Estonia Familial Hypercholesterolemia Screening and Beyond

Tõnu Esko

Vice Director, Institute of Genomics, University of Tartu

Research Scientist, Broad Institute of MIT and Harvard

estonian genome center
university of tartu

A unique place to fulfill the promises of Big Data:

World leader in public IT-services and ambitious start-up community

ESTONIA

Population: 1.3 Million
Size: 45 227 km²
Capital: Tallinn
Language: Estonian
Member of EU
Currency: Euro
GDP: 17B EUR

REPUBLIC OF ESTONIA
E-RESIDENCY

taxify

e-estonia.com
The digital society

WELCOME TO ESTONIA

TransferWise

skype™

FREE WIFI

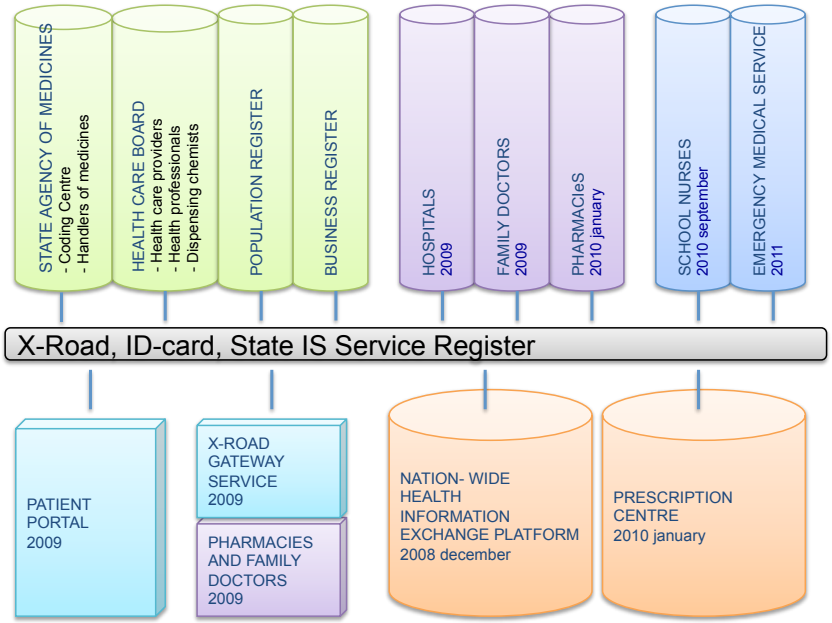
Let's do it!
World Cleanup 2015

Estonian e-Services

- 9 digits **personal identification code**
- **Mandatory** ID document for all Estonian residents
- Enables secure digital authentication and signing
- Active cards: **1 209 594** (95% of citizens) [13 Sept 2013]

- *Public e-services*

- *Electonic Health Information System*



Estonian Biobank

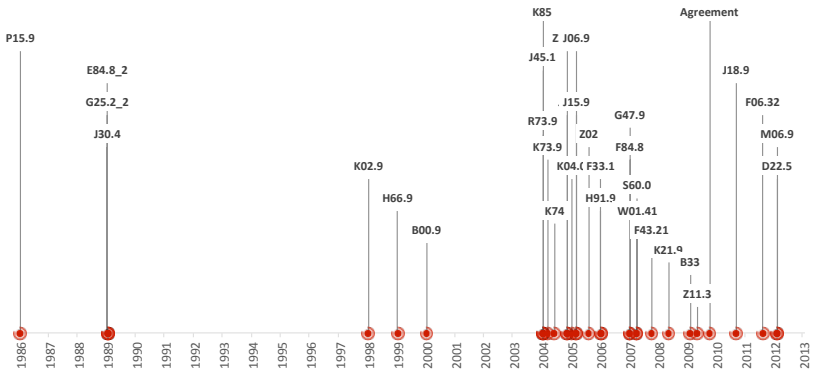
- Estonian Genome Center, University of Tartu
- A prospective, longitudinal, population-based database with health records and biological materials
- 150,000 participants - 15% of the adult population
- Individuals are recruited by medical personnel
- Broad informed consent
- Legislation: Estonian Human Genes Research Act

estonian genome center
university of tartu

Resources and setup

Sample collection (DNA, plasma, WBC)
200,000+ by 2020

Health data – linking with national health registers



Disease trajectories

Omics data

150 000 participants' samples genotyped
3 000 whole genomes, 2500 exomes
Molecular plasma profiles (sub-cohorts)

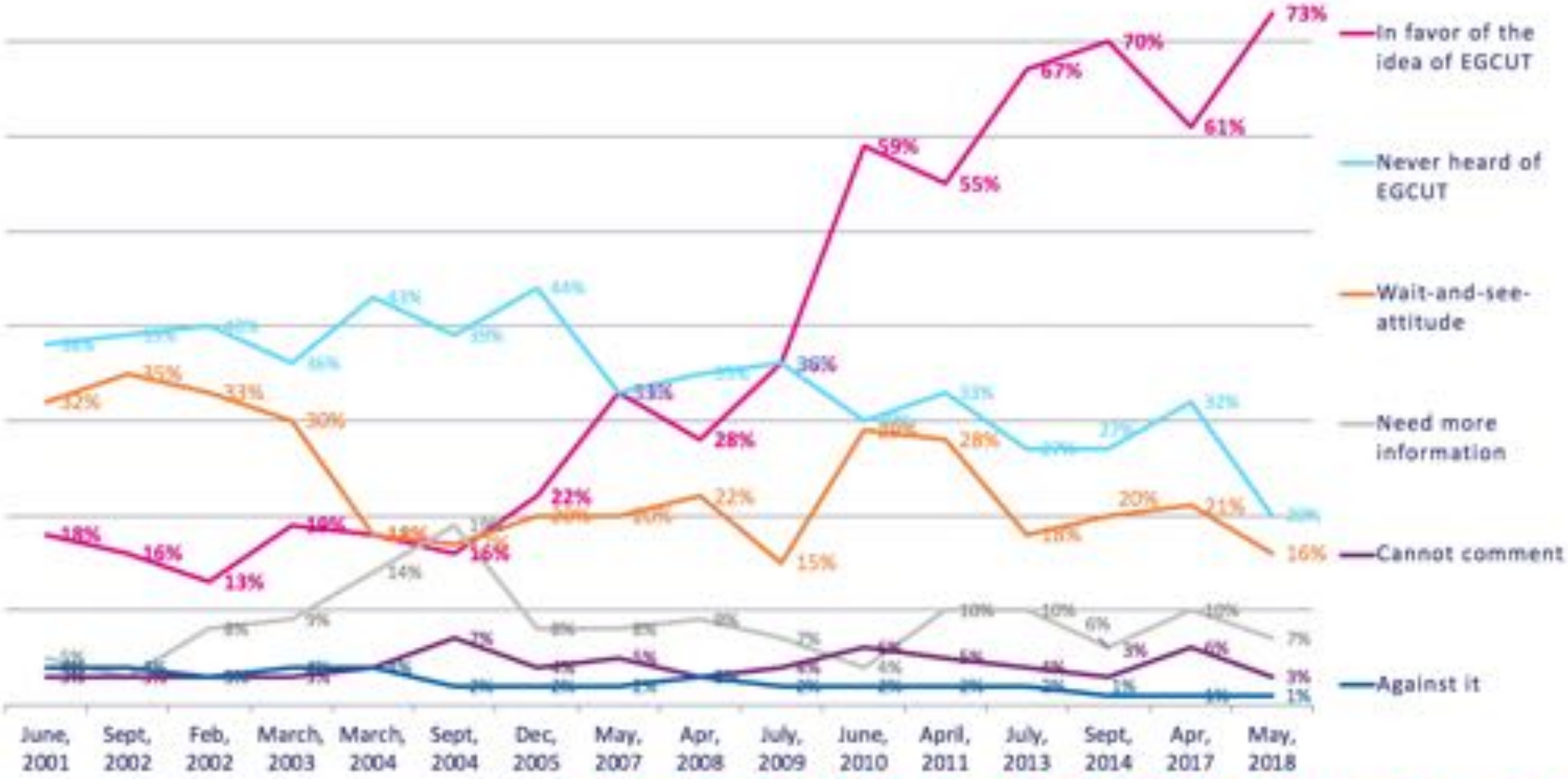
Latest genome analysis technology

iScan

HiSeq2500

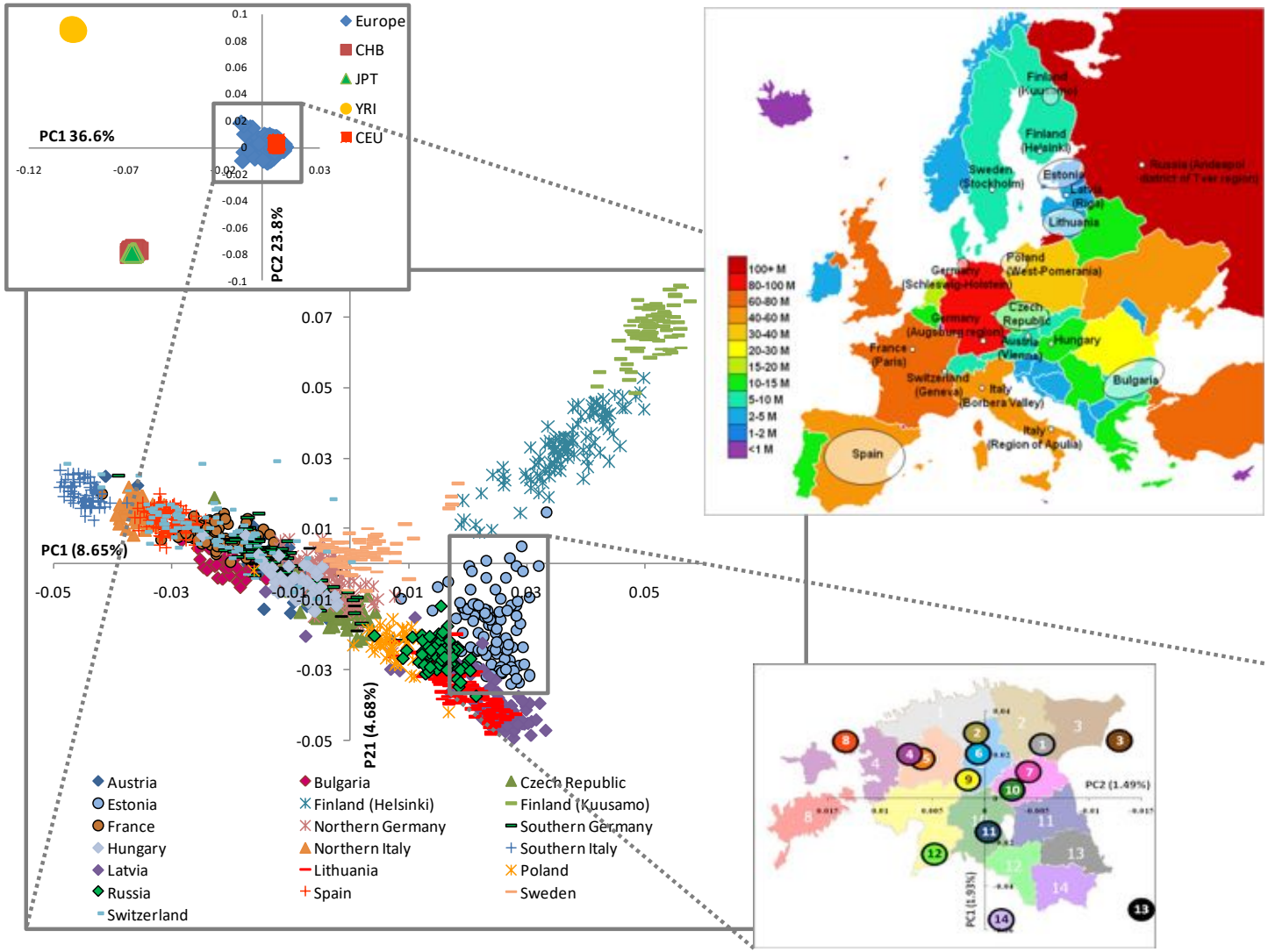
MiSeq

Public opinion and awareness



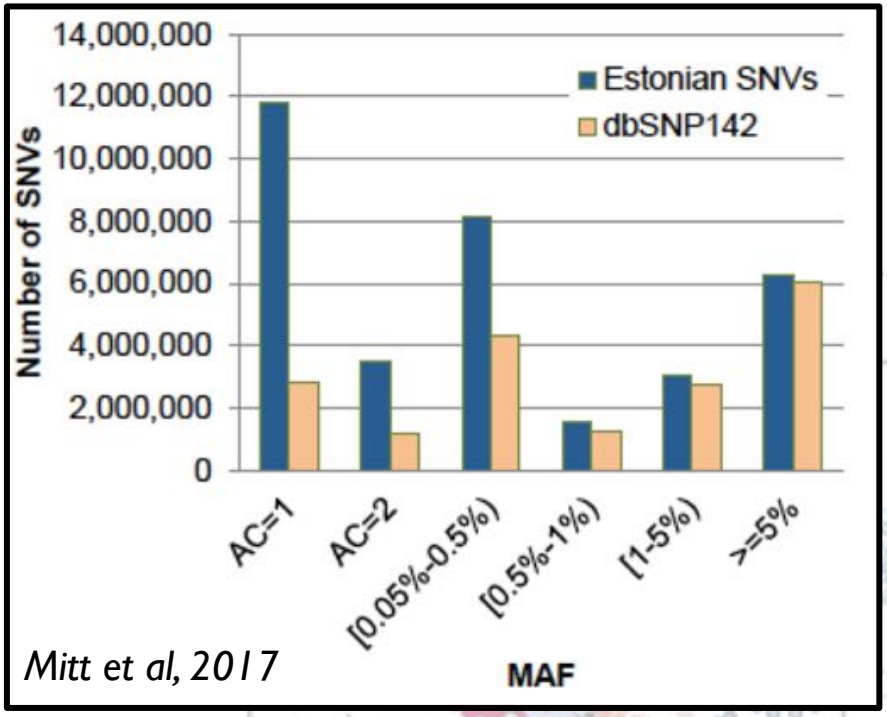
Do we have enough information?

Genetic map of Europe

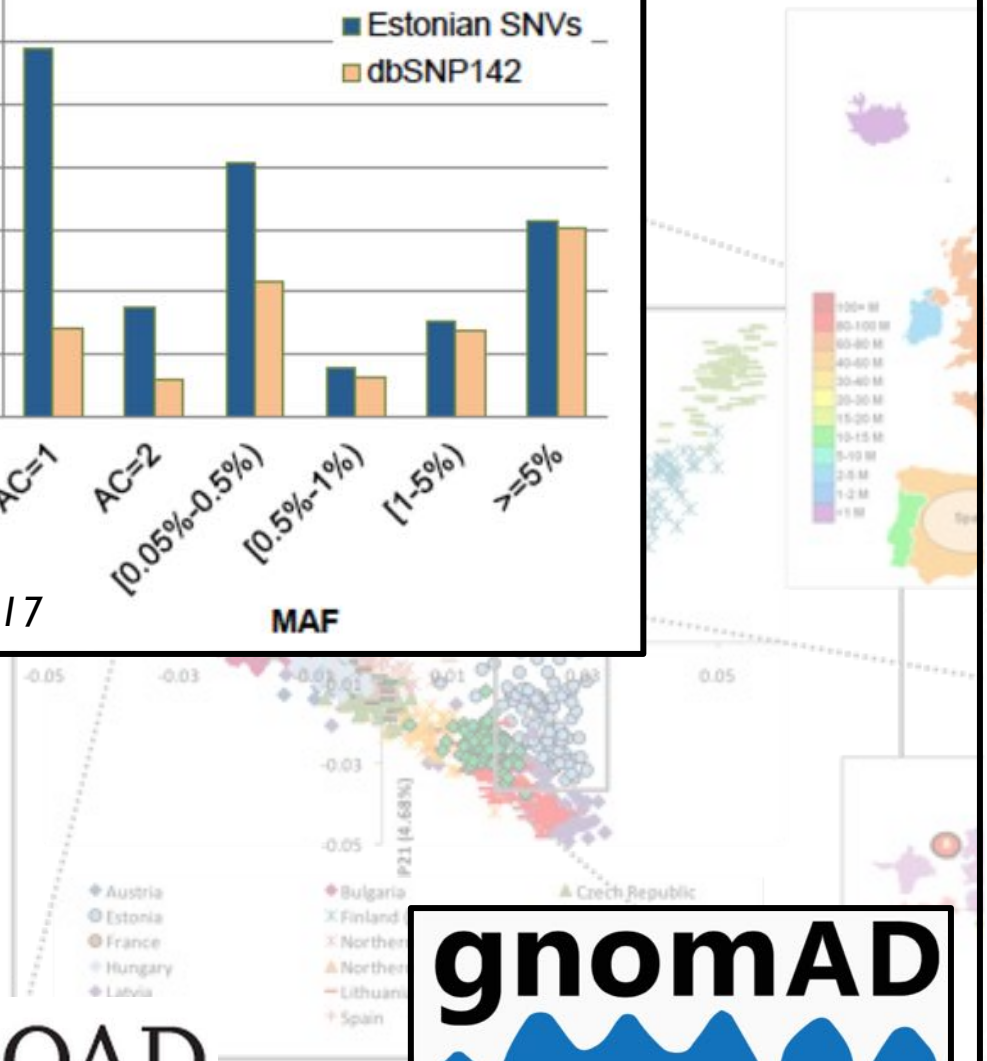


Nelis & Esko et al, 2009

Estonian population WGS panel



Mitt et al, 2017



Single nucleotide variant: 1-55505447-C-T

	Exomes	Genomes	Total
Filter	No variant	Pass	
Allele Count		2846	2846
Allele Number		31384	31384
Allele Frequency		0.09068	0.09068
Popmax Filtering AF (95% confidence)		0.1171	

Annotations

This variant falls on 2 transcripts in 1 gene.

5' UTR

- PCSK9
  - ENST00000302118 *
  - ENST00000452118

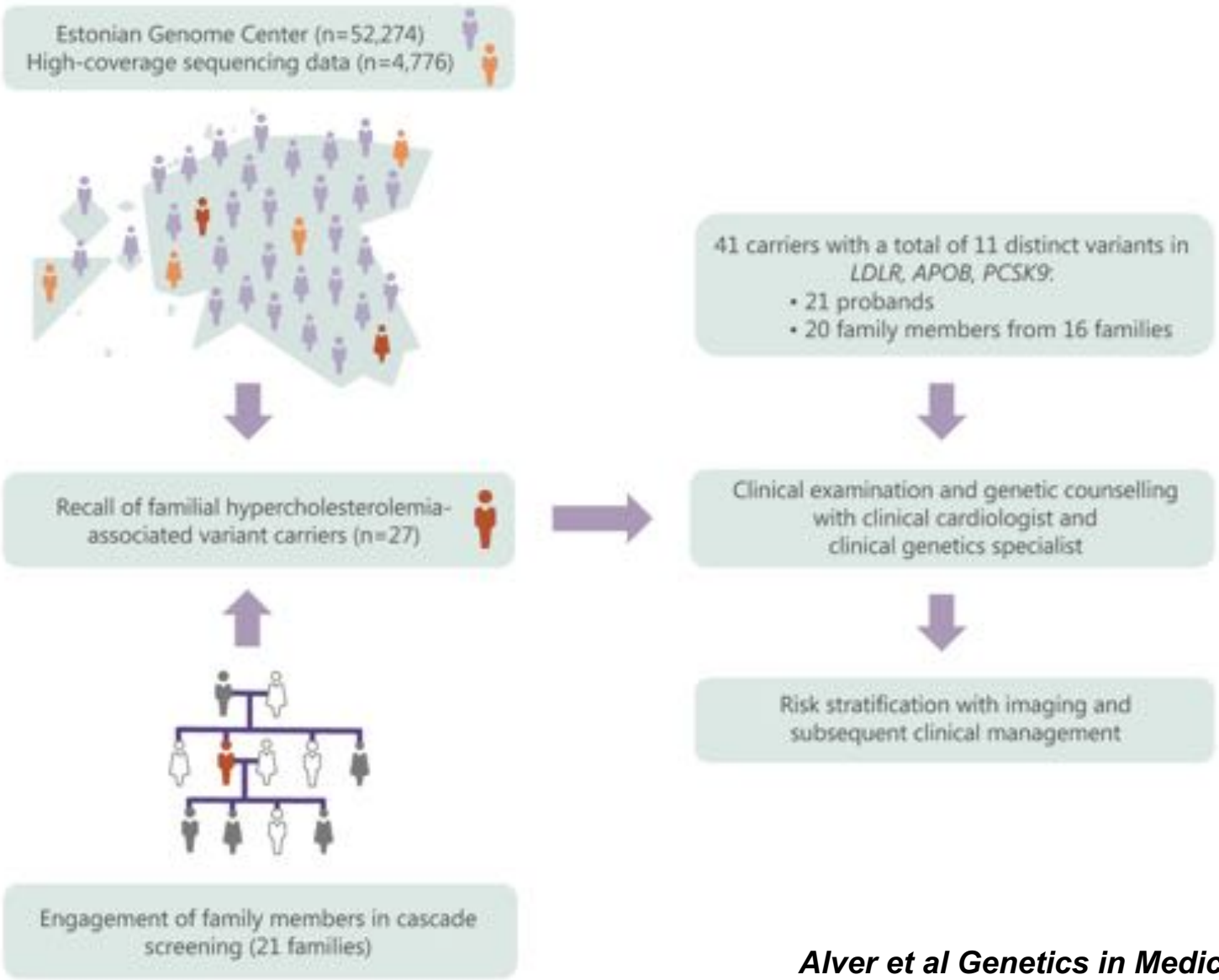
Population Frequencies

Population		Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Ashkenazi Jewish		54	290	5	0.1862
European (non-Finnish)	Overall	1876	15420	107	0.1217
	Southern European	15	106	1	0.1415
	North-western European	1158	8588	72	0.1348
	Other non-Finnish European	267	2138	15	0.1249
	Estonian	436	4588	19	0.09503
	Bulgarian	0	0	0	0.000
	Swedish	0	0	0	0.000
	Male	1082	8620	70	0.1255
	Female	794	6800	37	0.1168
East Asian		186	1560	5	0.1192
European (Finnish)		351	3474	19	0.1010
Other		108	1086	5	0.09945

NEXT 10 BROAD INSTITUTE

gnomAD
genome aggregation database

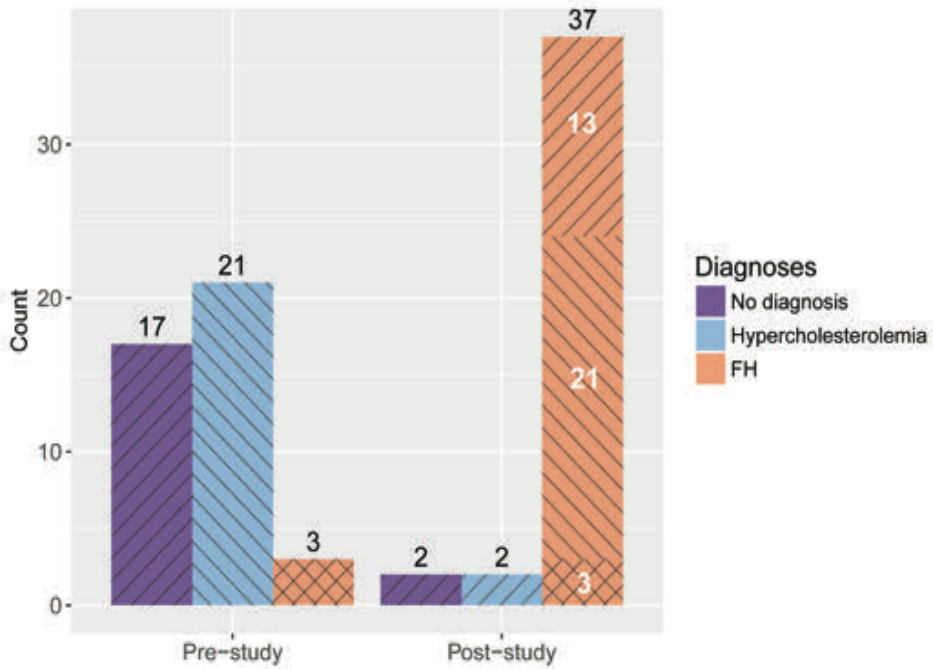
Genotype-first approach to Healthcare
Familiar Hypercholesterolemia & Hereditary Breast Cancer



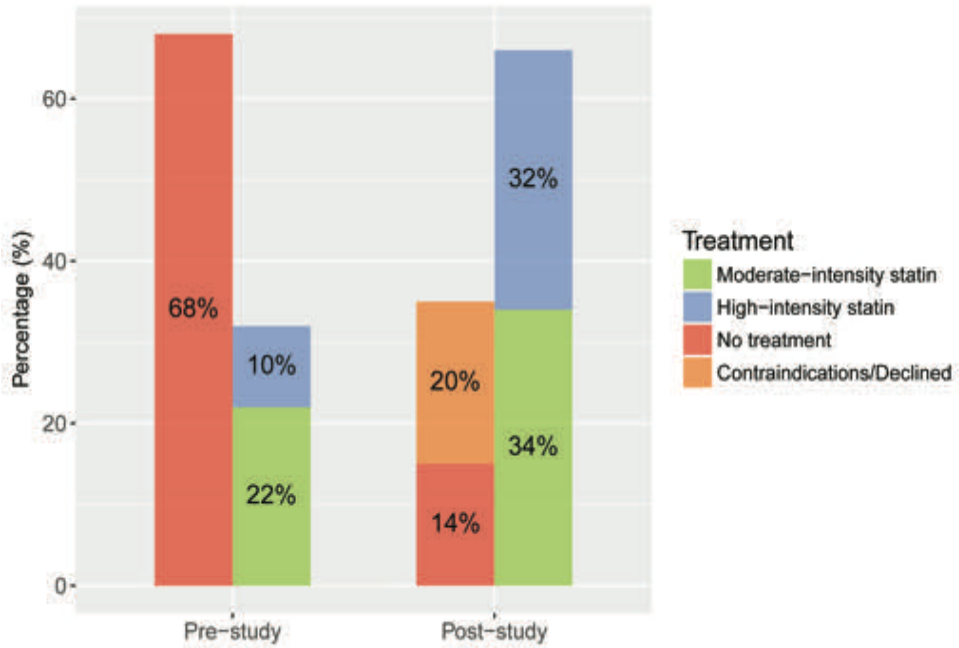
Alver et al Genetics in Medicine 2018

Genotype-first approach to Healthcare
Familiar Hypercholesterolemia

FH and hypercholesterolemia diagnoses pre- and post-study



Treatment recommendations pre- and post-study



Alver et al Genetics in Medicine 2018

Immediate response

BRCA

- 19/20 appreciate return of results
- (1/20 difficult to say)
- Responders tend to feel relaxed, calm and content rather than tense or upset.
- Some report feeling worry
- Information received is rated informative and valuable.
- 20/20 thought they received enough information

FH

- 22/22 appreciate return of results
- Responders tend to feel clarity and relief, and do not feel indifference or confusion.
- Information received is rated informative and valuable.
- 22/22 thought they received enough information

estonian genome center
university of tartu

Dr Liis Leitsalu

Beyond mendelian genomics at national scale?

estonian genome center
university of tartu

Jaan Tamm

Your Data

- (•) Male ( ) Female
- Age 54
- Weight 89
- Height 171
- Waist 86
- [ ] Hypertension
- [ ] Myocardial Infarction

Genetic risk of type 2 diabetes

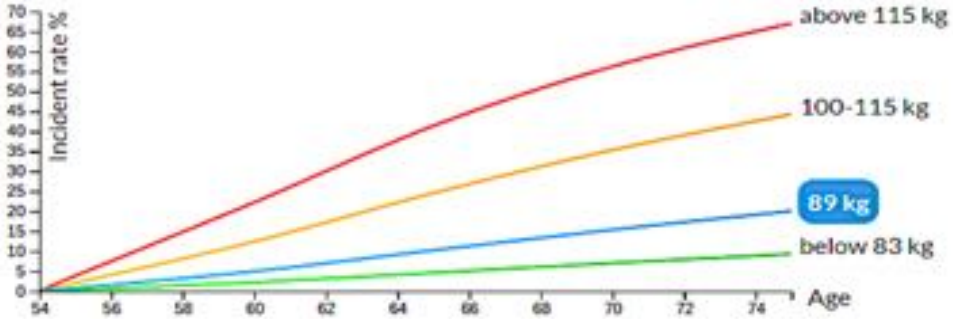
Seven persons out of 10 have lower genetic risk than you.

Two persons out of 10 have higher genetic risk than you.

Your genetic risk of type 2 diabetes is **average**. Your added lifestyle risk is **low**.

Your total risk of type 2 diabetes is **low**.

Risk of type 2 diabetes depends on body weight



Your 10-year risk of developing type 2 diabetes is **2%**. Your probability of developing type 2 diabetes before age 70 is **15%**.

An average person similar to you, but with lower body weight, has up to **50% lower** diabetes risk.

TARTU ÜLIKOOL

eesti geenivaramu

Farmakogeneetika

Üheks põhjuseks, miks inimesed reageerivad ravimitele erinevalt on variatsioonid geenides, mis on vajalikud ravimi toimimiseks organismis. Praeguseks on tuvastatud mitmeid ravimivastuses olulisi geneetilisi markereid. Käesolevas testis määrati Teil 6 geeni markereid, mis mõjutavad 16 erinevat ravimi toimeainet.

Testitud geenivariantide põhjal on võimalik anda alljärgnevad suunised:

Geen	Genotüüp	Hinnang	Soovitus	Mõjutatud ravimi toimeained
CYP2C19	*1/*1	Tavapärane ravimi lagundamine	+	Estsitalopraam, Tsitalopraam, Klopidogrel, Sertraliin,Vorikonasool,Esomeprasool, Lansoprasool,Pantoprasool, Klomipramiin, Amitriptüliin
CYP2C9	*1/*1	Tavapärane ravimi lagundamine	+	Fenütoiin
CYP3A5	*3/*3	Aeglane ravimi lagundamine, Tavapärane muster	+	Takroliimus
DPYD	*5/*9A	Tavapärane ravimi lagundamine	+	Kapetsitabiin, Fluorouratsiil
CYP2C9&VKORC1	*1/*1 & 1639G>A, genotüüp; GA	Tavapärane doosisoovitus	+	Varfariin
SLCO1B1	TC	Tavapärasest kõrgem müopaatia risk	!	Simvastatiin

Näidis

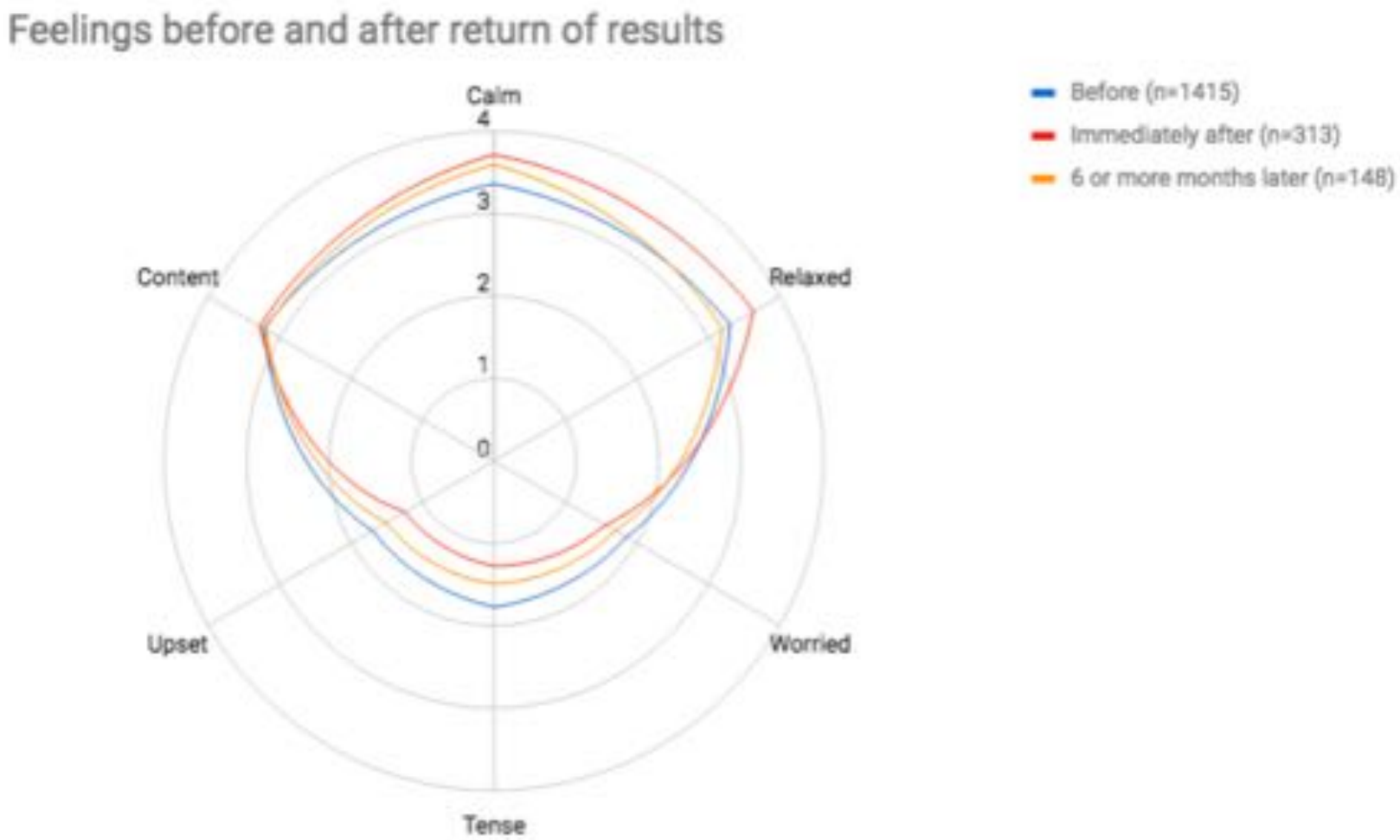
+ - Tarvitada tavapäraselt. ! - Tarvitada ettevaatusega, võib vajada doosi muutmist ! - Tarvitada väga ettevaatlikult, oht kõrvaltoimeteks.

SLCO1B1

Statiinidest indutseeritud müopaatia ehk lihaskahjustus on harvaesinev seisund. Selle puhul esinevad ravimi võtmise foonil lihasnõrkus, -valulikkus, õised lihaskrambid, kõõluste valulikkus ja vereanalüüsides lihaskahjustusele viitavad muutused.

Kui Teile on antud ravimit kirjutatud ning on esinenud vastavaid tervisekaebusi, informeerige neist oma raviarsti.

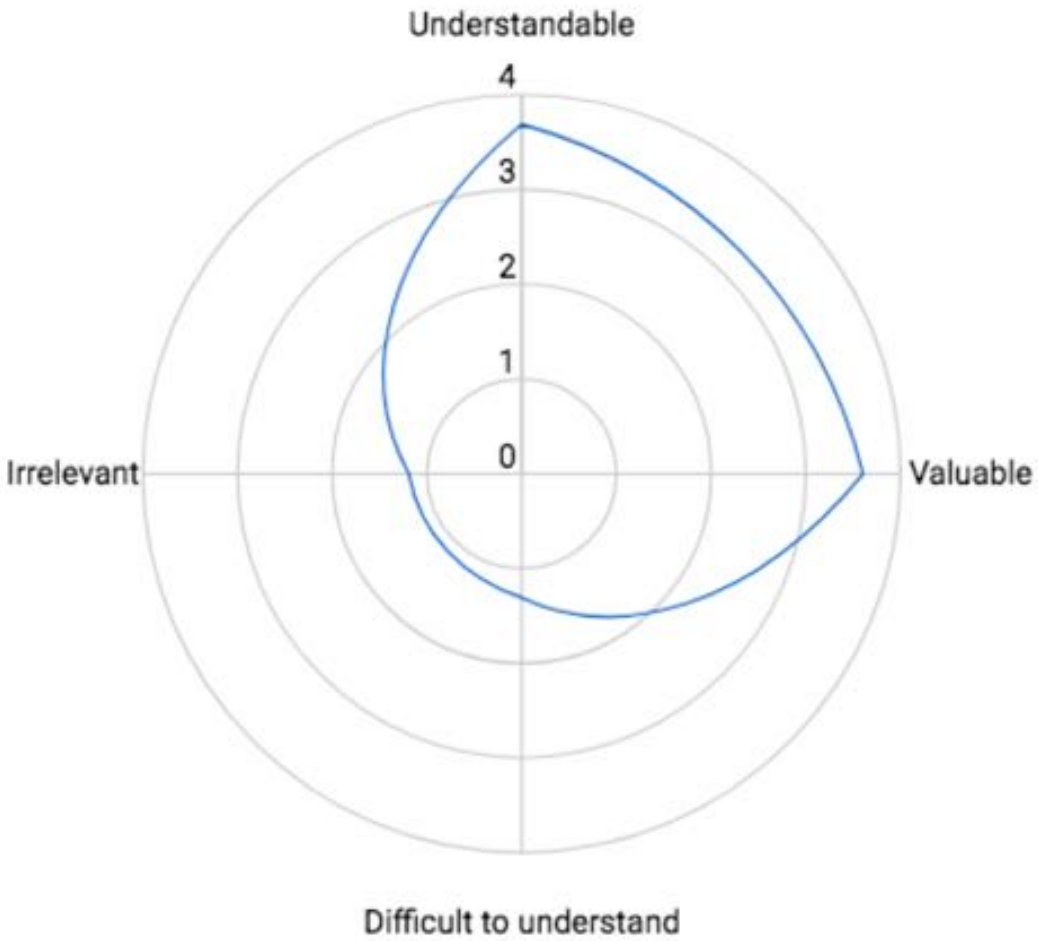
Participants opinion towards genetic feedback



estonian genome center
university of tartu

Leitsalu et al unpublished

Impressions of explanations and counseling



Approximately 24-40 sessions per week by 4 genetic counsellors

Ave. length of GC session 35 min

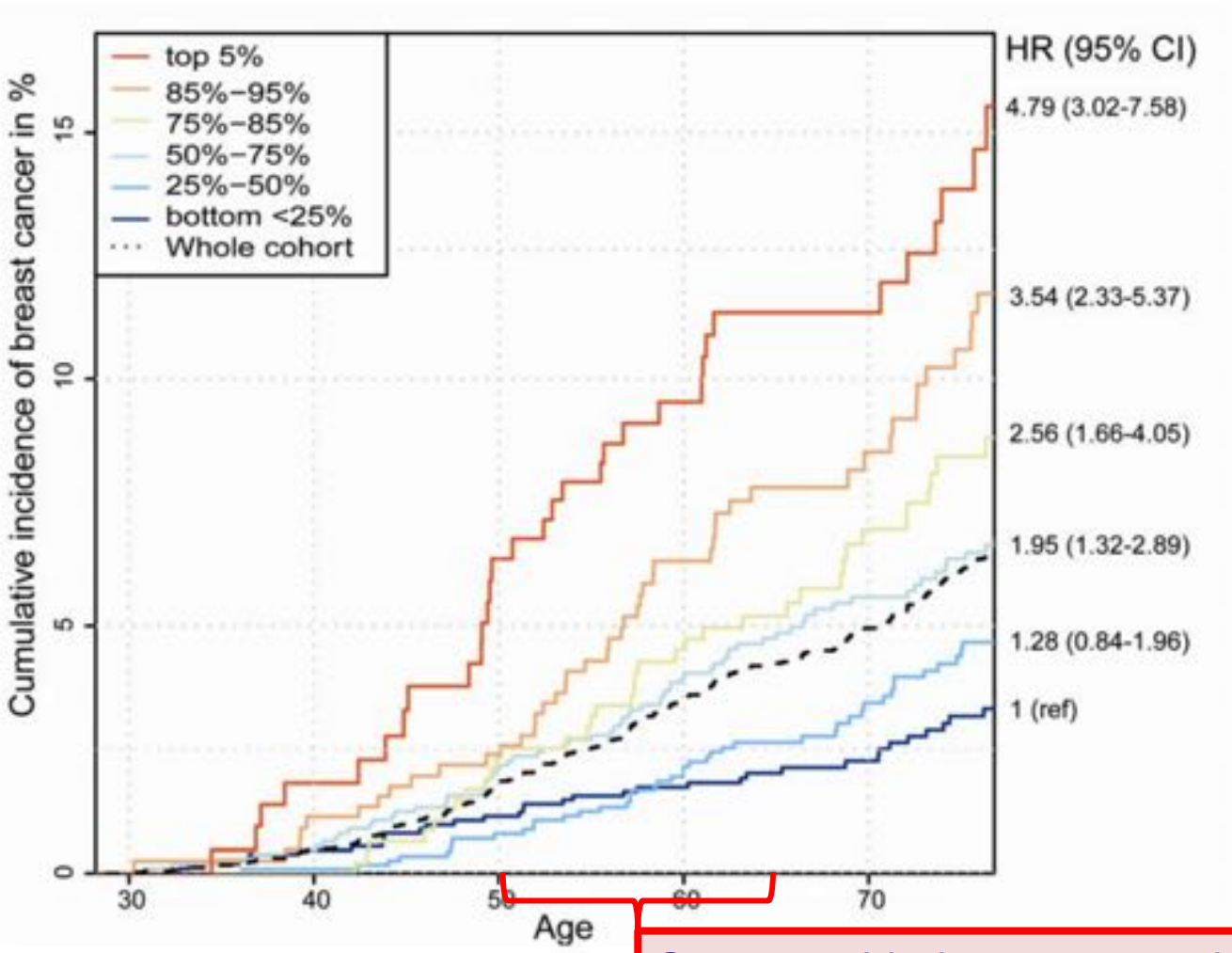
Semi-structured

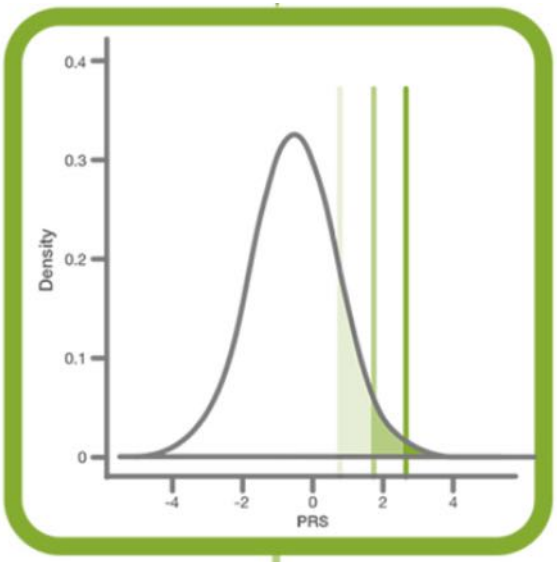
estonian genome center
university of tartu

Polygenic prediction of breast cancer: comparison of genetic predictors and implications for screening

CSH Cold Spring Harbor Laboratory
bioRχiv
THE PREPRINT SERVER FOR BIOLOGY

Kristi Läll, Maarja Lepamets, Marili Palover, Tõnu Esko, Andres Metspalu, Neeme Tõnisson, Peeter Padrik, Reedik Mägi, Krista Fischer





State provided mammography screening programs

Vision for future

estonian genome center
university of tartu

Tervise Arengu Instituut
National Institute for Health Development

SOTSIAALMINISTEERIUM

Kingime Eestile juubeliks 100 000 uut geenidoonorit

Liitu geenidoonoritega ning anna hindamatu panus enda ja meie rahva tervisesse

Hakkan geenidoonoriks

estonian genome center
university of tartu

Is Estonia (Europe) ready for personalized medicine?

- E-health, EMR and other e-infrastructures are in place
- Genome analysis technology is available
- Scientific and medical expertise is here
- Genomic variations with effects on human health and behavior have been identified
- People are interested in personalized, genome based health related information

estonian genome center
university of tartu

Thank you!
www.biobank.ee

Republic of Estonia
Ministry of Social Affairs

NEXT 10 BROAD INSTITUTE

Regionaalhaigla

Eesti Haigekassa

Tervise Arengu Instituut
National Institute for Health Development

Tartu Ülikooli Kliinikum A.D. 1804

E-HEALTH
Estonian e-Health Foundation

QureTEC

Tartu Ülikool Universitas Tartuensis 1632

BIOIT

STACC
Software Technology and Applications Competence Center

Estonia.eu
Positively surprising

Welcome to Estonia

EAS
Enterprise Estonia

European Union
Regional Development Fund

Investing in your future