



**EP PerMed**  
European Partnership  
for **Personalised Medicine**

**ICPerMed**  
INTERNATIONAL CONSORTIUM

ICPerMed & EP PerMed Conference on Personalised Medicine Research  
**Day 2, 27 November 2025**

## SESSION 3

**Andres Metspalu**

University of Tartu, Institute of Genomics

From biobanking to polygenic risk scores  
and personal prevention





# From biobanking to polygenic risk scores and personal prevention

***Andres Metspalu***

Estonian Genome Centre, IG and IMCB, University  
of Tartu, ESTONIA

ICPerMed & EP PerMed Joint Conference

26-27. November 2025 PRAGUE



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# Why personalized prevention?

Chronic diseases remain the main cause of morbidity and mortality in Europe and the problem is getting worse from year to year:  
Not enough medical doctors and of course, money.

The traditional reactive healthcare model, which focuses on treating established diseases, must evolve into personalized prevention, which prioritizes early diagnosis and risk reduction.

1.5% of the health care budget is not simply enough to prevent disease, starting from early detection of the disease risks.

**We have too many patients** because we do not prevent disease as much as we could using current research evidence on genomics , technologies (arrays and WGS) and IT/AI solutions.

### **The EU Cancer Plan**

Promotes personalised prevention, particularly within the framework of the 31.2 Roadmap to Personalised Prevention.

### **ICPerMed and EP PerMed**

Bring together 60 European partners to advance personalised medicine in healthcare systems.

### **The 1+Million Genomes (1+MG) and Genomic Data Infrastructure (GDI) initiatives**

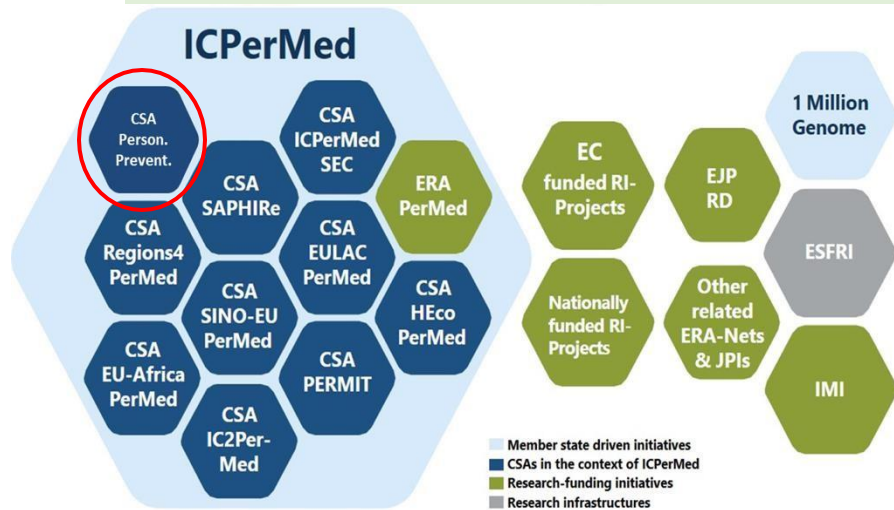
Facilitate secure access to genomic data to enhance research and healthcare services.

### **The European THCS Partnership**

Supports healthcare system transformation by promoting digitalisation and innovation for a more sustainable and efficient care model.

# The PROPHET project

The overall objective of PROPHET is **co-create with stakeholders a Personalized Prevention Roadmap** for the future healthcare, in order to **support the definition and implementation** of innovative, sustainable and high-quality **personalized strategies** that are **effective in preventing** chronic diseases.



- **European Union: Horizon - CSA Staying Healthy (2021) (HORIZON-HLTH-2021-STAYHLTH01)**
- **Consortium: 18 partners**
- **Starting Date : September 1<sup>st</sup>, 2022**
- **Duration : 48 months- Budget: €3,000,000**



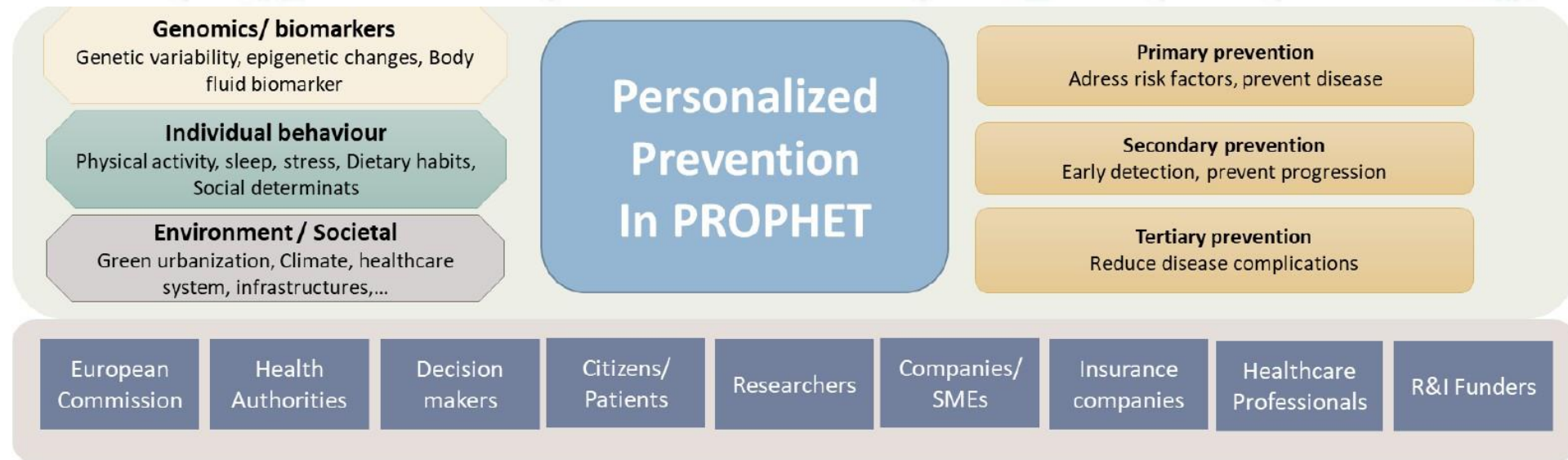
PROPHET is funded by the European Commission under the Horizon Europe Research and Innovation Programme under Grant Agreement N° 101057721



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# Definition of Personalized Prevention in PROPHET



# PROPHET Definition of Personalized Prevention

OPEN

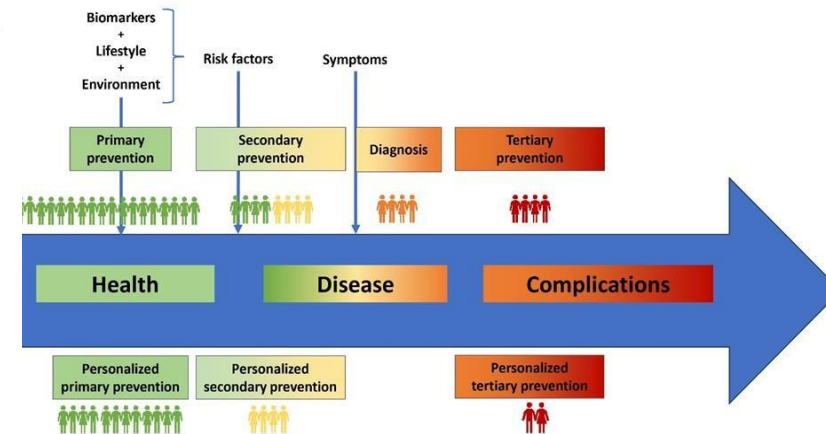
Editorial 387

## The PROPHET project paves the way for personalized prevention in the future healthcare

Roberta Pastorino<sup>a</sup>, Angelo Maria Pezzullo<sup>a</sup>, Tommaso Osti<sup>a</sup>, Roza Adany<sup>b</sup>, Pascal Borry<sup>c</sup>, Floris Barnhoorn<sup>d</sup>, Eva Fadil<sup>e</sup>, Mark Kroese<sup>f</sup>, Andres Metspalu<sup>g</sup>, Beatriz Perez-Gomez<sup>h,i</sup>, Markus Perola<sup>j</sup>, Daniela Quaggia<sup>k</sup>, Serena Scollen<sup>l</sup>, Mahsa Shabani<sup>m</sup>, Stefan Swartling Peterson<sup>n</sup>, Carla van El<sup>o</sup>, Astrid Vicente<sup>p</sup> and Stefania Boccia<sup>a,q</sup>

European Journal of Cancer Prevention 2024, 33:387–389

UK, <sup>m</sup>Department of Criminology, Criminal Law and Social Law, University of

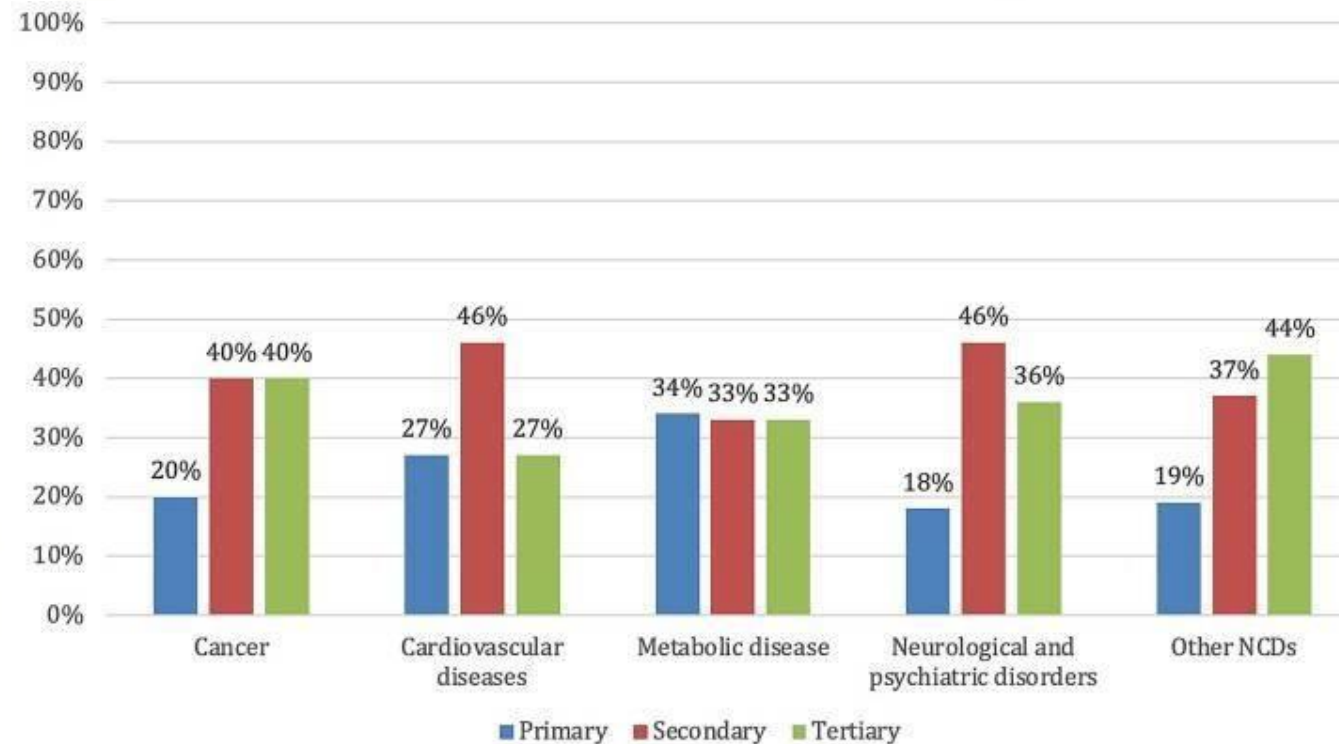


*“Personalised prevention aims to prevent onset, progression and recurrence of diseases through the adoption of targeted interventions that consider the biological information\*, environmental and behavioural characteristics, socio-economic and cultural context of individuals. This should be timely, effective and equitable in order to maintain the best possible balance in lifetime health trajectory”, Pastorino et al. Eur J Cancer Prev 2024*



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# Distribution of the EU-funded projects on personalized prevention by disease type and prevention level



Maio *et al*, 2025

<https://doi.org/10.3389/fpubh.2025.1561328>



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25/11/2025



# SRIA – Strategic Research and Innovation Agenda



The SRIA outlines the major areas that must be addressed in order to fully realize the potential of personalised prevention.

# Europe's Beating Cancer Plan

**Flagship 7:** Alongside the 'Genomic for Public Health' project, the European Initiative to Understand Cancer ([UNCAN.eu](https://uncan.eu)), planned to be launched under the foreseen Mission on Cancer to increase the understanding of how cancers develop, will also help identify individuals at high risk from common cancers using **the polygenic risk scores technique**. This should facilitate personalised approaches to cancer prevention and care, allowing for actions to be taken to decrease risk or to detect cancer as early as possible.



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# The European 1+ Million Genomes project: Genome of Europe reference genomes

## 1+MG Declaration of Cooperation 2018

cross-border access to genomic data (i.e., whole genome sequences; WGS) of 1+ million European citizens by 2027

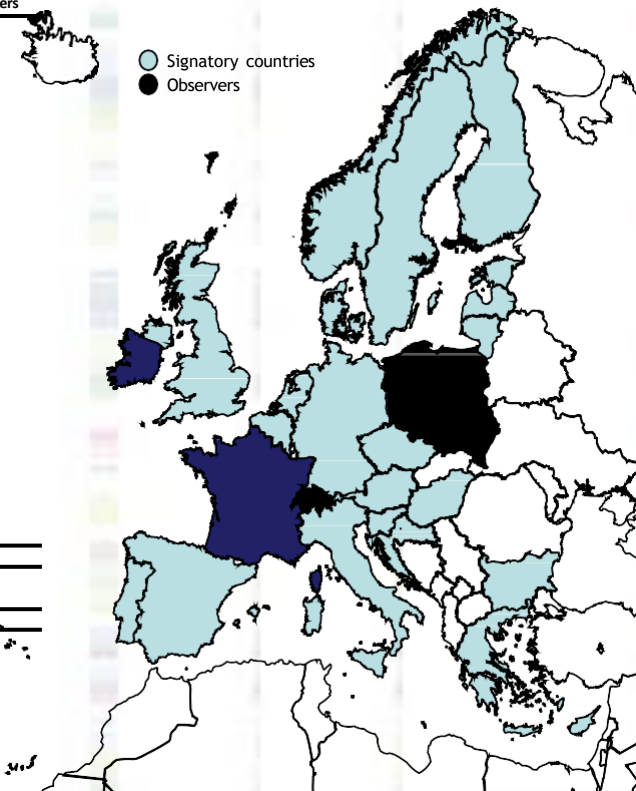


26 signatory countries; 2 observers; 12 working groups



(since 2021) Working Group 12 (coordinator **A.Uitterlinden**): “Genome of Europe” : Creation of “reference genomes” (WGS 30x) of >500,000 European citizens (>40 subgroups by country of origin). Starting in 2024

Country	Population Size	Samples in GoE by population size	samples in GoE by population size - including observers
AUSTRIA	8,901,064	10,566	9,417
BELGIUM	11,521,238	14,514	12,936
BULGARIA	6,520,000	9,265	8,258
CROATIA	4,284,889	6,285	5,602
CYPRUS	896,000	1,550	1,381
CZECHIA	11,023,631	14,731	13,129
DENMARK	5,850,189	7,072	6,303
ESTONIA	1,308,739	1,841	1,641
FINLAND	5,533,793	7,308	6,513
GERMANY	83,020,000	101,177	90,177
GREECE	10,635,997	14,620	13,031
HUNGARY	9,937,628	13,302	11,856
ITALY	59,236,213	78,811	70,243
LATVIA	1,893,223	2,382	2,123
LITHUANIA	2,795,680	4,082	3,638
LUXEMBOURG	634,730	1,000	891
MALTA	525,285	1,000	891
NETHERLANDS	17,475,415	22,550	20,098
NORWAY	5,415,166	6,730	5,998
PORTUGAL	10,340,000	14,519	12,941
SLOVENIA	2,107,007	2,457	2,190
SPAIN	47,394,223	60,626	54,035
SWEDEN	10,379,295	12,953	11,545
FRANCE	66,732,539	85,206	75,942
IRELAND	5,042,151	6,311	5,625
<b>Signatory countries</b>	<b>389,404,095</b>	<b>500,858</b>	<b>446,405</b>
<b>Observers</b>	<b>POLAND 38,081,000</b>	<b>48,980</b>	<b>43,655</b>
	<b>SWITZERLAND 8,670,300</b>	<b>11,152</b>	<b>9,939</b>
	<b>436,155,395</b>	<b>560,990</b>	<b>500,000</b>



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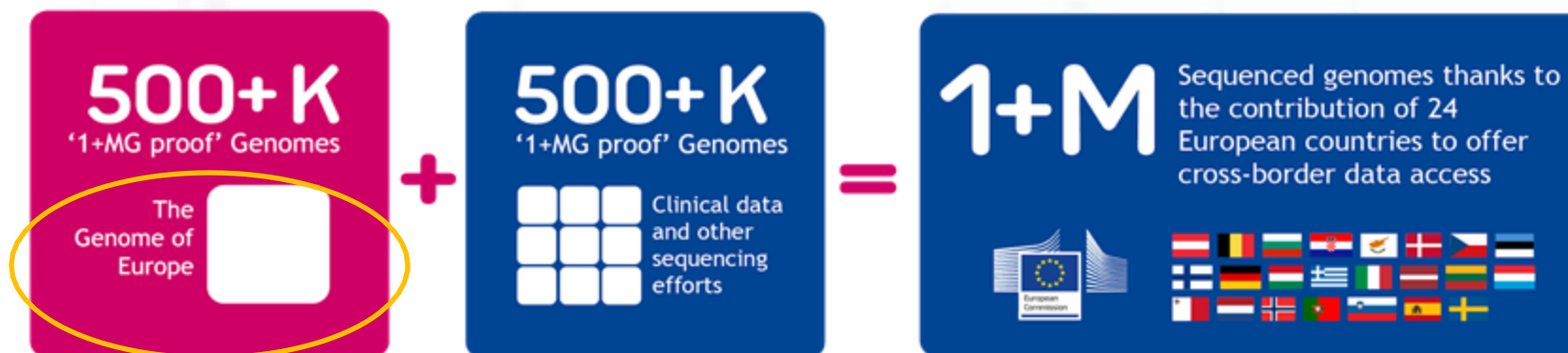
# 1+ Million Genome by 2027 in Europe



## WG12: Genome-of Europe

European commitment to achieve access to at least 1 million sequenced genomes by 2022

B1MG is creating legal guidance, best practices, recommendations and an infrastructure to achieve the goal



**WG 12: GoE**

1MG WG12 Proposal

-First discussed at the 9th Signatory meeting 26 Nov 2020

-Approved by member states on Sept 3 2021



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# 1+ MG Working groups

- The European 1+ million genomes project: Genome of Europe reference genomes
- WG1 Scope, stakeholders and governance
- WG2 Ethical, Legal, and Societal Issues (ELSI)
- WG3 Common standards and min. dataset for clinical and phenotypic data
- WG4 Good sequencing practice
- WG5 Federated, secure, interoperable and privacy-respecting framework and access governance
- WG6 Health economics and outcome research
- WG7 Involvement of the private sector
- WG8 Use case - Rare diseases
- WG9 Use case – Cancer
- WG10 User case Common and complex diseases, population genomics
- WG11 Covid19
- WG12 Pharmacogenomics



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# Genome of Europe

- Focus on general citizens as “normal control population”
- Focussed on creating overview of genetic variation across Europe: across country borders and as inclusive as possible
- A reference genome is important for ALL use cases: what is “normal” commonly seen genetic variation, in a particular ethnic/population background? (As compared, e.g., to a mutation for a rare disease, a tumour mutation, susceptibility alleles, clinical variants)
- Minimal phenotype is required (e.g., age, sex, country of origin). Focus is on genetic variation, not on linking it to disease/phenotypes, which happens in other 1+MG WG's (e.g., WG 8, 10, 11, 12)
- Various sequencing technologies (short read, long read), various sequencing centres
- GoE is a crucial starting point and requirement for implementing genetics broadly into health care in hospitals, screening programs, and in society
- Project is ongoing, started in November 2024.



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# WG10 - Common complex disease- and population genomics

## Proposed general plan:

- Use SNP arrays for the major part of the population and impute the arrays using the Genome of Europe WGS reference database (WG12)
- Develop algorithms that in addition to genomic (-omics) risks include environmental and lifestyle risks.
- Use the data for polygenic risk scores (PRS) and pharmacogenomics (PGx).
- Identify people with high disease risk and/or ADRs and establish population-based early intervention programs for the prevention of various common and complex diseases.

# 1-MG: Next Steps for WG10: a European Genome Program



- **Sequence 1 million genomes**
- **Genotype 50 million samples**

- Proposal for 1+MG WG10 (Complex Diseases): 5-10 year project
  - Finalize WGS of > 1 million genomes: 500k reference genomes + 500k clinical genomes
  - Expand GDI database to hold – at least – 1 mil WGS genomes + 50 mil array genotyped genomes + GWAS data
  - Design a 1+MG Pan-European Array (based on the GoE reference genomes) to genotyped biobanks/cohort studies with EU-specific content
  - Genotype European biobanks with 1+MG PanEuropean array (-50 million samples (out of > 450 mil samples) BBMRI)
  - Run GWAS and create EU/country/region-specific PRS + determine frequency/effect-size of clinically actionable variants (e.g. PGx, FH, etc.)
  - Create a Pan-European GWAS/PRS/variant database

Slide from Ande Uitterlinden



# 1-MG: Next Steps for WG10: a European Genome Program

(In parallel):



- Using DNA information in health care and prevention (front runners: PGx, PRS for cancers, PRS for cardiovascular disease, PRS for diabetes, Fam. Hyperchol. Mutation screening, etc.)
- Engage in global collaborations: UK, USA, Caribbean Islands, Australia, Canada, (north- and sub-Saharan) Africa, South America, Middle East, China, Asia
- Make closer connections in EC/Brussels between DG Sante, DG RTD, and DG CNECT regarding application and implementation of use of genetic data in health care and prevention
- Involve industrial partners both for technology (WGS, array), as well as (European) pharmaceutical companies



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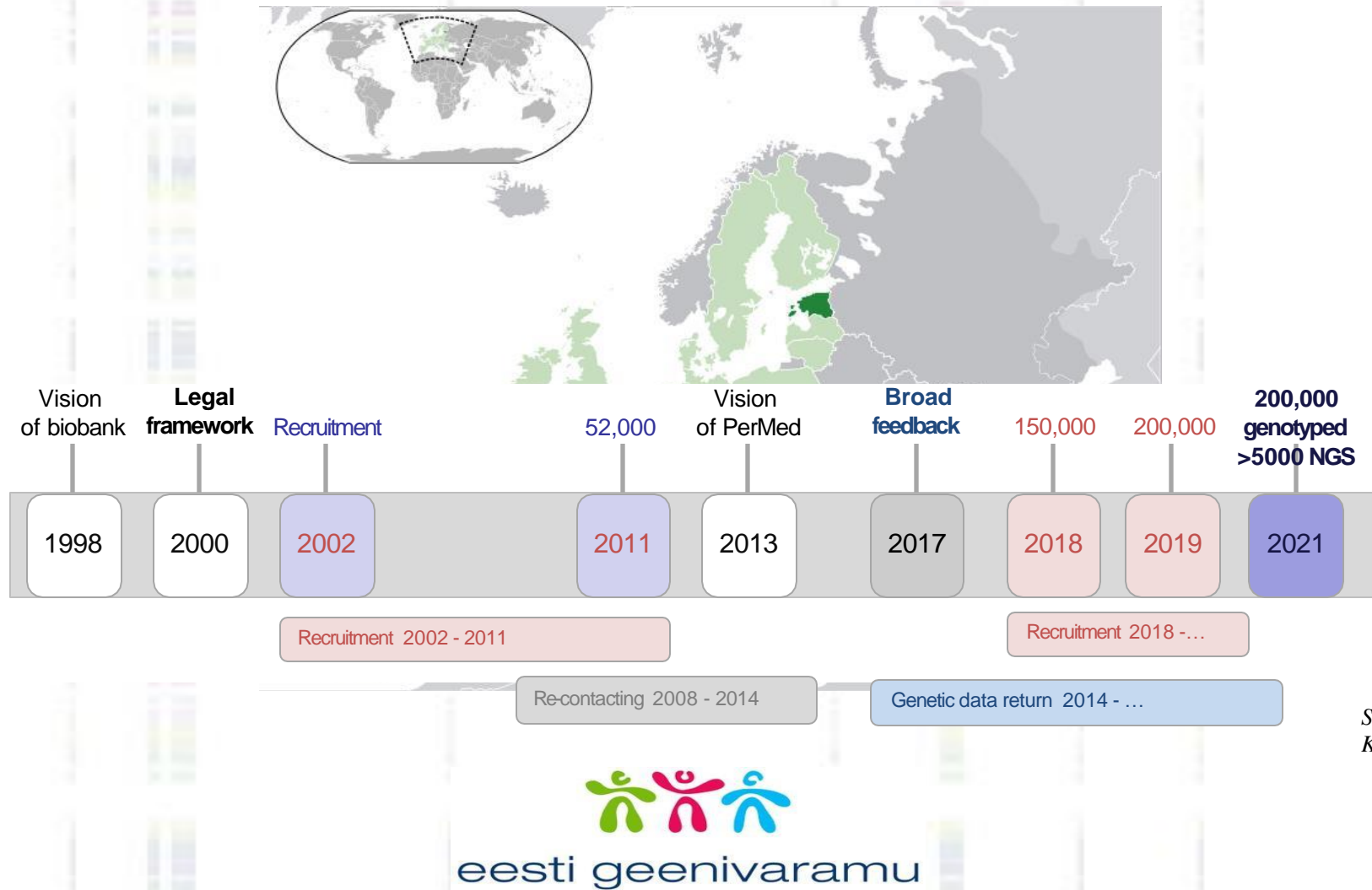
# Estonian Biobank (started in 1999!)

1. Prospective, longitudinal, volunteer-based, **213 000 individuals = 20% of the adults (18 years and up) population of Estonia**
2. Health records, diet, physical activity, etc. DNA, plasma, 3000 WGS, 2500 WES, for all GSA array and NMR data for 250 molecules
3. Open for research and development: Clear access rules, broad informed consent, HGR Act.



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# Estonian Biobank timeline



Slide:  
Katrin Männik

# Human Genes Research Act

Passed 13.12.2000

RT I 2000, 104, 685

## § 3. Chief processor of Gene Bank

(1) The chief processor of the Gene Bank is the University of Tartu whose objective as the chief processor of the Gene Bank is to:

- 1) promote the development of genetic research;
- 2) collect information on the health of the Estonian population and genetic information concerning the Estonian population;
- 3) **use the results of genetic research to improve public health**

**Access rules:** send application to EstBB -> scientific committee-> ethical review, ->release the data

**“Tools to the data”** rule, all computing in our servers in special space just for the customer. Fees apply.



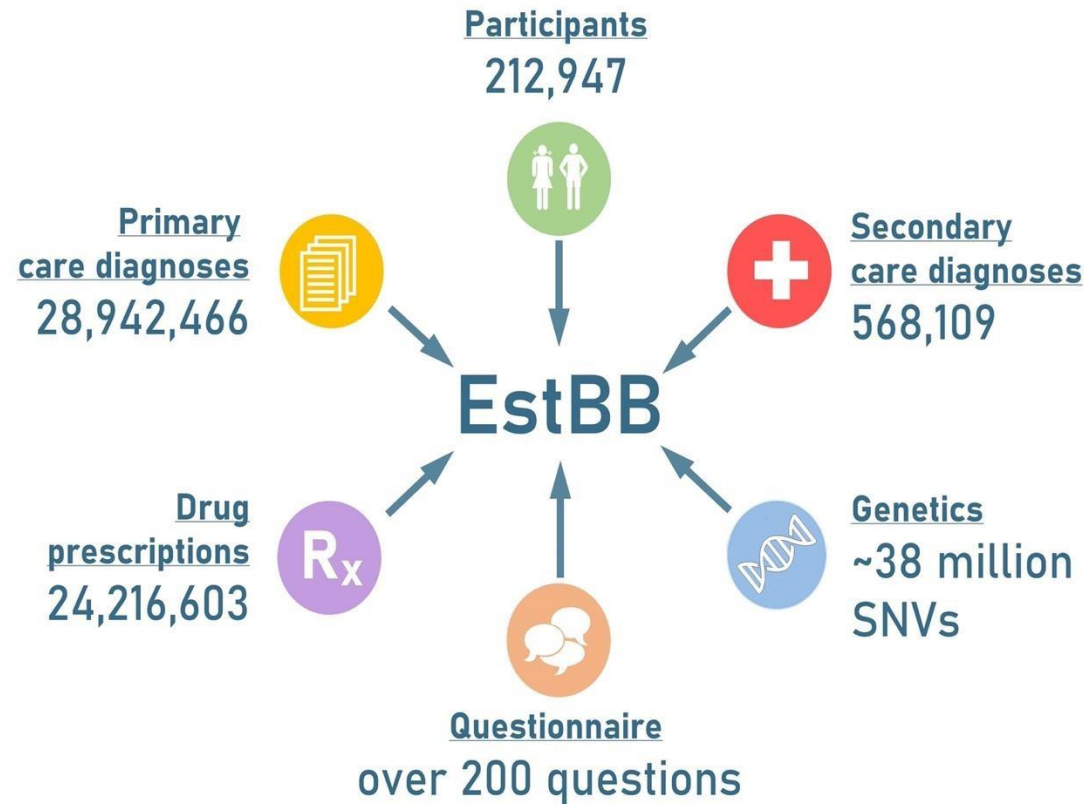
# New Human Gene Research Act



- **High – quality biobank data from research used in healthcare and services**
- **Zero tolerance for discrimination based on genomic features**

Slide from Raili Sillart

# EstBB Baseline Data

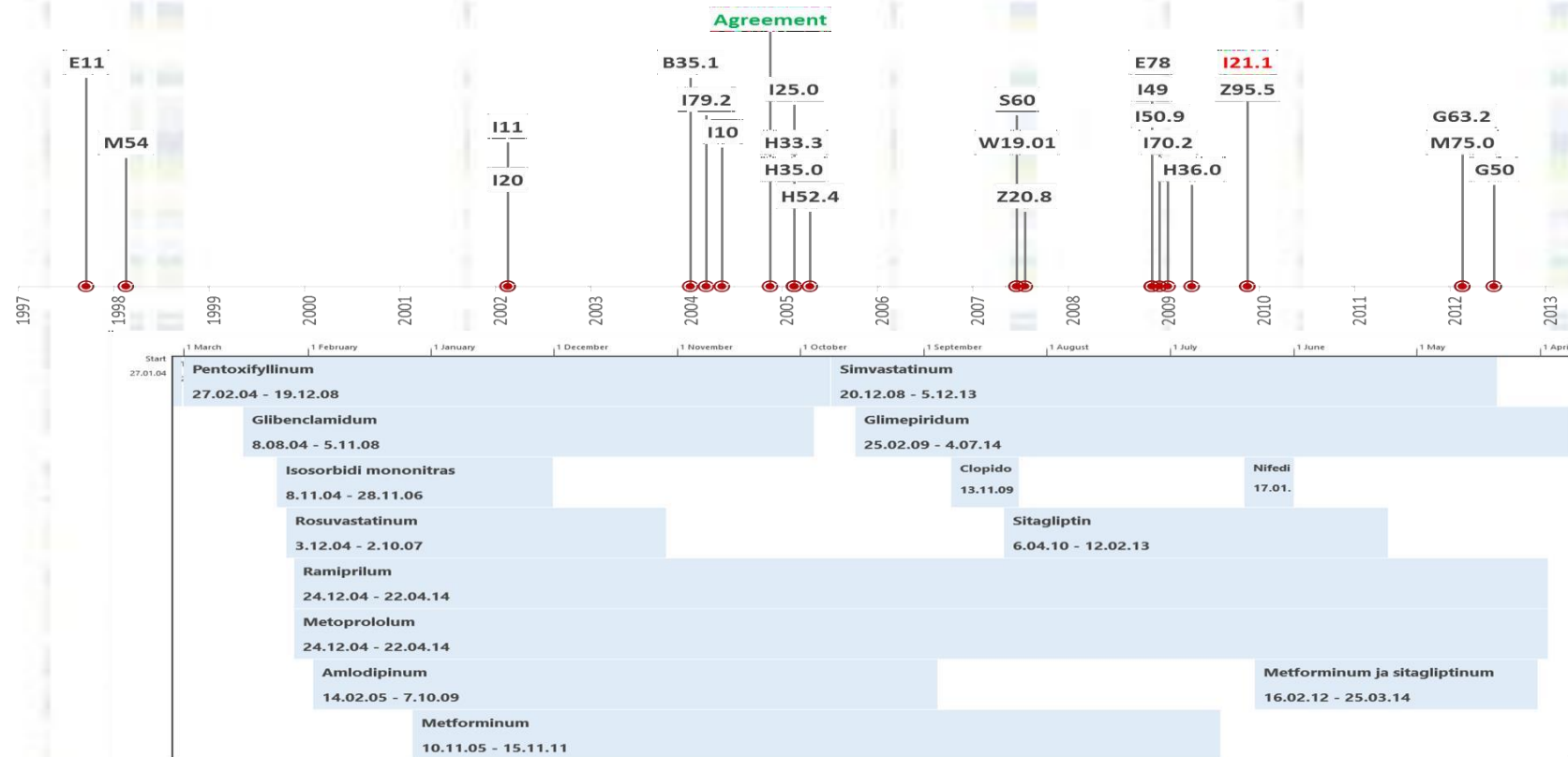


**+10,000 PacBio long-read genomes**



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# Disease trajectories + treatment info for people in the biobank

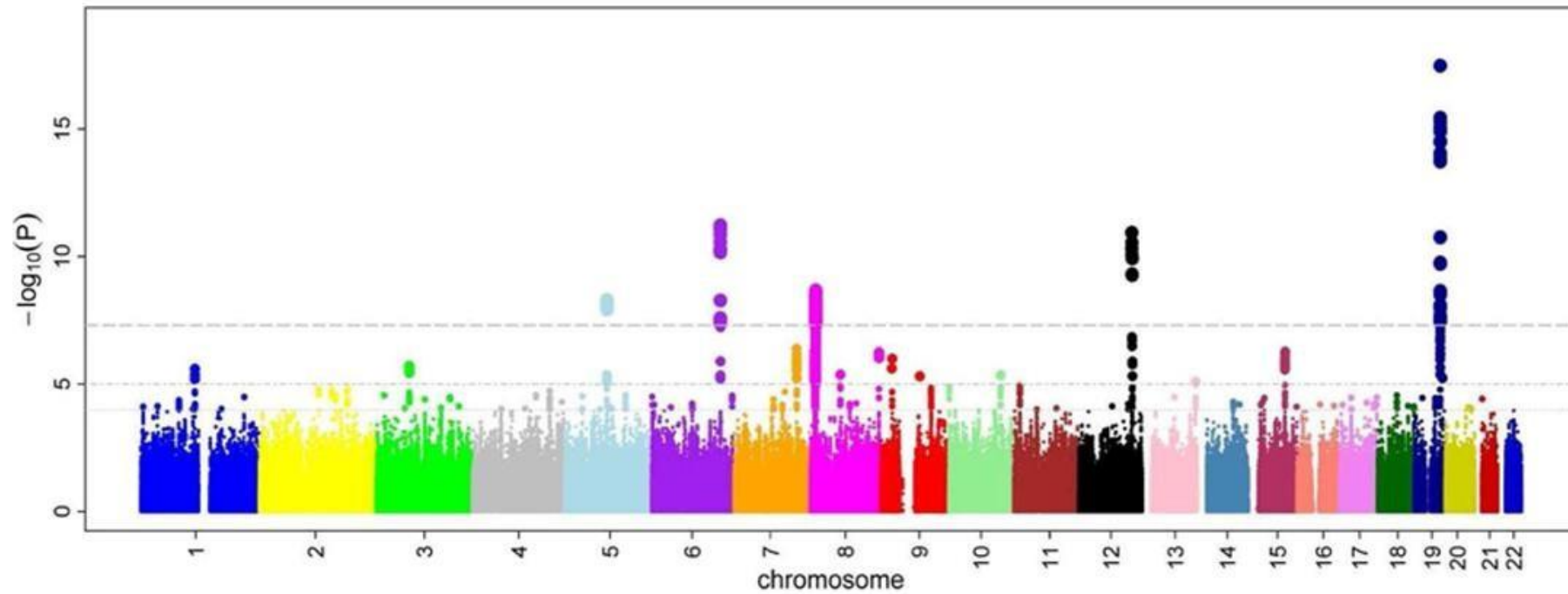


Male, born 1944



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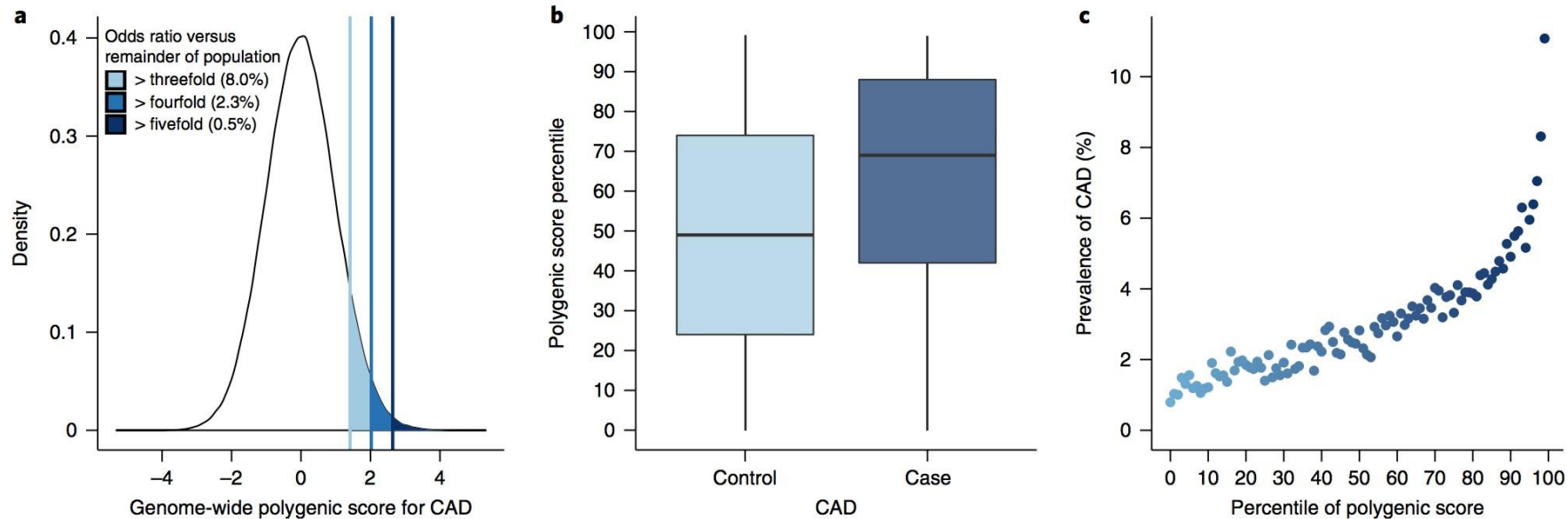
# Manhattan plot GWAS



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# CAD polygenic risk score (PRS)



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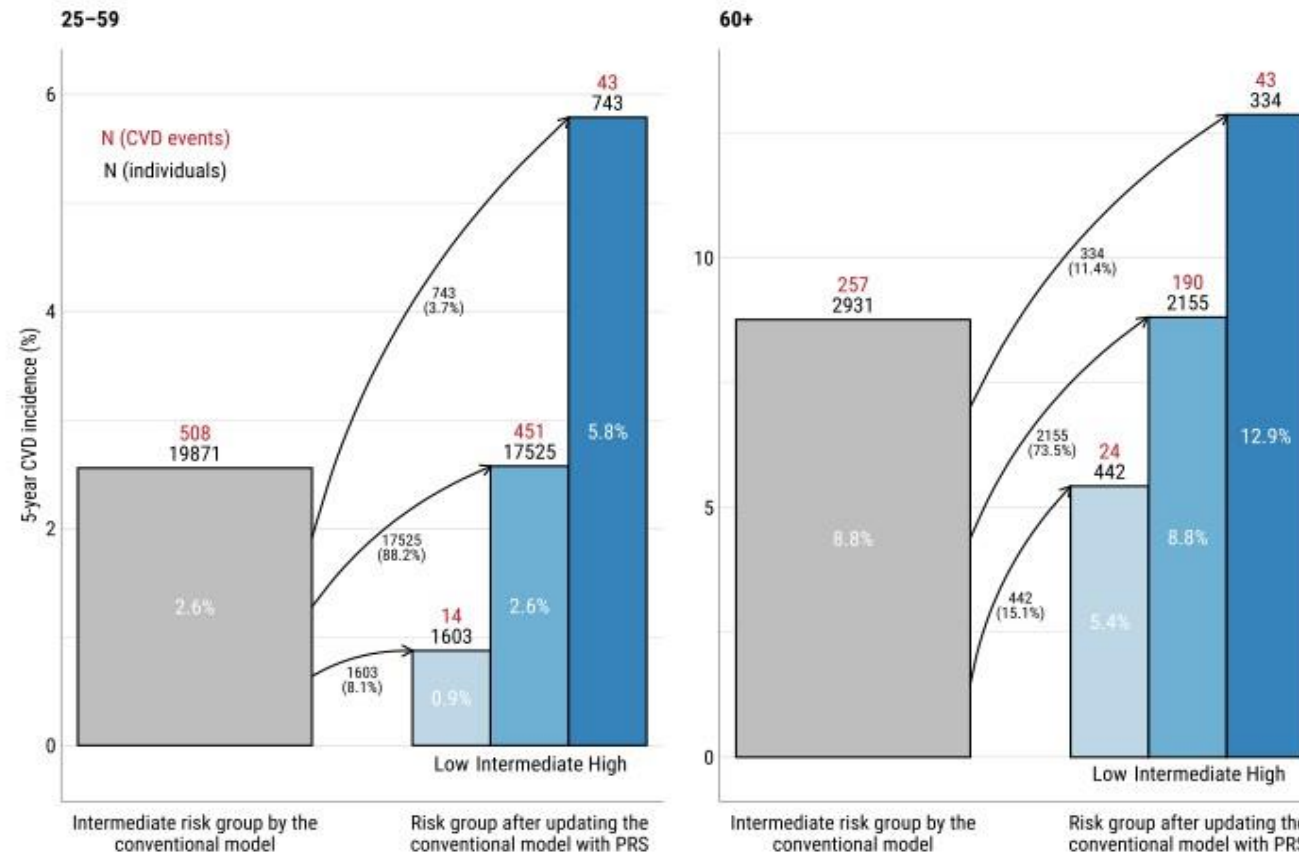
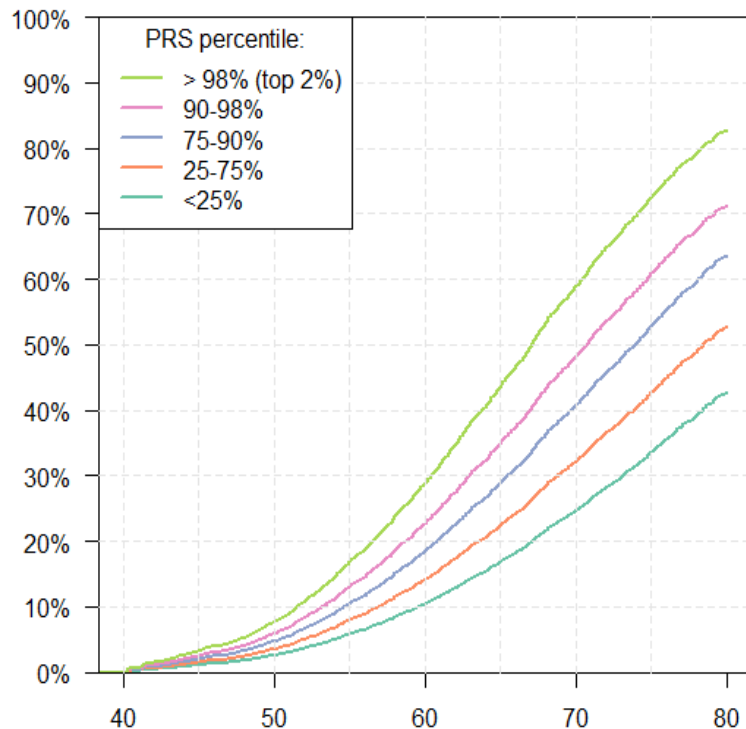


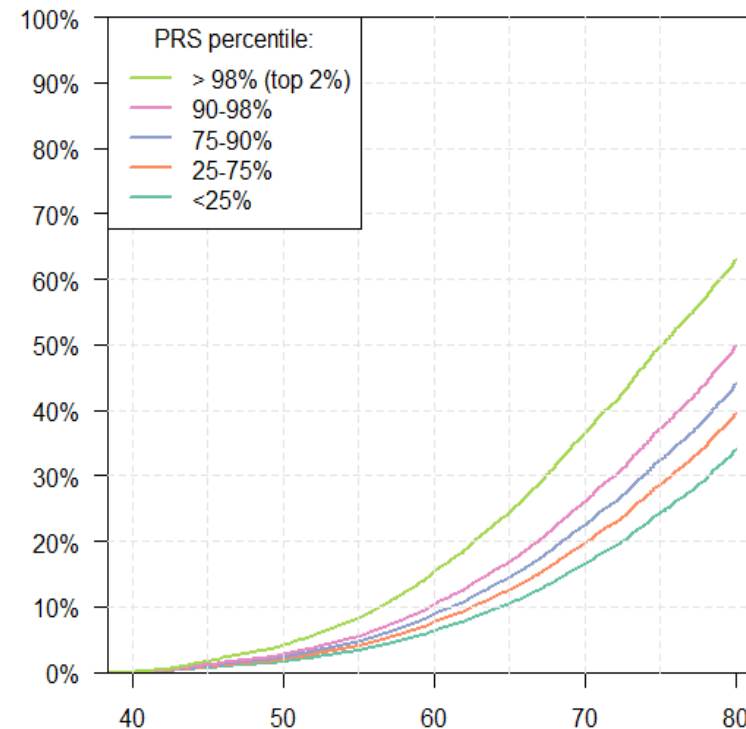
Figure: 4 SCORE2 + PRS (the most innovative medical technology for early detection of the disease risks)

medRxiv preprint doi: <https://doi.org/10.1101/2025.04.02.25324383>

**Cumulative incidence of CAD in men (age 40-80)**



**Cumulative incidence of CAD in women (age 40-80)**



Cumulative incidence of fatal or non-fatal CVD event in 23 750 men (2 277 events during follow-up) and 49 955 women (3 237 events) of the Estonian Biobank cohort (age 40-80, no prevalent CVD at recruitment). The plot is based on fitted Cox model, using age as time scale and accounting for competing events (non-CVD death).

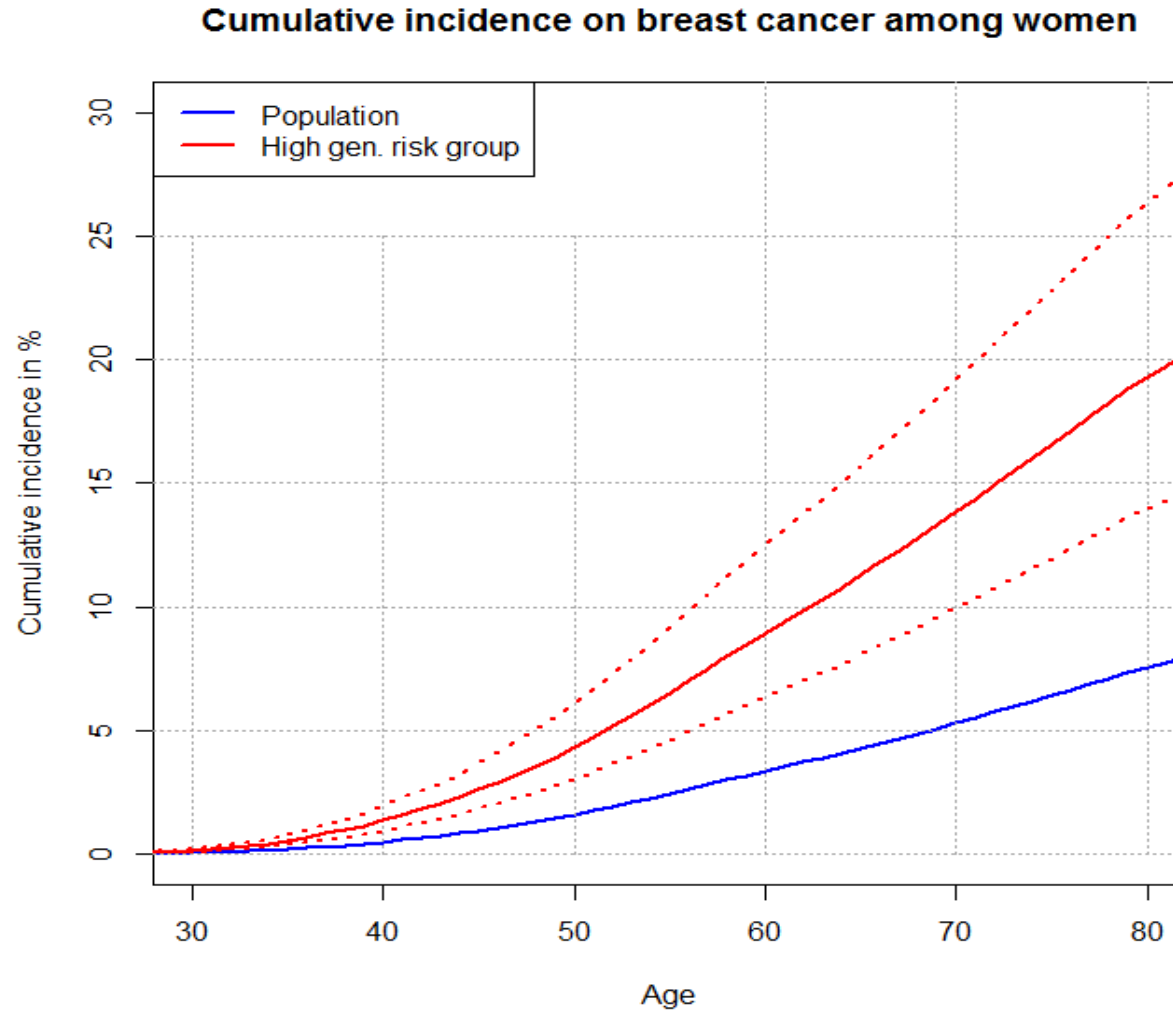
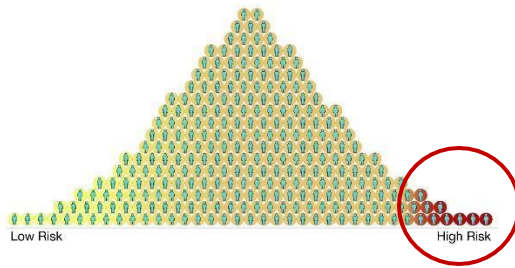
*Analysis: K. Fischer and T. Puusepp*



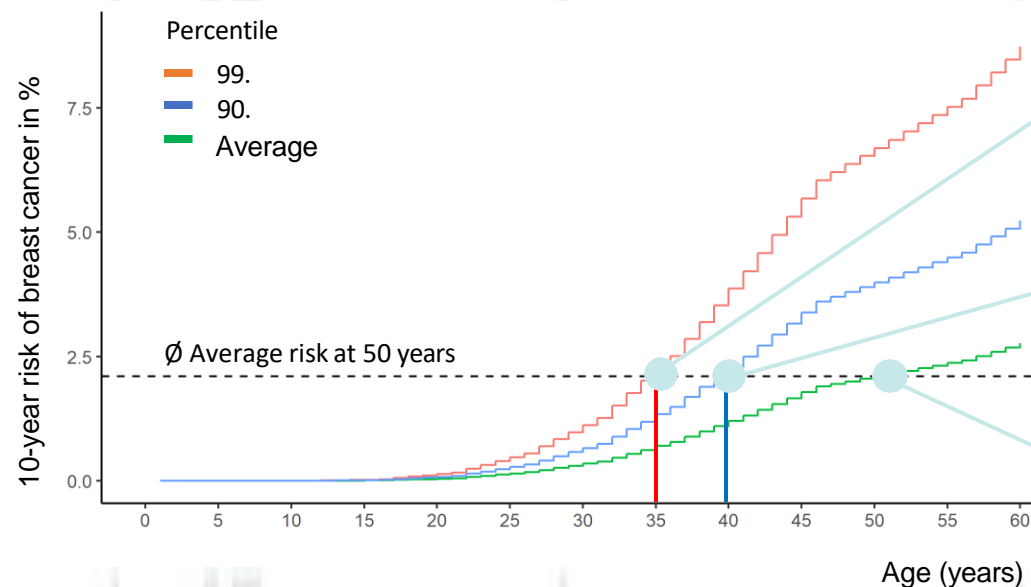
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# Breast cancer: population vs top 5% Based on Polygenic Risk Score - PRS



# The breast cancer PRS test AnteBC defines the age to start personalised breast cancer screening



## Very high risk (red, percentile 99)

1% of women with a high risk already exceed the risk threshold of an average 50-year-old woman at the age of 35.

## High risk (blue, percentile 90)

10% of women at high risk exceed the risk threshold of an average 50-year-old woman at age 40.

## Average risk (green, percentile 50)

Current screening threshold risk level



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Slide from Dr. Peeter Padrik



# The PROBLEM with breast cancer screening

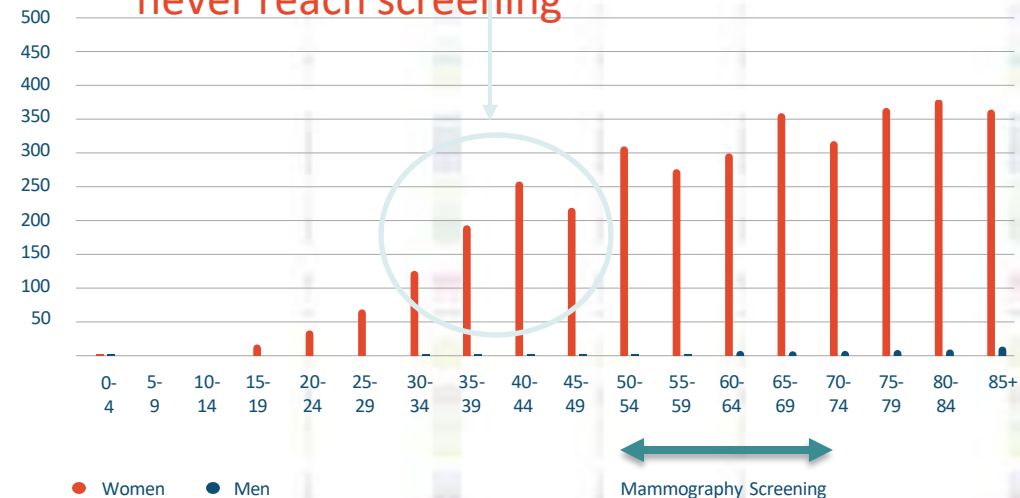


- Mammography screening reduces breast cancer mortality by 20-30% in average risk level in age 50-69
- But also has negative aspects & costs
- The benefits & harms ratio, and also cost-efficiency are not satisfactory for mammography screening for all women under 50

## SOLUTION:

Personalised PRS risk-based screening for women ages 30-49, earlier mammography for high PRS risk women

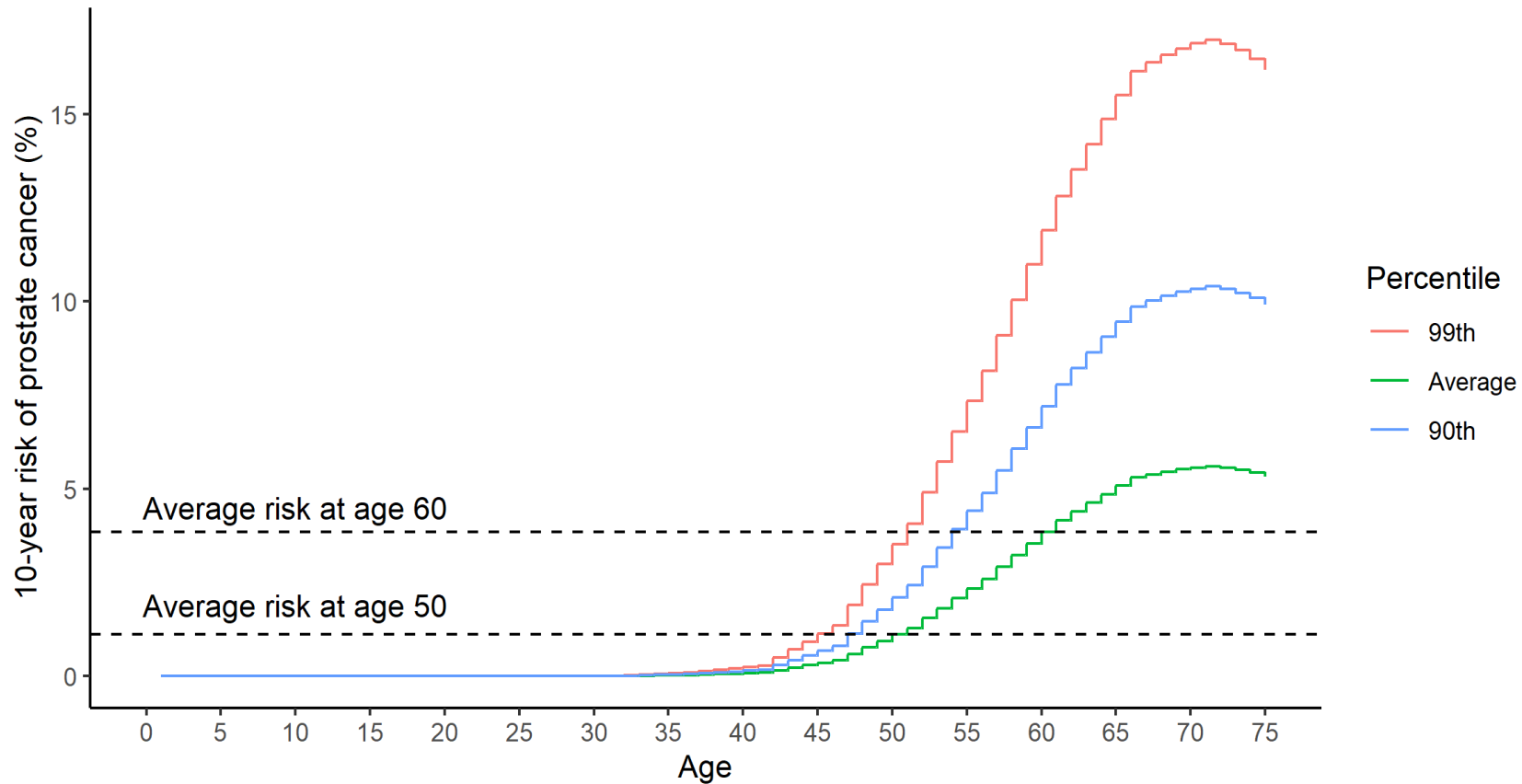
! 20% of breast cancer cases are diagnosed among women younger than 50, they never reach screening



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Slide from Dr. Peeter Padrik

# The prostate cancer PRS test AntePC defines prostate cancer risk levels



Padrik et al, <https://doi.org/10.3390/cancers17071056>

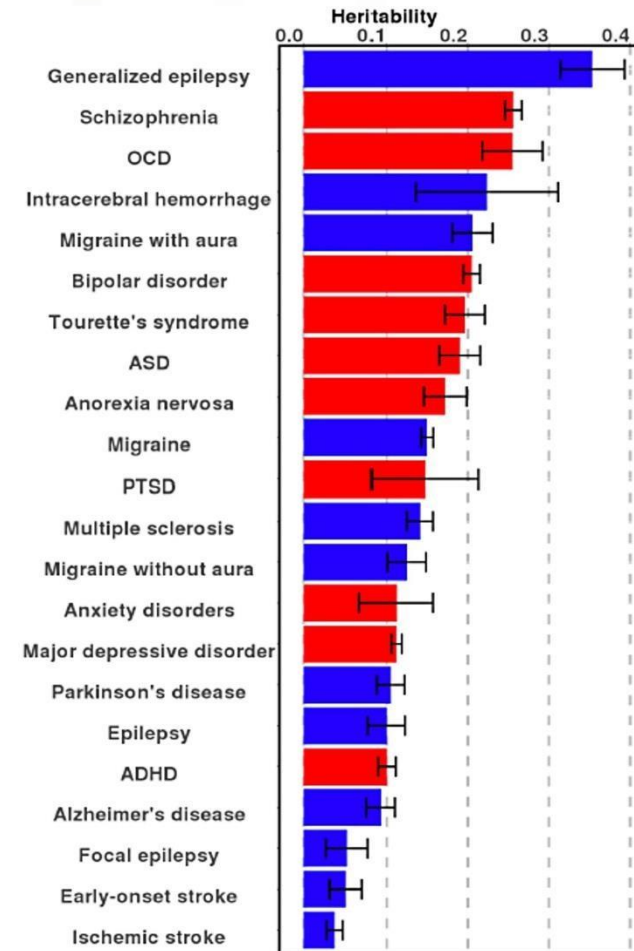


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# Parkinson's disease

- Parkinson disease (PD) is the second most common neurodegenerative disorder worldwide.
- In Europe, USA
  - Prevalence: 66 - 1500 / 100 000
  - Incidence: 10 - 18 / 100 000
- In Estonia
  - Prevalence: 314 / 100 000
  - Incidence: 18 / 100 000

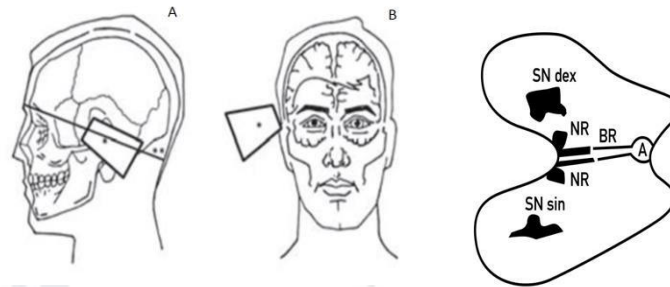
Kadastik-Eerme, 2019



Brainstorm, 2018

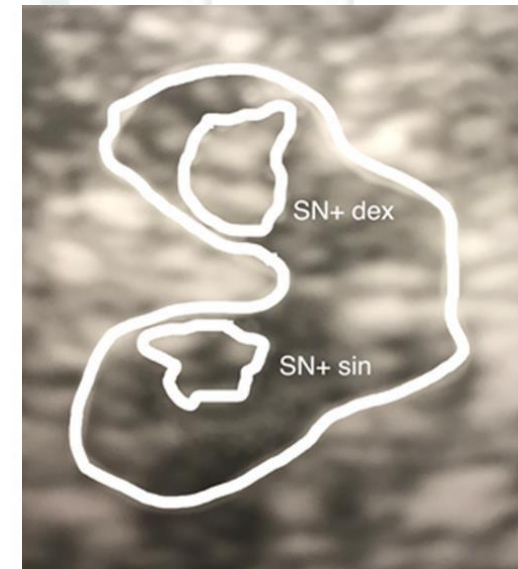
# Transcranial brain sonography

## Sonographic examination



- Mesencephalic brain stem - butterfly shape
- Image freezing (SN is visible)
- SN encircling and measuring (cm<sup>2</sup>)

*The echo intensity and increased size of the SN area = SN hyperechogenicity (SN+)*



Dr. Toomas Toomsoo



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# Characteristics of individuals in high and low PD-PRS groups

	High PD-PRS (N = 107)	Low PD-PRS (N = 97)	P-value
N	107	97	
Sex, male (%)	56 (52.3)	52 (53.6)	0.967
Age (years)	64.3 (7.3)	65.3 (7.0)	0.325
Family history of PD (%)	10 (9.3)	8 (8.2)	0.977
Newly diagnosed PD (%)	9 (8.4)	3 (3.1)	0.189
Area of echogenicity in SN (cm <sup>2</sup> )	0.21 (0.09)	0.15 (0.06)	<0.001
Occurrence of SN+ (%)	46 (43.0)	10 (10.3)	<0.001
Dream enactment behavior (%)	5 (4.7)	13 (13.4)	0.051
Constipation (%)	16 (15.0)	11 (11.3)	0.580
Depression (%)	20 (19.0)	27 (27.8)	0.190
Diabetes (%)	8 (7.5)	11 (11.3)	0.480
Migraine with aura (%)	10 (9.3)	2 (2.1)	0.056



# Polygenic Risk Score Combined with Transcranial Sonography Refines Parkinson's Disease Risk Prediction

Mart Kals, PhD,<sup>1</sup>  Anu Reigo, MD,<sup>1</sup> Maris Teder-Laving, MSc,<sup>1</sup> Mariliis Vaht, PhD,<sup>1</sup> Estonian Biobank research team, Tiit Nikopensius, PhD,<sup>1</sup> Andres Metspalu, MD, PhD,<sup>1,2</sup> and Toomas Toomsoo, MD, PhD<sup>3,4,\*</sup>

Aim: to determine the predictive value of marker combinations for the development of PD



# Vision: Genomics of the common disease – early detection and prevention

## PRS based population-wide analysis (compare to newborn screening)

1. Sequence ca 0.1% - 1% of the population and capture maximum amount of the genomic variation and use it for imputations.
2. Use SNP-arrays for the major (max) part of the population and impute the arrays
3. Use the imputed SNP data for PRS
4. We spent ca 70€ per individual to recruit 150 000 individuals in 2017-2018, acquire health data and genotype
5. **Take top (e.g.1%-2) of the high PRS individuals and apply intervention, where appropriate. In future we can go for more – like 5%!**
6. **Population scale Personal Prevention**

Genome of Europe –  
1+MG



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# Conclusions

**Large prospective biobanks** make it possible to move towards personalized genetic risk prediction and to use it in general medical practice for preventing or postponing the disease or adverse drug reactions.

**However**, we should move from the biobanks (very good for research and discovery) **to the population based personal prevention based on genomic data**, but using other data (environment, behavior) as well to amplify the potential risks.

**Whole population = biobank**

**Moreover**, we could move from the PRS to real diagnostics by implementing the secondary (diagnostic!) test to high PRS individuals, which can not be used on whole population e.g. ultrasound in PD, liquid biopsy in cancer risk etc.



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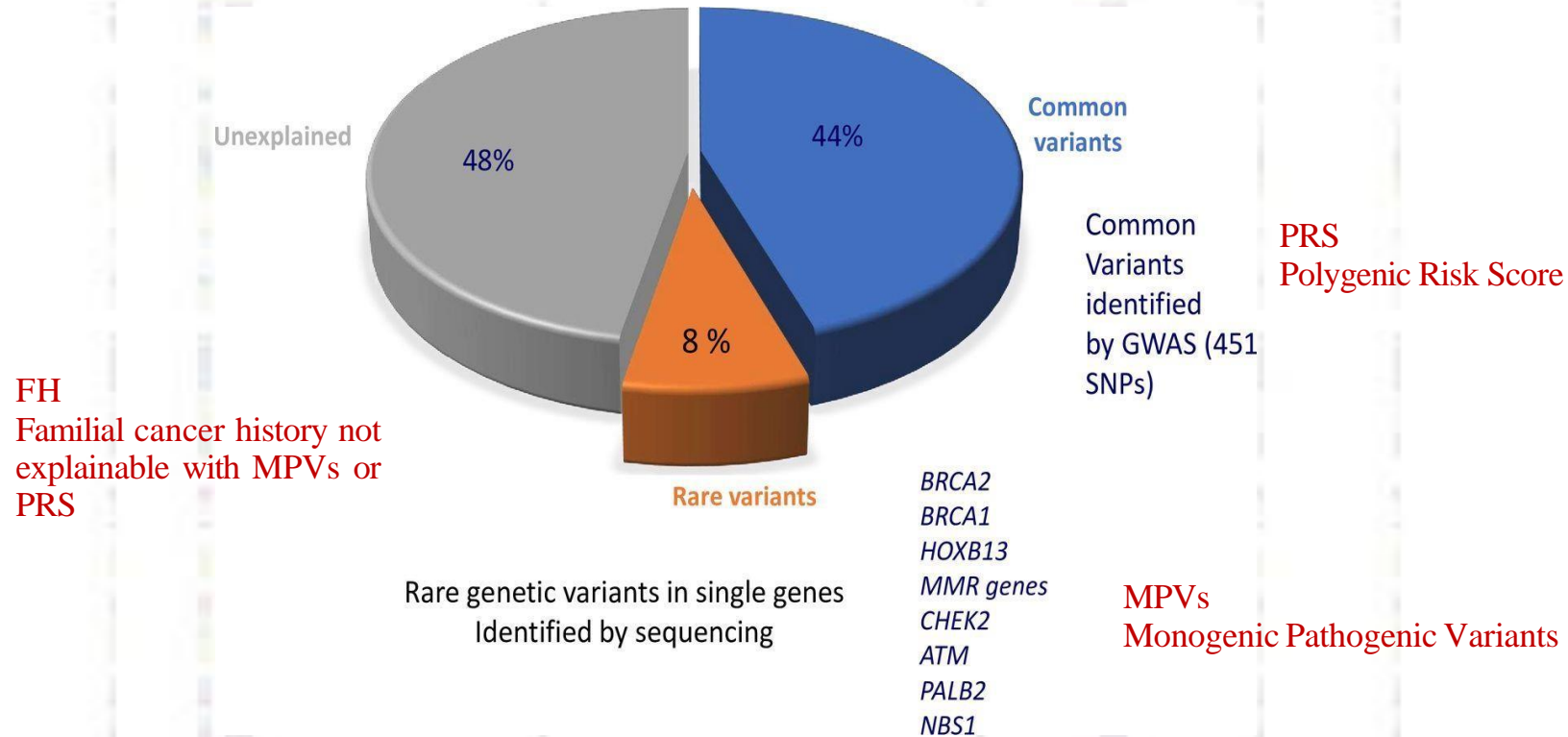
[andres.metspalu@ut.ee](mailto:andres.metspalu@ut.ee)



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[www.biobank.ee](http://www.biobank.ee)

# Prostate Cancer Heritable Risk



Rose Hall et al. J Med Genet 2024;61:915-926



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