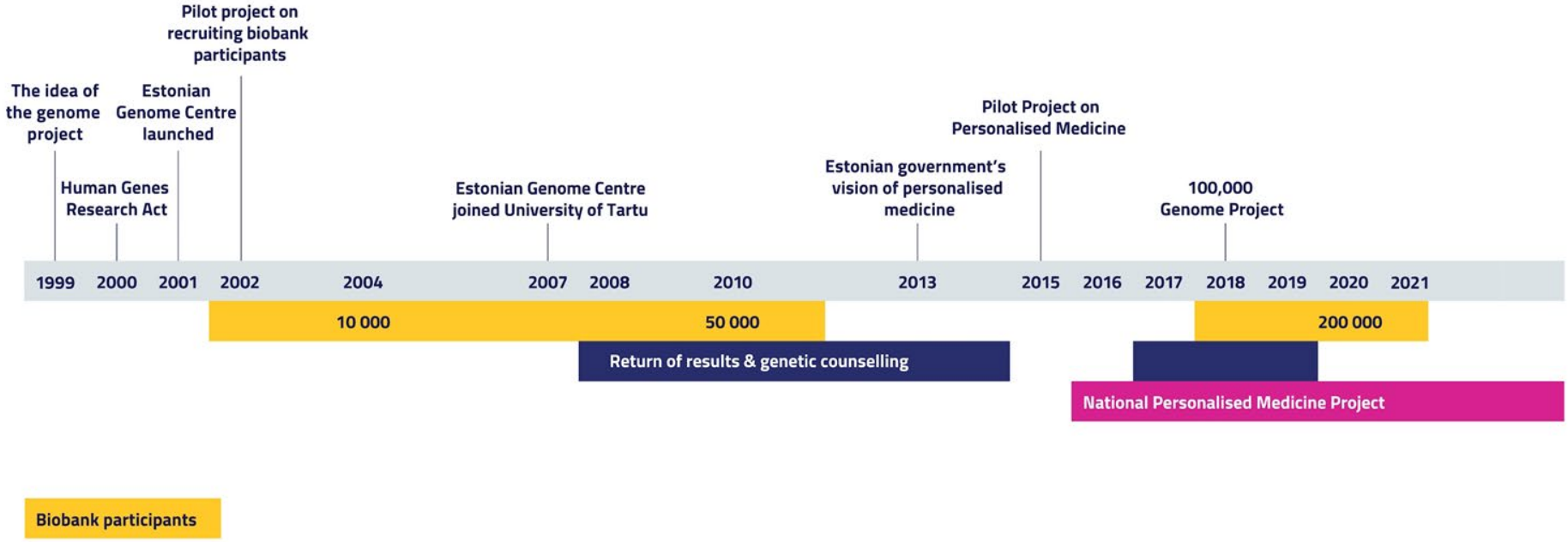
Will genomics help to support the long-expected shift towards prevention?

Lili Milani
Head of Estonian Genome Centre
Vice Director, Institute of Genomics, University of Tartu


Pilot project on recruiting biobank participants
The idea of the genome project
Estonian Genome Centre launched
Human Genes Research Act
Estonian Genome Centre joined University of Tartu
Estonian government's vision of personalised medicine
Pilot Project on Personalised Medicine
100,000 Genome Project
1999
2000
2001
2002
2004
2007
2008
2010
2013
2015
2016
2017
2018
2019
2020
2021
10 000
50 000
200 000
Return of results & genetic counselling
National Personalised Medicine Project
Biobank participants

202 282
biobank participants

– Health records, diet, physical activity, etc.
– DNA, plasma and cell samples

Estonian adult population

20% biopank participants

5000+ return of results (RoR)*

*RoR & genetic counselling

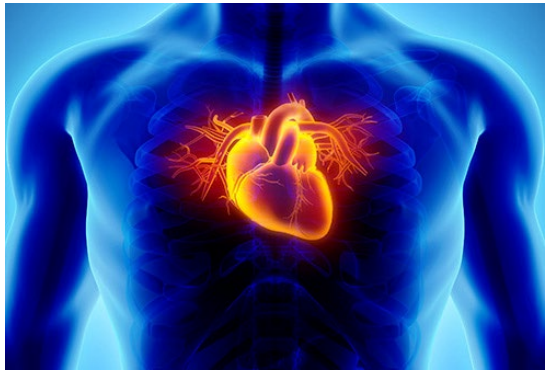
202 282 genotyped

3000 sequenced

– Estonian Human Genes Research Act
– Broad informed consent
– Open for research: Clear access rules

Whole-genome sequencing + genotyping + genotype imputation (+ validation)

1. 3000 whole genomes and 2500 whole exomes sequenced
2. Genotyping of 700K markers (Global Screening Array, Illumina)
3. Imputation and long-range haplotyping
4. Rare mutations and polygenic risk scores for common diseases



Familial hypercholesterolemia

Frequency >1:200

LDLR, APOB, PCSK9

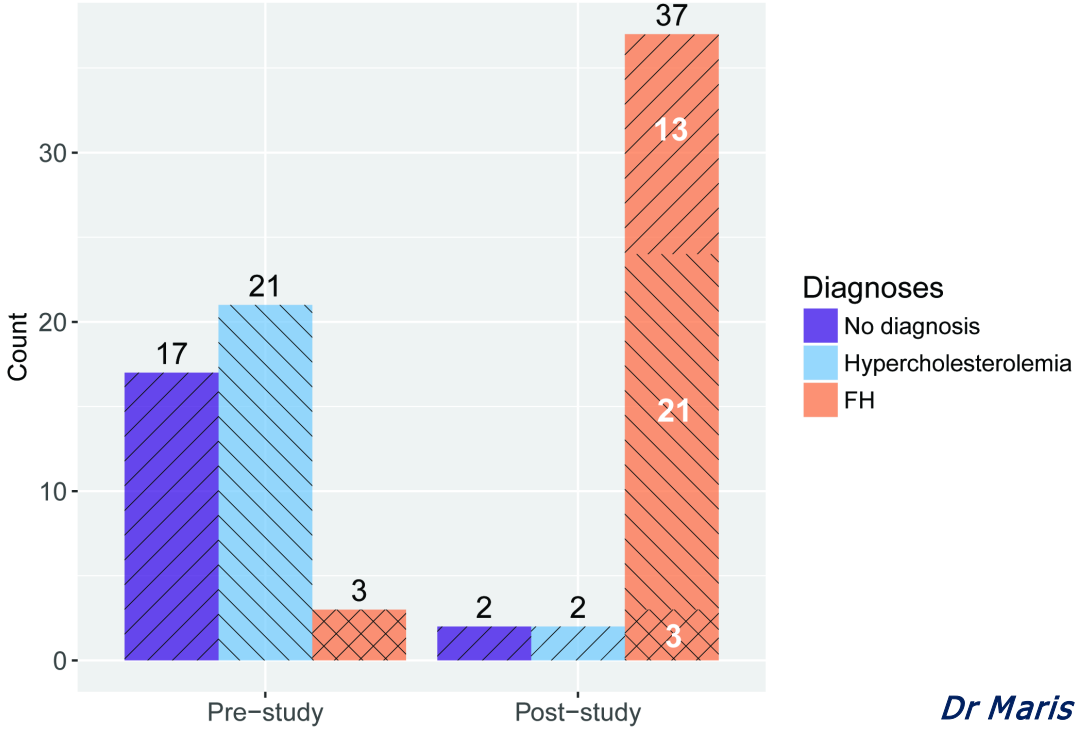
Familial breast cancer

Frequency >1:200

BRCA1, BRCA2

Diagnosed?

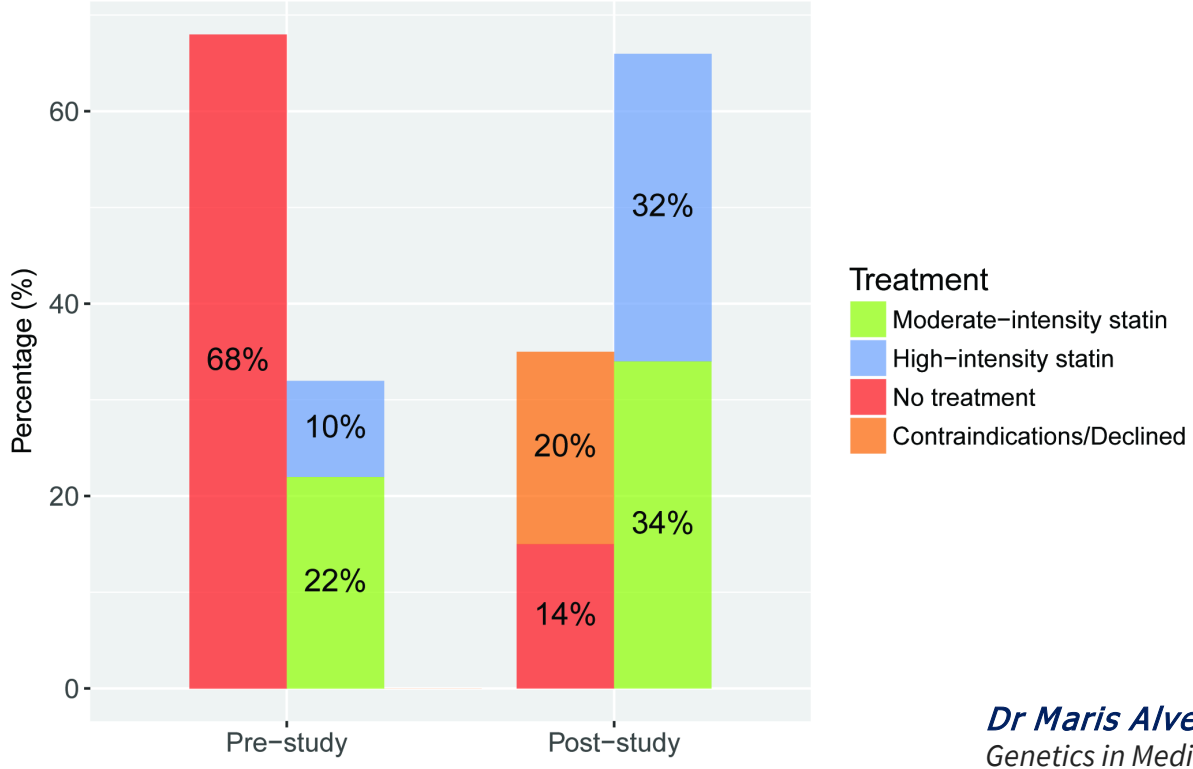
4776 genomes ❯ 41 mut (LDLR, APOB, PCSK9) ❯ 3 diagnosed



Dr Maris Alver, Dr Tõnu Esko
Genetics in Medicine 2018

Treatment?

33% pre-study › 66-86% post-study



Dr Maris Alver, Dr Tõnu Esko
Genetics in Medicine 2018

Familial breast cancer (1:200): Recall by genotype

22 BRCA1/2 mutation carriers

17 with family history of breast cancer

1 referred to medical geneticist

(2 diagnosed with BrCa and 2 diagnosed with PrCa)

Dr Liis Leitsalu, Dr Neeme Tõnisson, Marili Palover

Conclusions of FH & BRCA studies

Unawareness of the familial background of the diseases

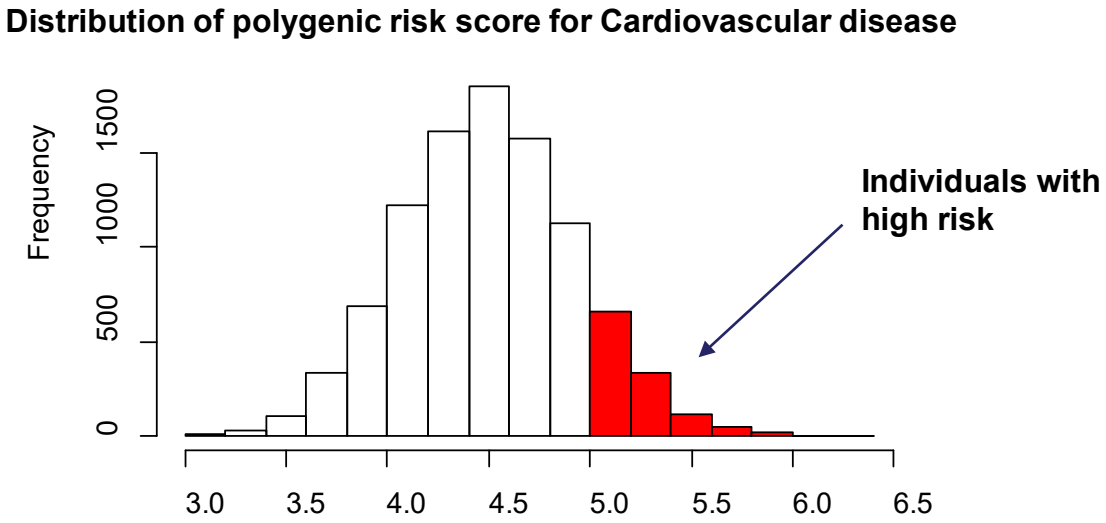
Low pre-established treatment adherence

Cardiologists & oncologists acknowledge the value of genetics-first approaches

Common complex diseases & Polygenic risk scores

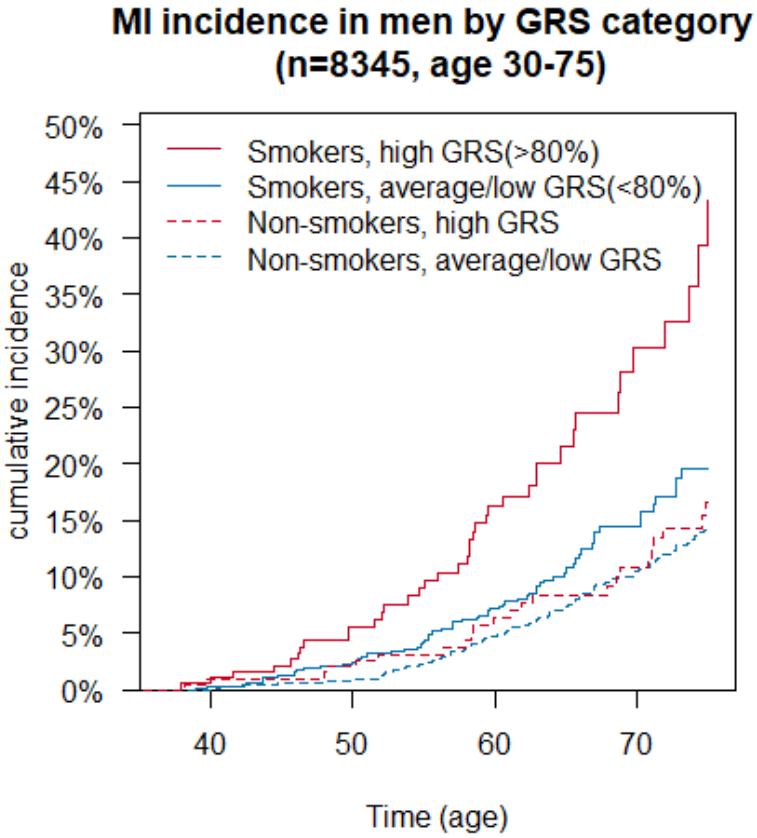
Polygenic risk scores for common diseases

- Effect of each single variant is small
- Variants and effect sizes can be summed into **risk scores**



Prof Krista Fischer, Kristi Läll

Incident Myocardial Infarction: analysis of 246 incident cases among men

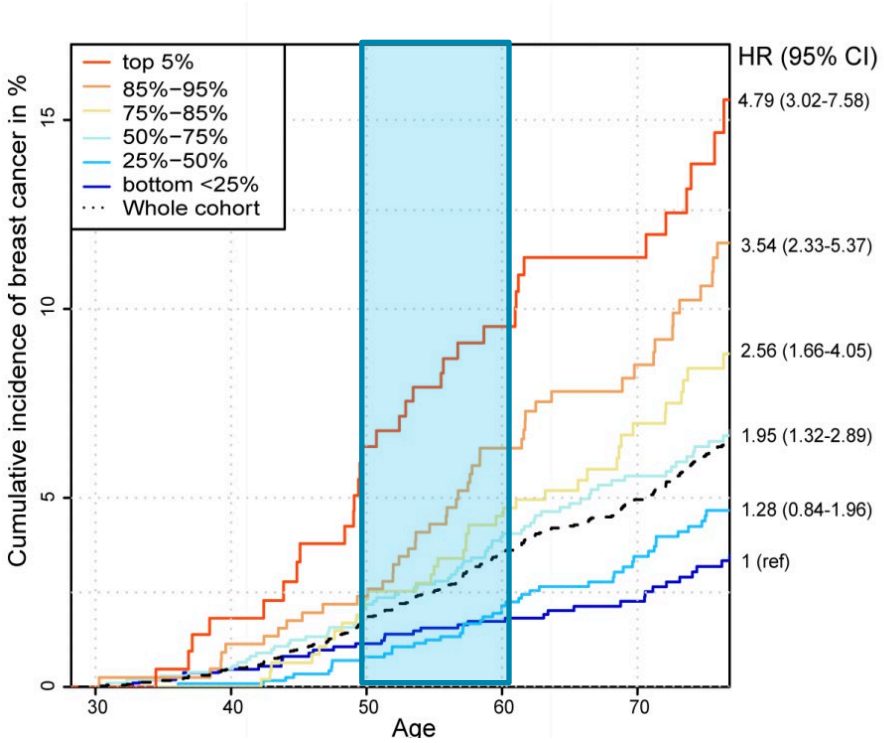


HR=2.2, $p=7.6*10^{-5}$ (compared to lower GRS)
40 cases (n=204)

No significant GRS effect seen among non-smoking men

Dr Kristi Läll, Prof Krista Fischer

PRS for breast cancer



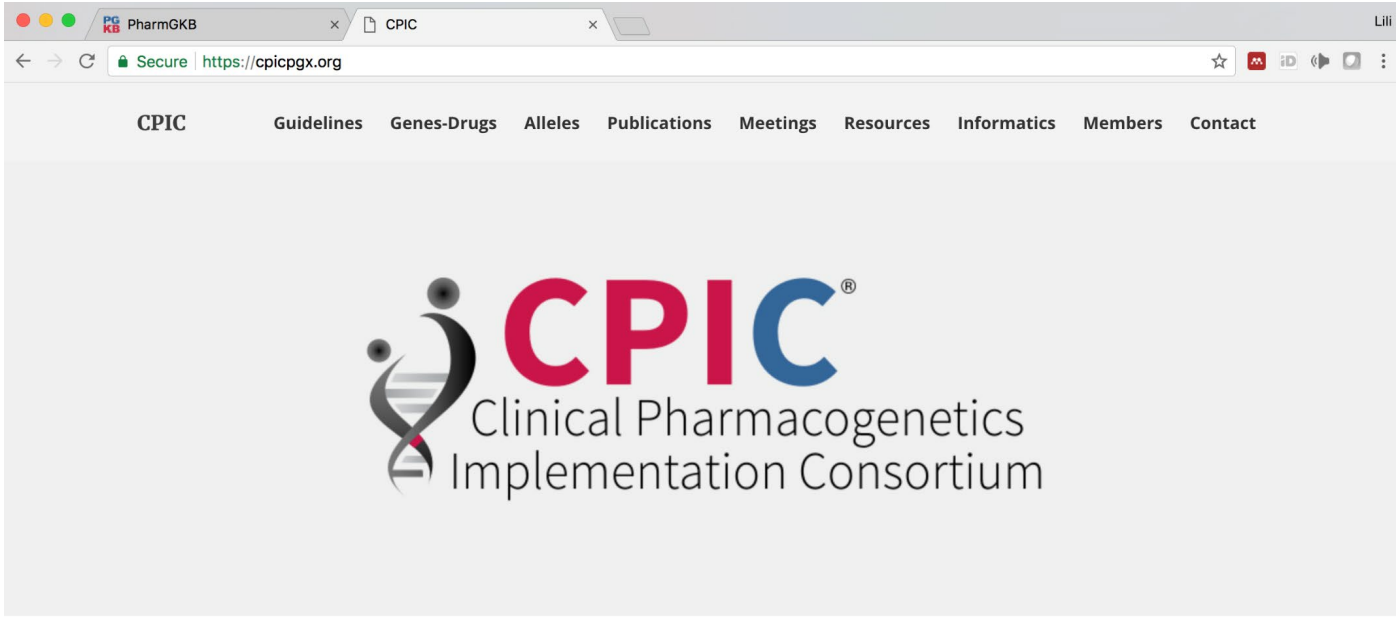
Dr Kristi Läll, Prof Krista Fischer
BMC Cancer 2019

Top 5% highest genetic risk score = 20% of cardiovascular deaths

Targeted disease prevention

Pharmacogenetics

>98% of individuals carry mutations that affect drug response

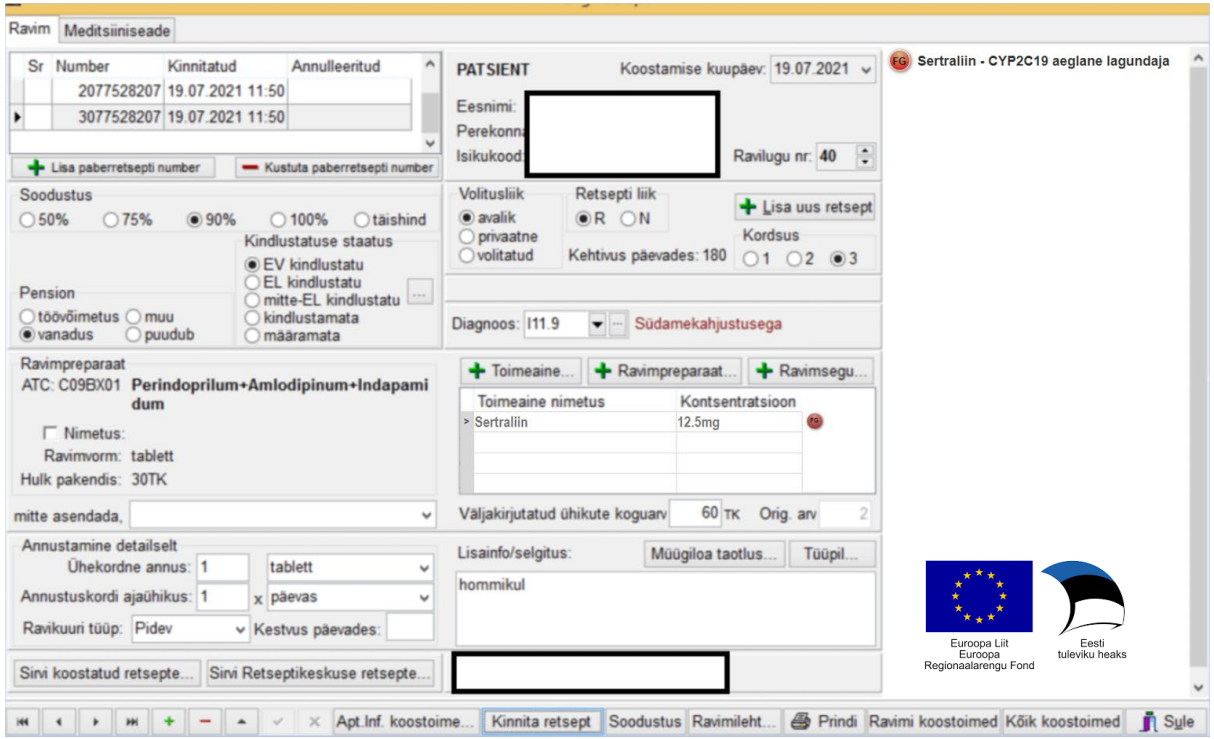


Pharmacogenetics report

Geen	Genotüüp	Hinnang	Soovitus	Mõjutatud ravimi toimeained
CYP2C19	*2/*2	Aeglane ravimi lagundamine	!	Estsitalopraam, Tsitalopraam, Klopidogrel, Sertraliin, Vorikonasool, Esomeprasool, Lansoprasool, Pantoprasool, Omeprasool, Klomipramiin, Amitriptüliin
CYP2C9	*1/*1	Tavapärane ravimi lagundamine	+	Fenütoiin
CYP2C9; VKORC1	*1/*1; rs9923231 (AA)	Tavapärasest madalam doosisoovitus	!	Varfariin
CYP3A5	*3/*3	Aeglane ravimi lagundamine, Tavapärane muster	+	Takroliimus
DPYD	*1/*5	Tavapärane ravimi lagundamine	+	Kapetsitabiin, Fluorouratsiil
IFNL3	rs12979860 (CC)	Tavapärane ravimi toime	+	Alfa-2b-peginterferoon, ribaviriin
SLCO1B1	rs4149056 (TT)	Tavapärane müopaatia risk	+	Simvastatiin
TPMT	*1S/*1	Tavapärane ravimi lagundamine	+	Tioguaniin, Merkaptopuriin, Asatiopriin

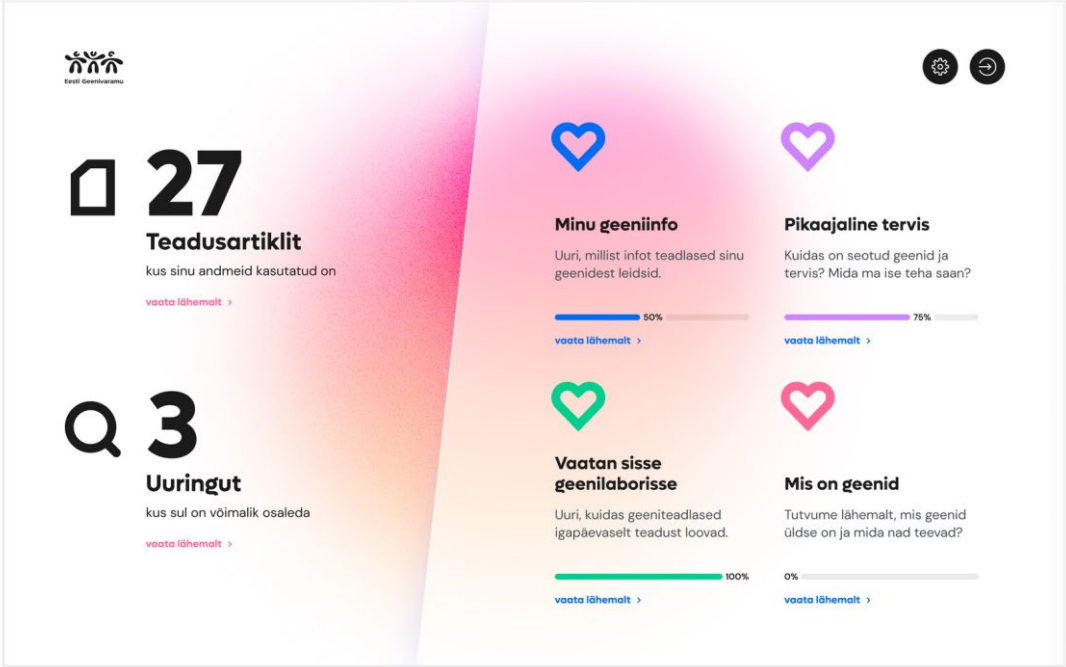
+ - Tarvitada tavapäraselt. ! - Tarvitada ettevaatusega, võib vajada doosi muutmist. ! - Tarvitada väga ettevaatlikult, oht kõrvaltoimeteks.

Translation into digital prescription recommendations in the clinic



Marko Arrak, Dr Sulev Reisberg

Coming soon: Estonian biobank portal



UNIVERSITY OF TARTU

estonian genome center

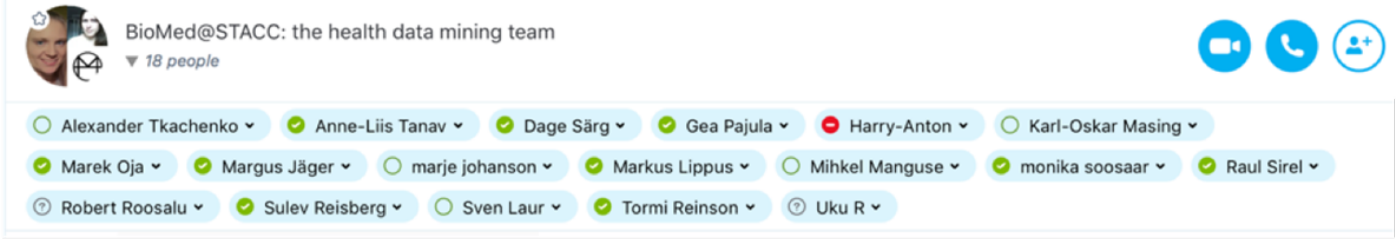
Andres Metspalu, Tõnu Esko, Krista Fischer, Reedik Mägi, Maris Alver, Kristi Krebs, Kristi Läll, Mart Kals, Tom Haller, Liis Leitsalu, Neeme Tõnisson, Marili Palover, Maarja Lepamets, Anu Reigo, Kelli Lehto, Tuuli Jürgenson, Helene Alavere, Ene Mölder, Kristjan Metsalu, Kairit Mikkel, Mari-Liis Tammesoo, Steven Smit, and many more.

BIIT

STACC Software Technology and Applications Competence Center

NEXT 10 BROAD INSTITUTE

Prof. Jaak Vilo, Hedi Peterson, Sulev Reisberg, Sven Laur, Dage Särg, jt.



Republic of Estonia Ministry of Social Affairs

Kalle Killar, Anneli Laansoo, Silja Elunurm, Raili Sillart, jt.

Tervise Arengu Instituut National Institute for Health Development

Prof Toomas Veidebaum, Annika Veimer, Piret Kuhlbars, Pille Kink, Helen Lepa, jt.

Eesti Haigekassa

Liis Kruus