From Biobanking to Precision Medicine

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Estonian Genome Center
University of Tartu

FEAM Spring Conference 2016

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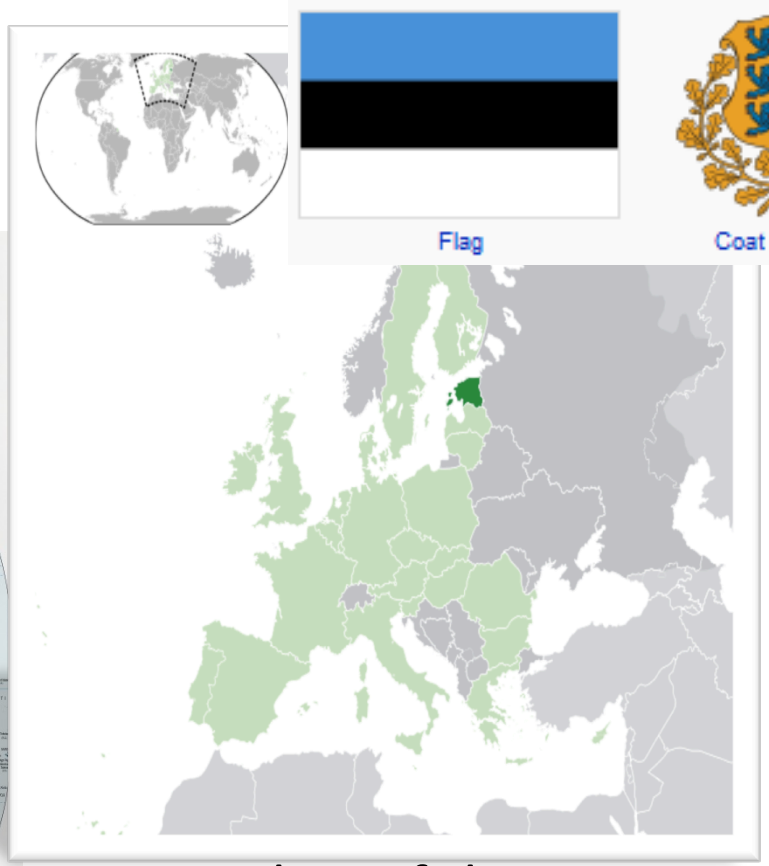
Republic of Estonia



- Population size: ~1.3 million
- Territory: 45 000 km^2

Member of the European Union since 2004

Schengen Treaty since 2007

EUR as our currency since 2011

Per Med Definition in EU documents

- Personalised medicine refers to a medical model using molecular profiling for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention

This is the EU H2020 definition of the Per Med.

Background of the Estonian Genome Center

- EGC is the Research institute of the University of Tartu, which keeps the Estonian Biobank
- Longitudinal, prospective, population based biobank, established in 2000
- 52,000 gene donors recruited (5% of the adult population), follow-up is on-going
- Supported by the government (HGR Act)

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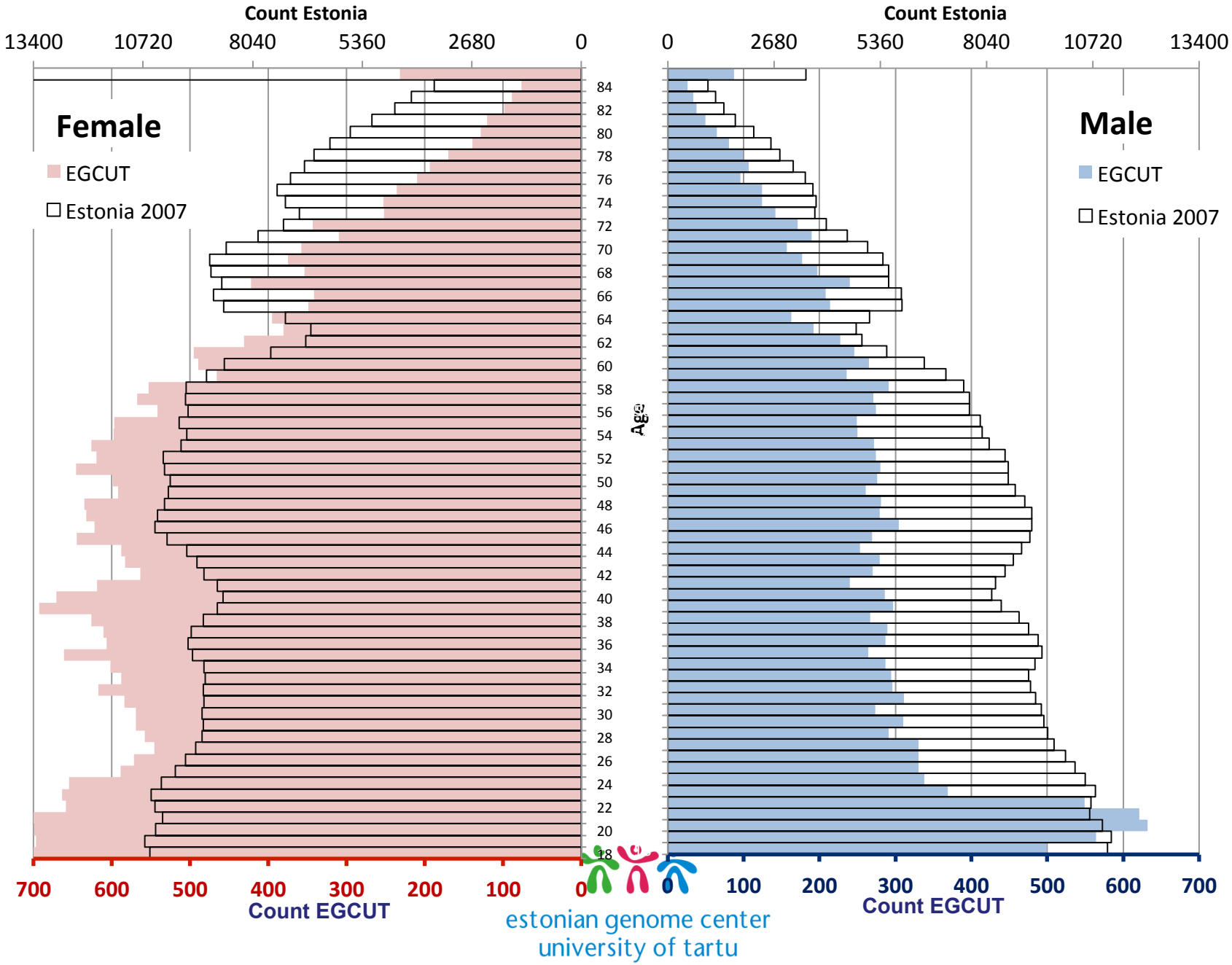
§ 3. Chief processor of Gene Bank

- (1) The chief processor of the Gene Bank is the University of Tartu, whose objectives as the chief processor are 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.

Population pyramid (50155 participants)



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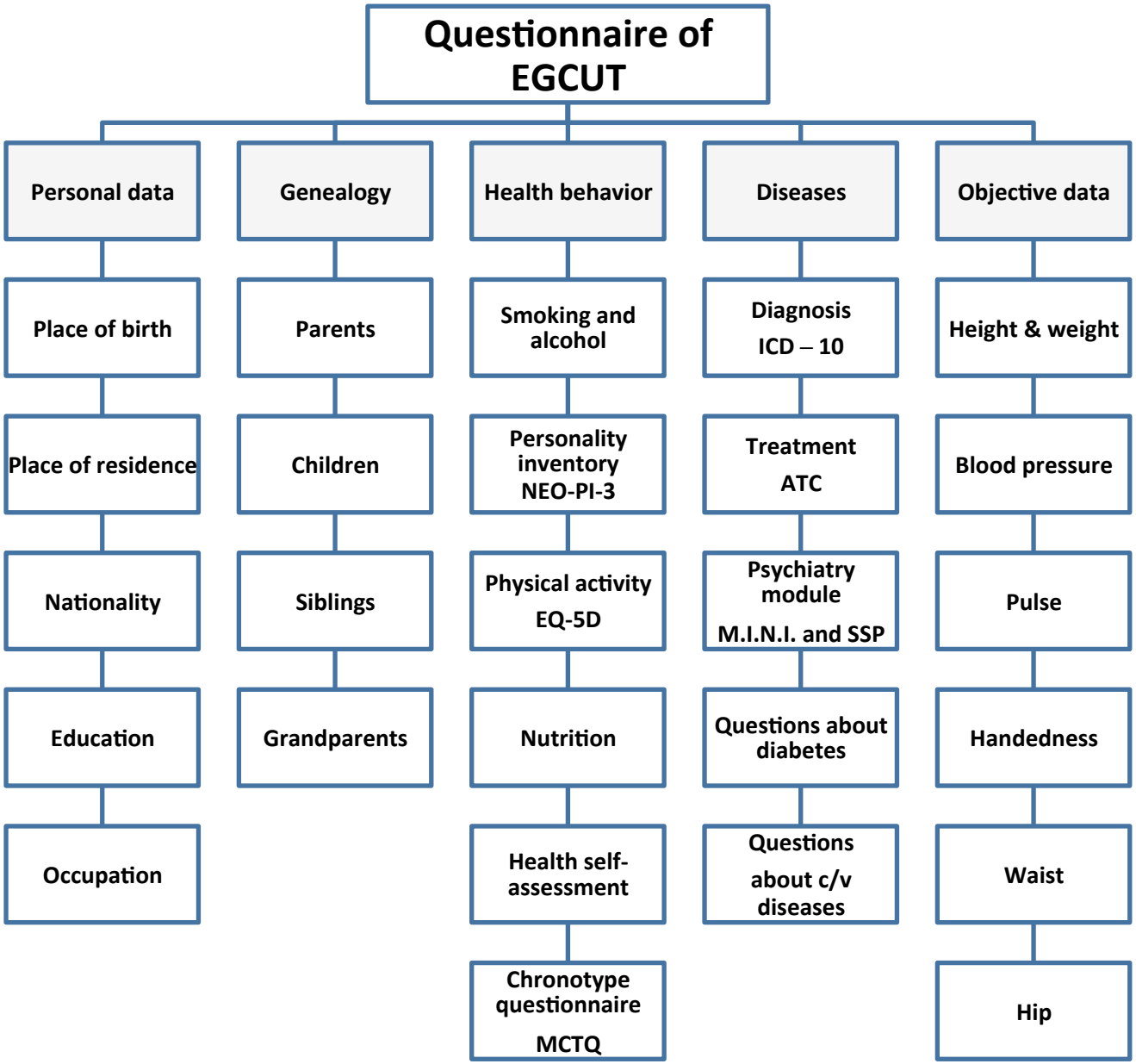

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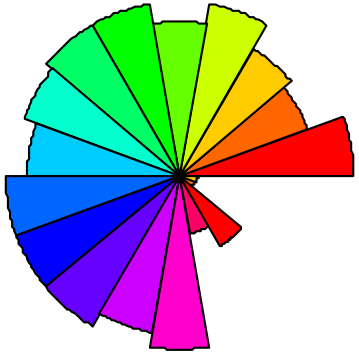
A cluster analysis of nutrition data with 8 clusters



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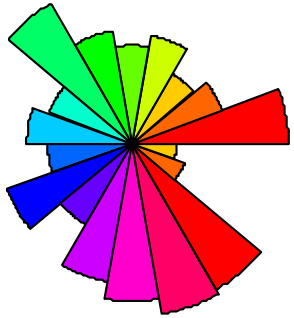

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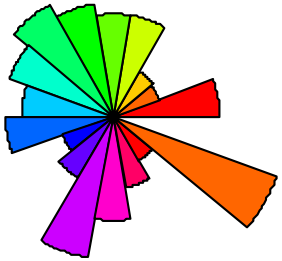

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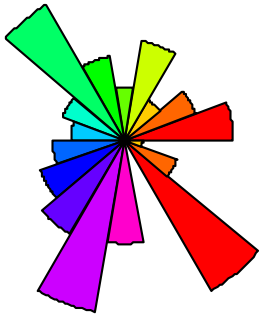

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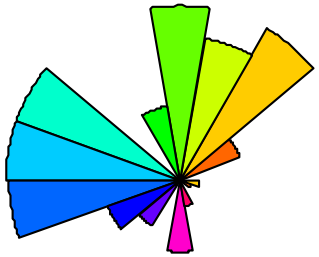

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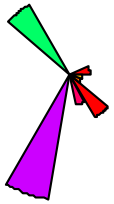

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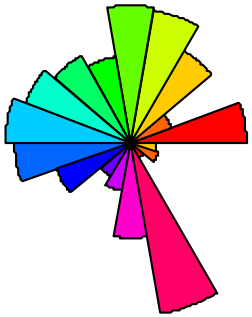

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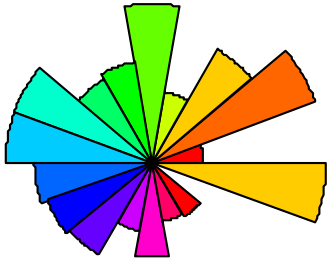

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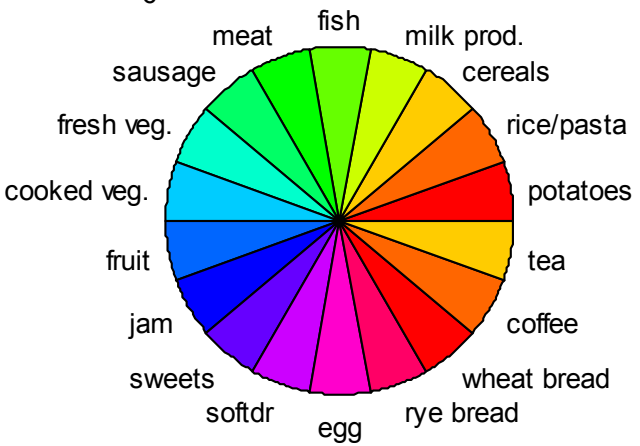

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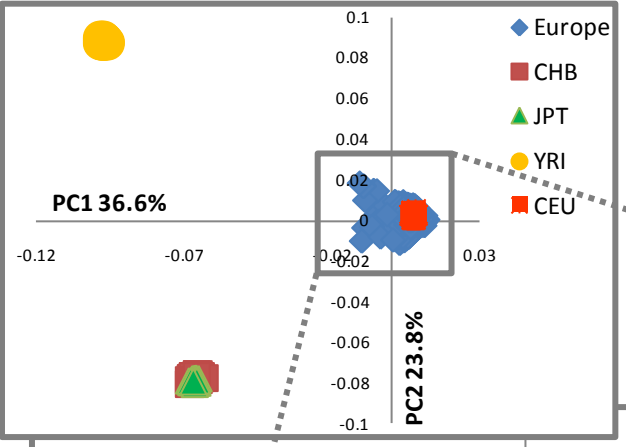
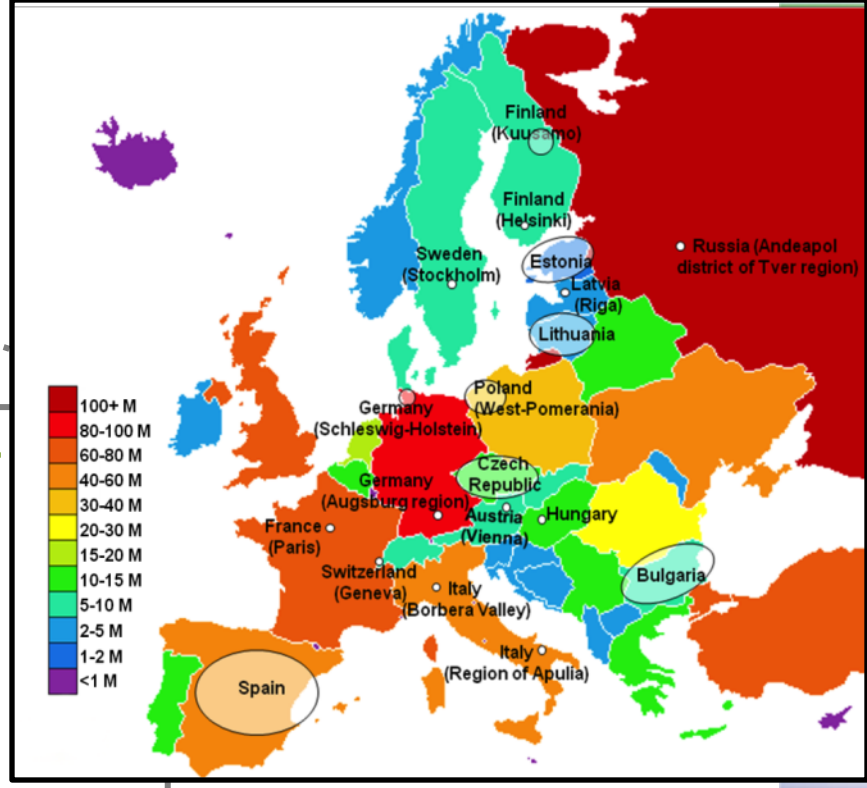
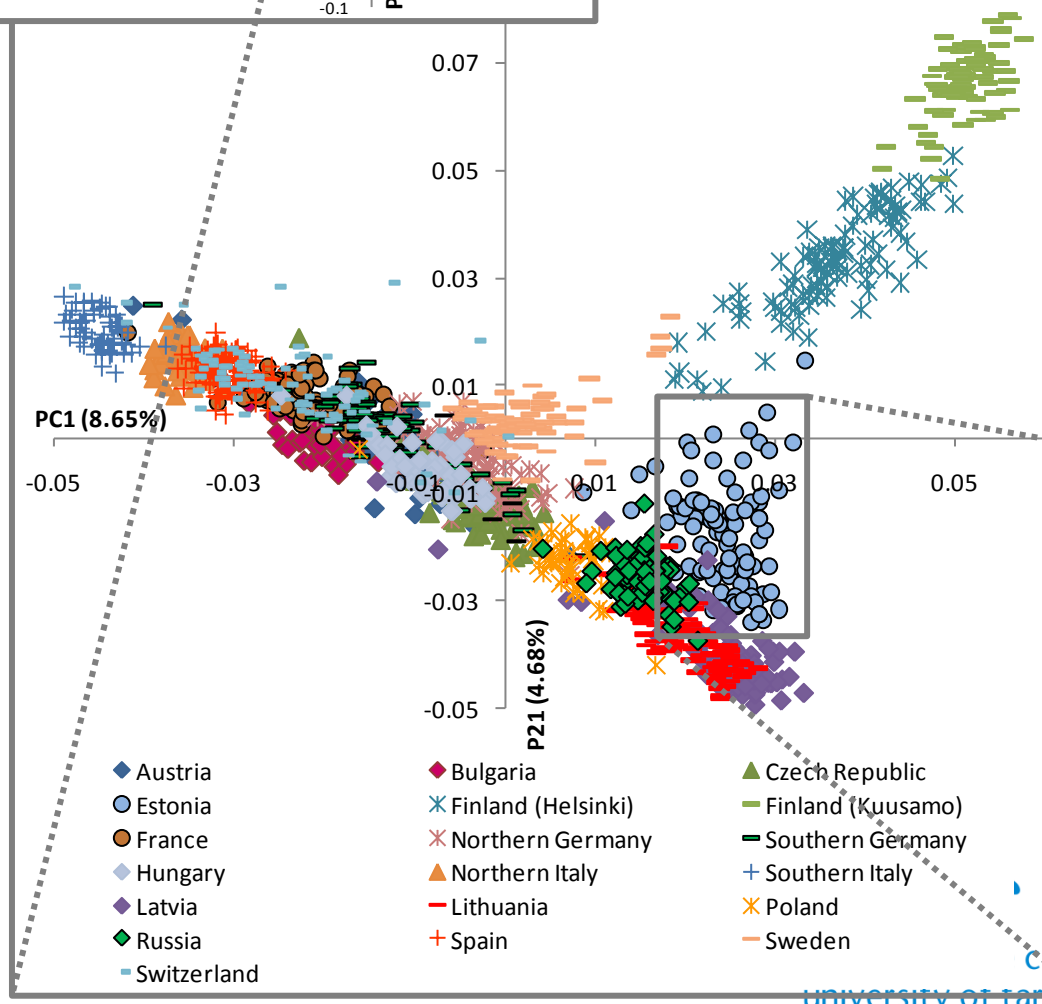
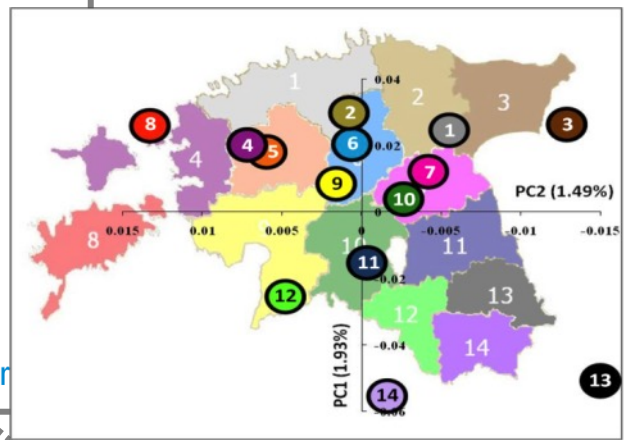
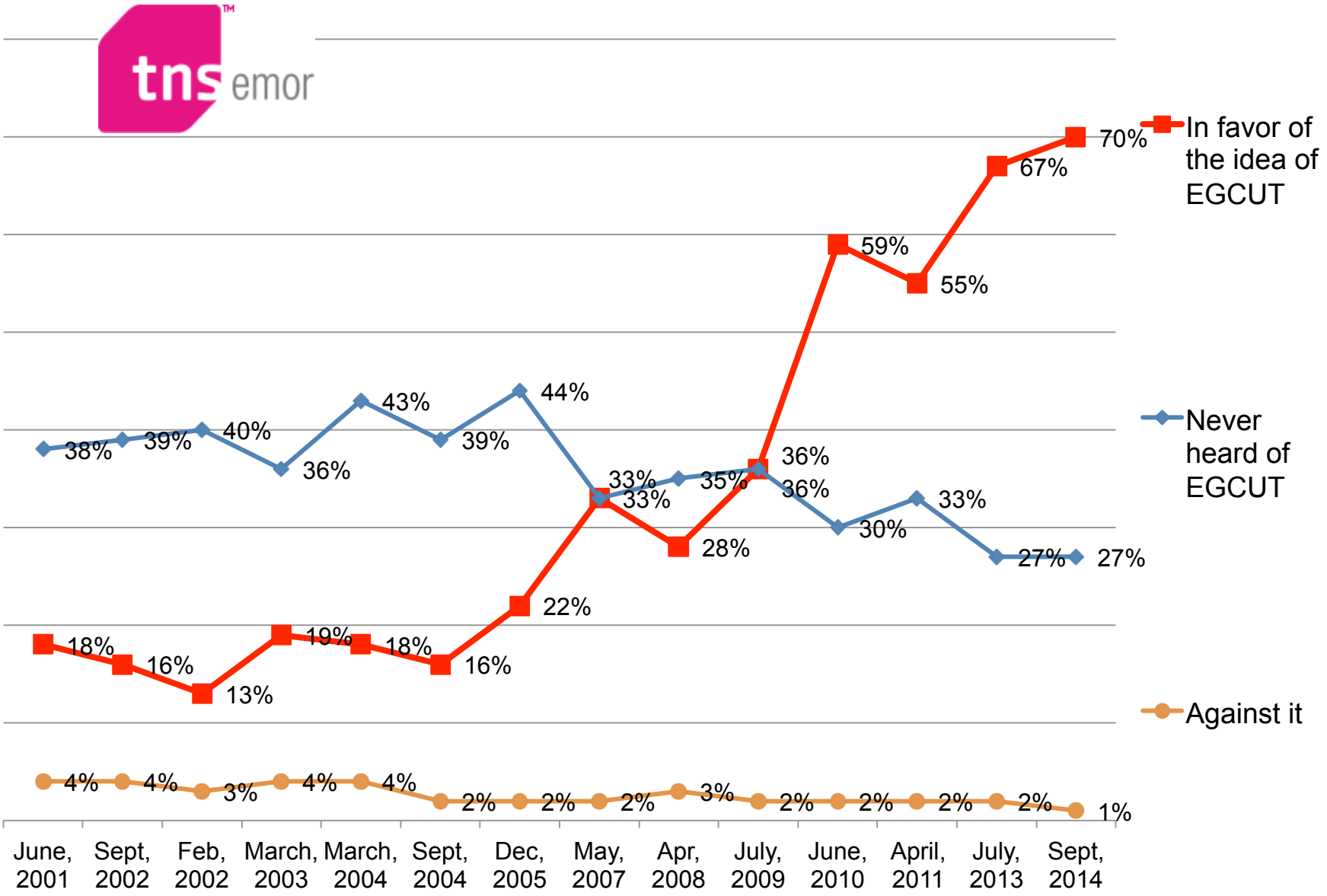

Europe
CHB
JPT
YRI
CEU
PC1 36.6%
PC2 23.8%
0.1
0.08
0.06
0.04
0.02
0
-0.02
-0.04
-0.06
-0.08
-0.1
-0.12
-0.07
-0.02
0.03


100+ M
80-100 M
60-80 M
40-60 M
30-40 M
20-30 M
15-20 M
10-15 M
5-10 M
2-5 M
1-2 M
<1 M
Finland (Kuusamo)
Finland (Helsinki)
Sweden (Stockholm)
Estonia
Latvia (Riga)
Lithuania
Russia (Andeapol district of Tver region)
Poland (West-Pomerania)
Germany (Schleswig-Holstein)
Germany (Augsburg region)
Czech Republic
Austria (Vienna)
Hungary
France (Paris)
Switzerland (Geneva)
Italy (Borbera Valley)
Bulgaria
Italy (Region of Apulia)
Spain


PC1 (8.65%)
P21 (4.68%)
0.07
0.05
0.03
0.01
-0.01
-0.03
-0.05
-0.05
-0.03
-0.01
0.01
0.03
0.05
Austria
Bulgaria
Czech Republic
Estonia
Finland (Helsinki)
Finland (Kuusamo)
France
Northern Germany
Southern Germany
Hungary
Northern Italy
Southern Italy
Latvia
Lithuania
Poland
Russia
Spain
Sweden
Switzerland


PC2 (1.49%)
PC1 (1.93%)
1
2
3
4
5
6
7
8
9
10
11
12
13
14

Public opinion and awareness of the EGCUT 2001-2014



e-Health

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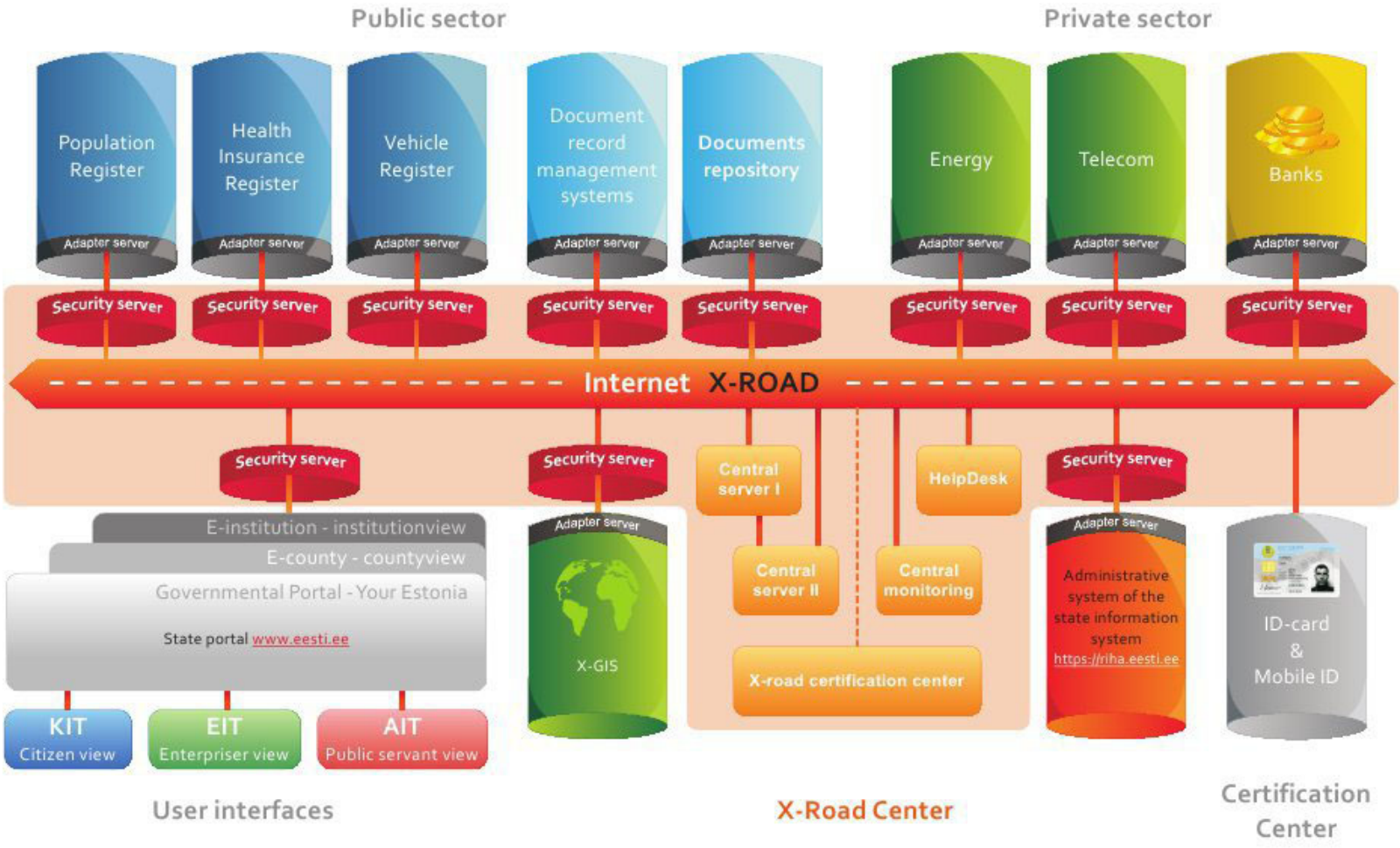
Estonian Information System's Authority

Estonian information system



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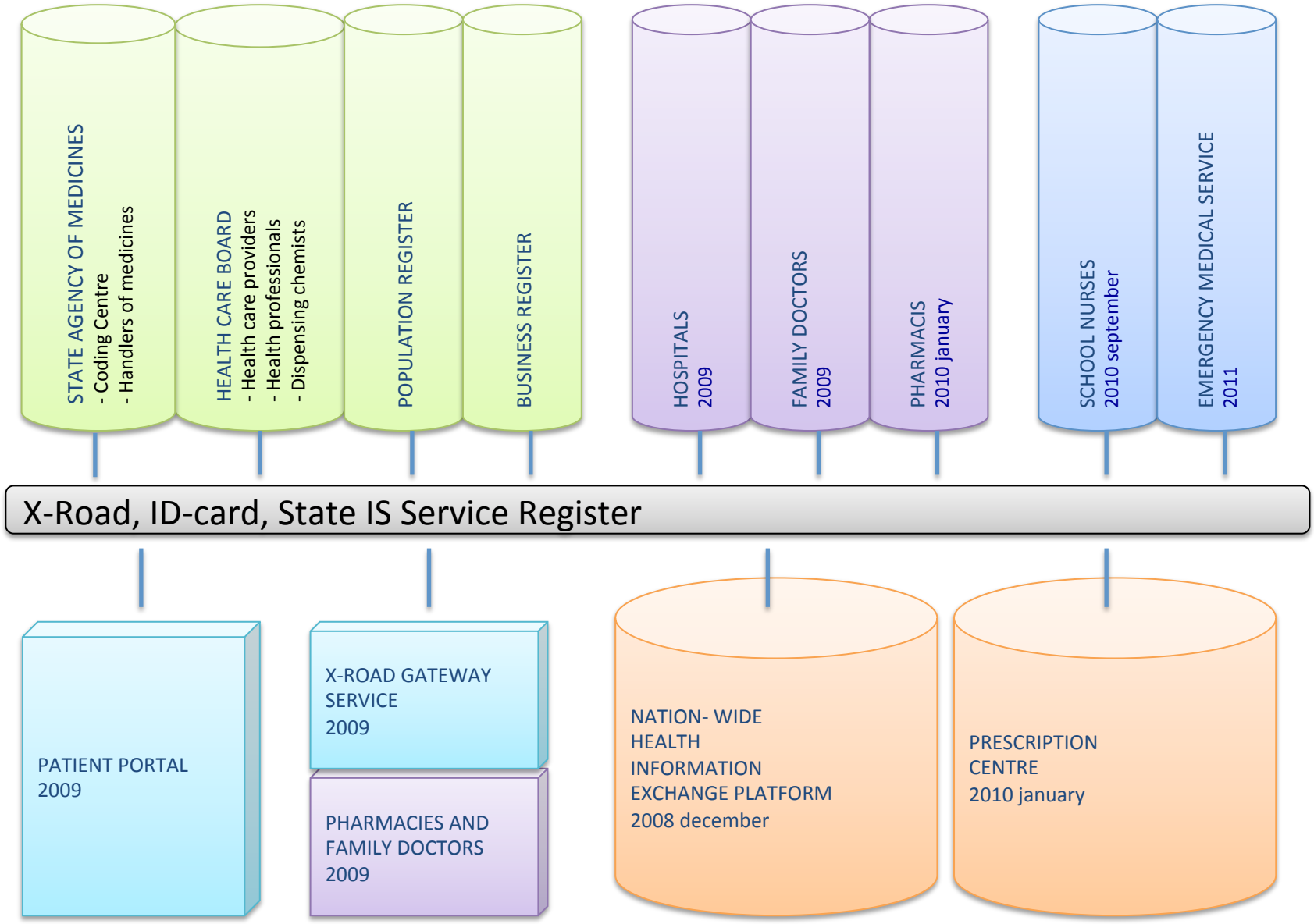

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The Estonian ID card

- The ID card is a **mandatory** ID document for all Estonian residents from the age of 15
- Enables secure digital authentication and signing
- A digital signature has the same legal consequences as a hand-written signature
- Does not have any additional information
  - No bank account, no health information etc.
- Active cards: **1 221 948** (08.09.2014)
  - Digital signatures: 174 385 946
  - Estonian Population 1 286 540 (01.01.2013)
  - Estonia has been issuing electronic ID car
    2002
  - Also Mobile-ID

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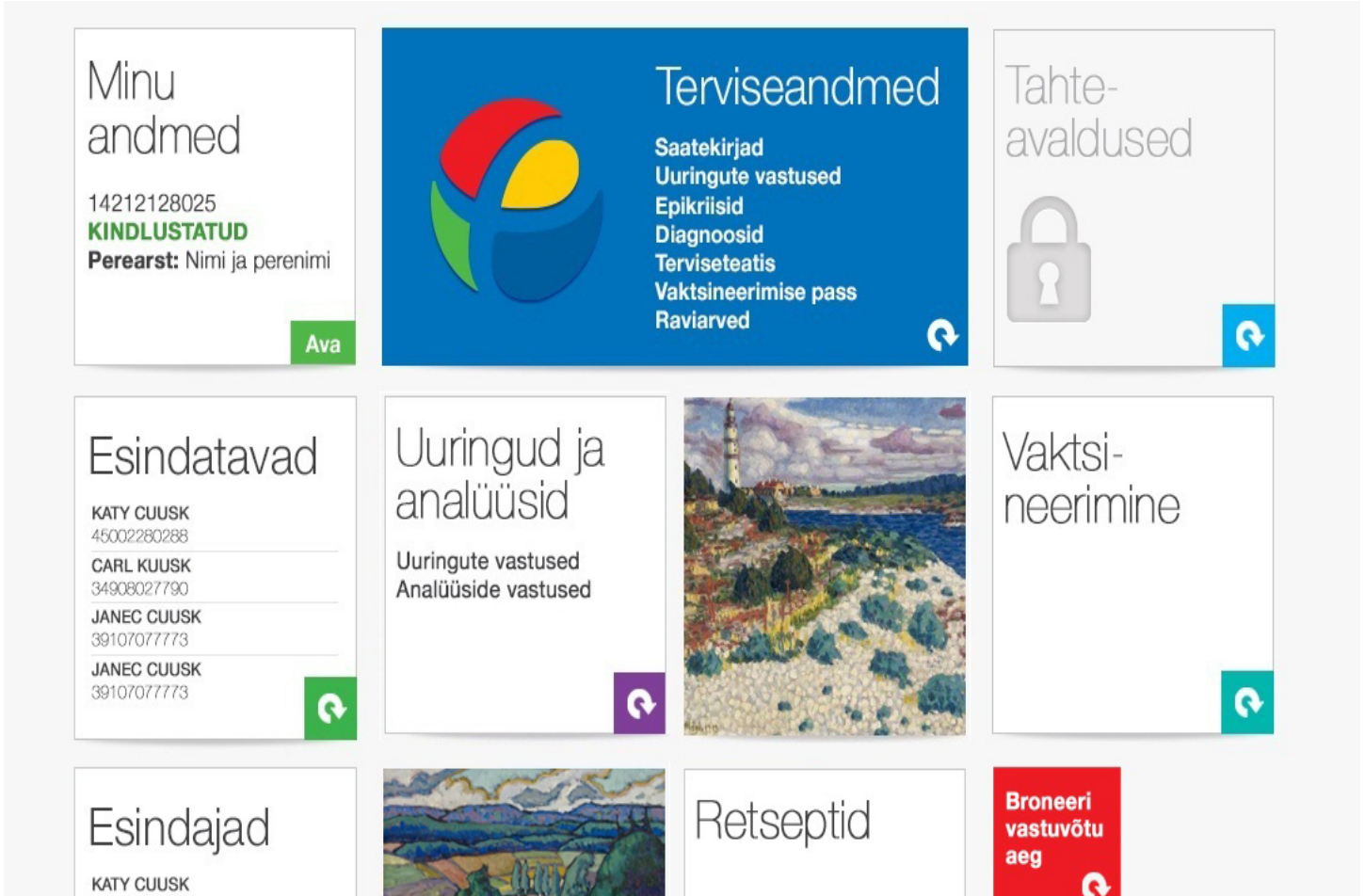
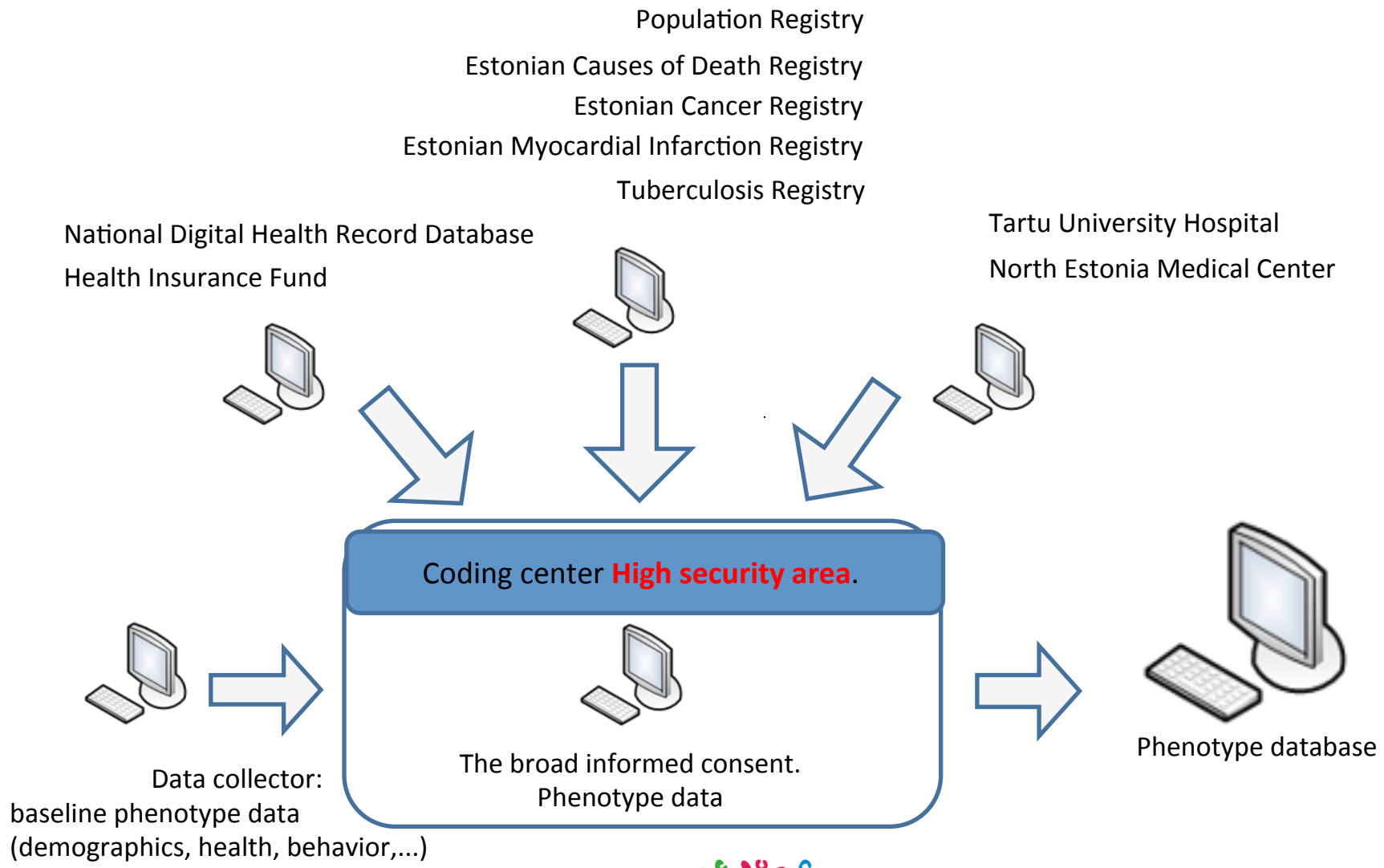
Authentication

National Patient Portal

***1.1 mio** persons medical data*



From questionnaires to the national registries



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Disease trajectory (for all 50 000 subjects)

e.g. male, born 1970, age 37, joined 2007, high school, no sports, walking 2h/week, smoking 20 cigarettes per day, 2 strong drinks per week (2x40cl), height 178, weight 87, BMI 27.5, BP 130/78 mmHg

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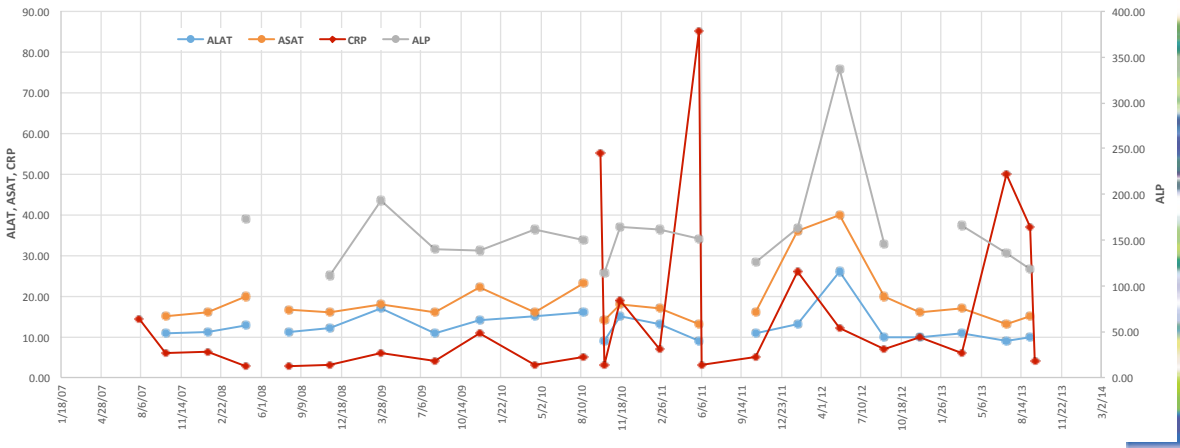
Hospital Clinical Labs

Profile	#N
Basophils	35806
Eosonophils	35784
Hemoglobin	31725
Lymphocytes	36424
Red Blood Cells	64019
White Blood Cells	65203

- *Trajectory*



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Deep (30x) Whole Genome Sequencing of 2500 subjects

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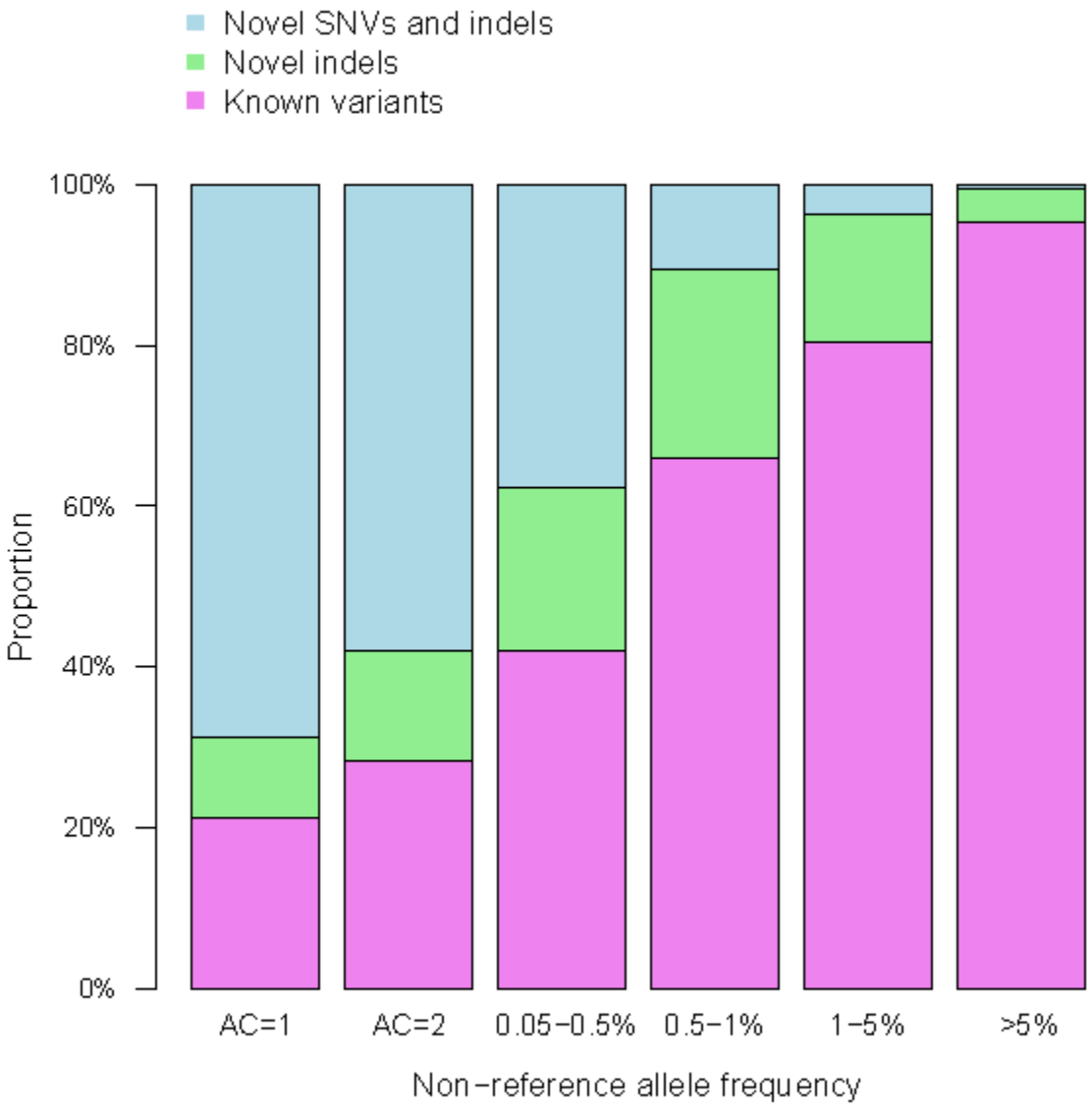
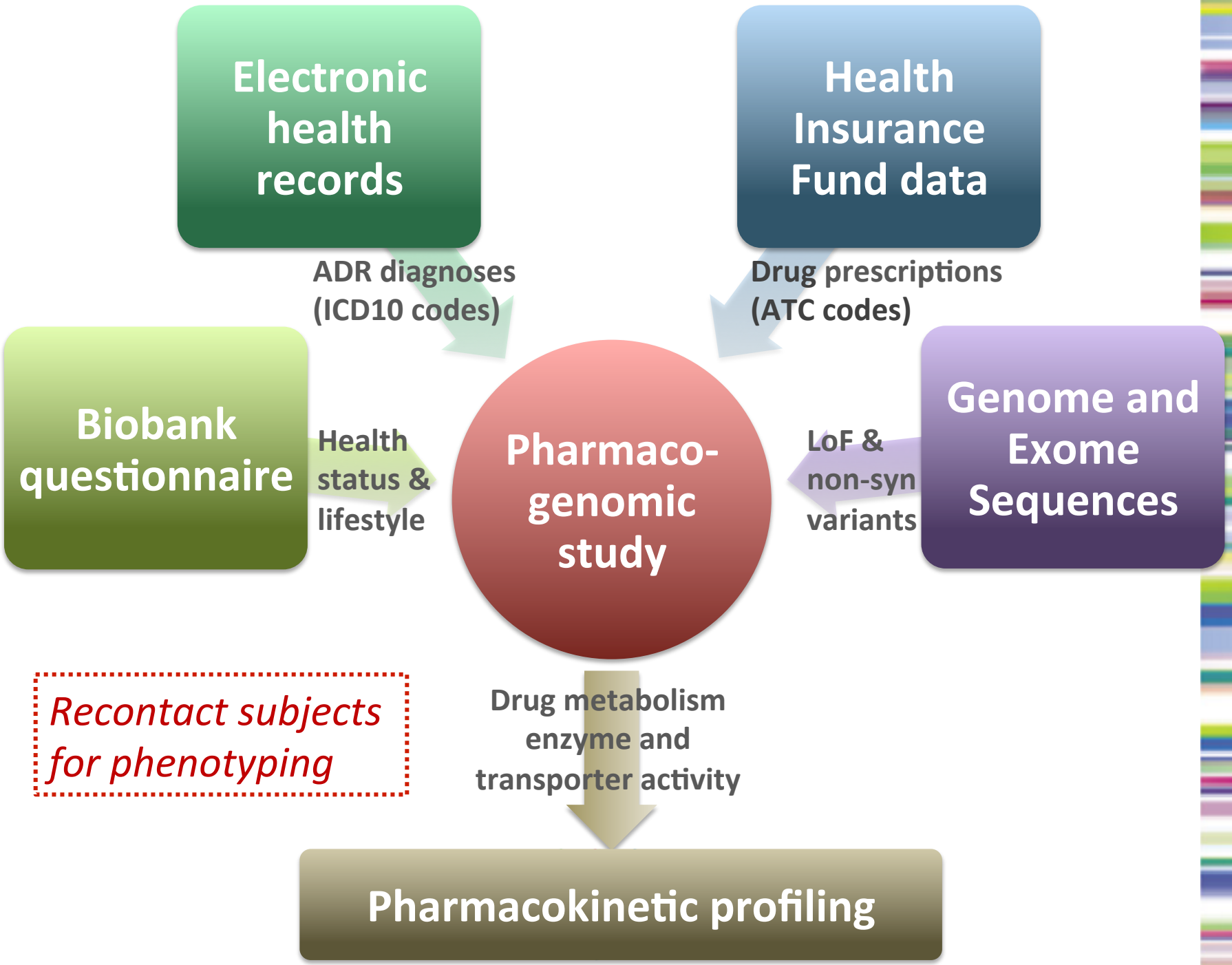
Novel and known variants

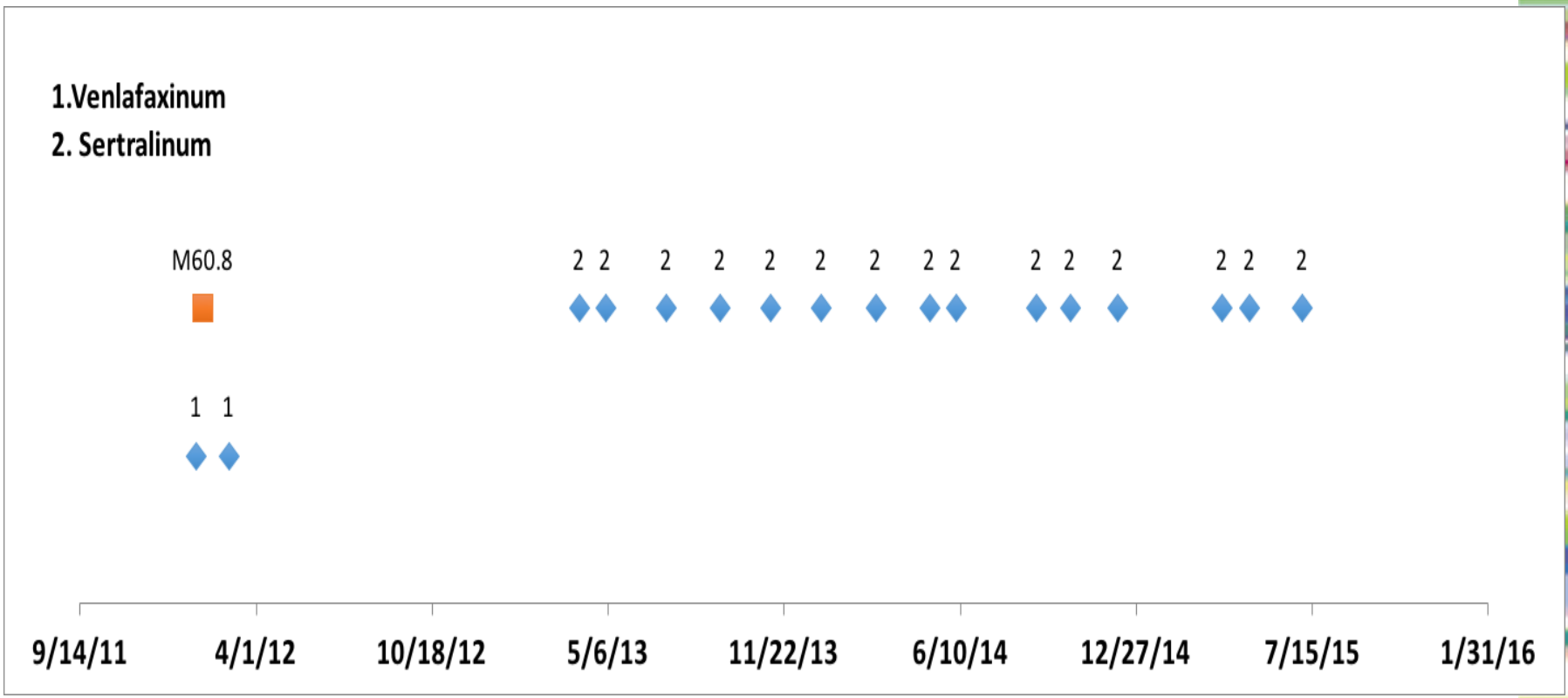


Average human

- 3 million mutations
  - 5000 unique
  - Loss of function
    - 120 heterozygous
    - 18 homozygous


Electronic health records
Health Insurance Fund data
ADR diagnoses (ICD10 codes)
Drug prescriptions (ATC codes)
Biobank questionnaire
Health status & lifestyle
Pharmaco-genomic study
LoF & non-syn variants
Genome and Exome Sequences
Recontact subjects for phenotyping
Drug metabolism enzyme and transporter activity
Pharmacokinetic profiling

Drug prescriptions for subject with LoF mutation in CYP2D6



Venlafaxinum is mainly metabolised by CYP2D6 and Sertralinum by CYP2B6.

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Individuals with mutations in lipid pathway

Gene	Position	Mutation	Prior reporting	Sex	Age	Phenotype	LDL-C (mg/dl)	Statins	Mutation	Status
APOB	21229160	p.Arg3527Gln	ClinVar	Male	40	E78.0	186	-		OK
APOB	21229160	p.Arg3527Gln	ClinVar	Female	72	E78.0	235	yes		OK
APOB	21229160	p.Arg3527Gln	ClinVar	Female	25	E78.2	247	-		OK
APOB	21229160	p.Arg3527Gln	ClinVar	Male	72	E78.0	196	-		OK
APOB	21229160	p.Arg3527Gln	ClinVar	Male	27	-	212	-		OK
APOB	21229160	p.Arg3527Gln	ClinVar	Male	49	-	175	-		OK
APOB	21228842	p.Trp3633X	-	Male	87	-	38	-	**novel**	**?**
LDLR	11221373	p.Cys329Tyr	LOVD and UCL	Male	19	E78.0_6	211	yes		OK
LDLR	11221373	p.Cys329Tyr	LOVD and UCL	Female	36	E78.0	189	-		OK
LDLR	11224058	p.Ala431Ser	p.Ala431Thr p.Ala431Pro	Male	29	-	190	-	**novel**	OK
LDLR	11224074	p.Val436Ala (EXAC)	UCL	Female	73	E78	182	-		OK
LDLR	11217295	p.His250Arg	p.His250His	Female	76	E78.0	112	yes	**novel**	**probable**
LDLR	11230820	p.Arg633His (EXAC)	p.Arg633His p.Arg633Cys	Male	66	E78, I20.8, I25, Z95.1, Z95.2	92	yes		**probable**
LDLR	11216225	p.Arg215Cys (EXAC)	p.Arg215Ser	Male	58	-	162	-	**novel?**	**?**
LDLR	11223954	p.Gly396Ala (EXAC, SISU)	In duplication/ insertion context	Male	31	-	134	-	**novel?**	**?**
LDLR	11213349	p.Thr67Ile	-	Female	33	-	57	-	**novel**	**?**

Do we have enough information to start with the precision medicine?

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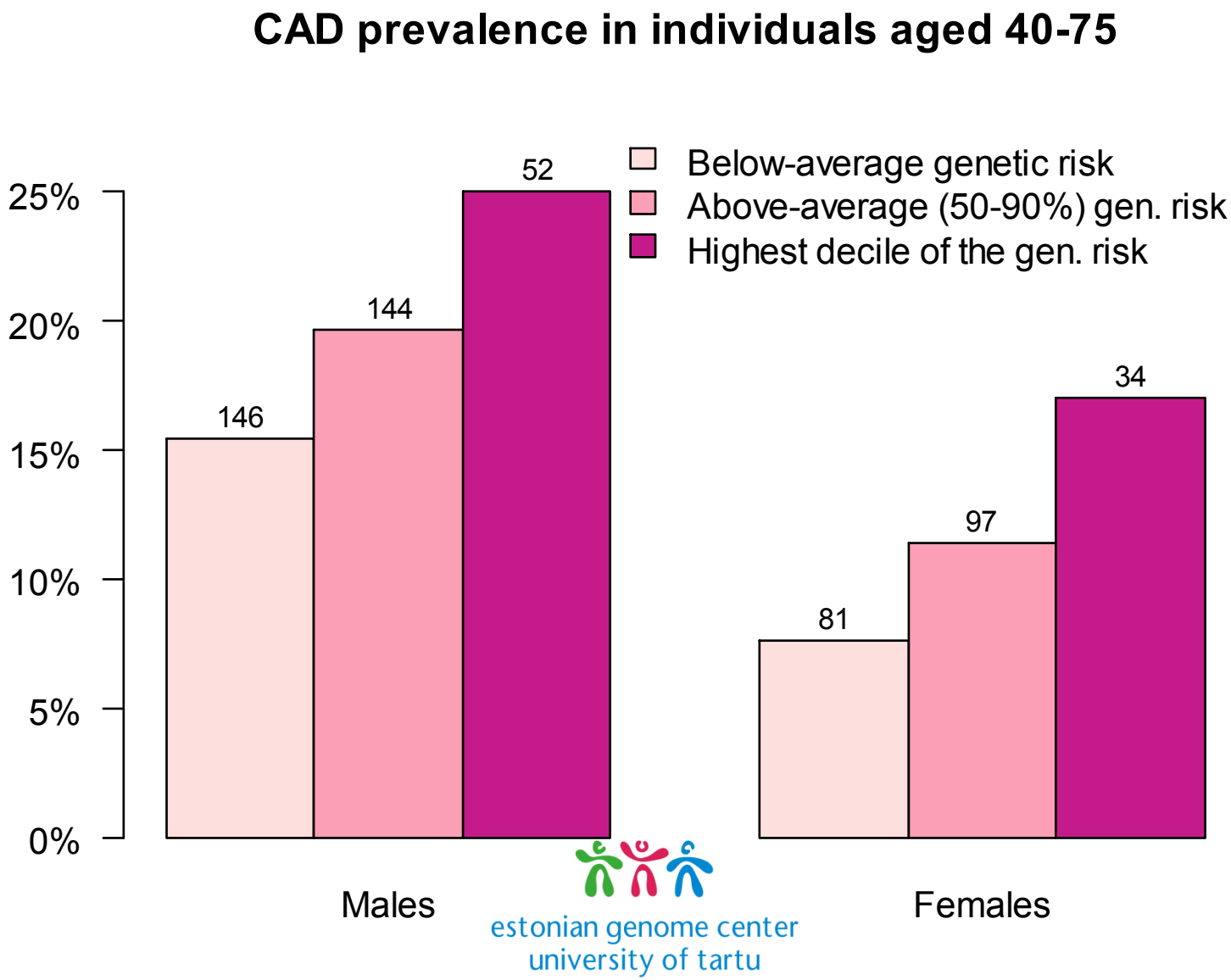
Coronary Artery Disease



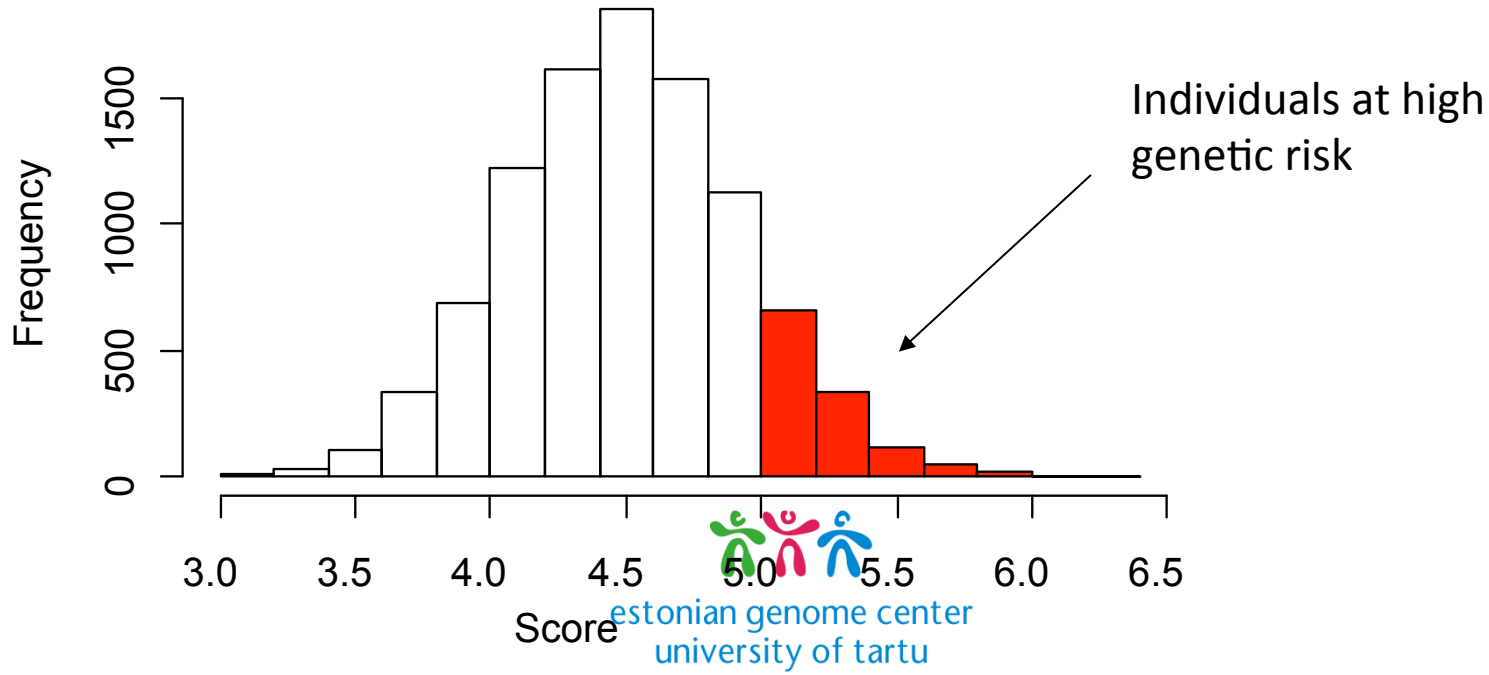
Polygenic risk scores

Calculated as $S = \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k$,

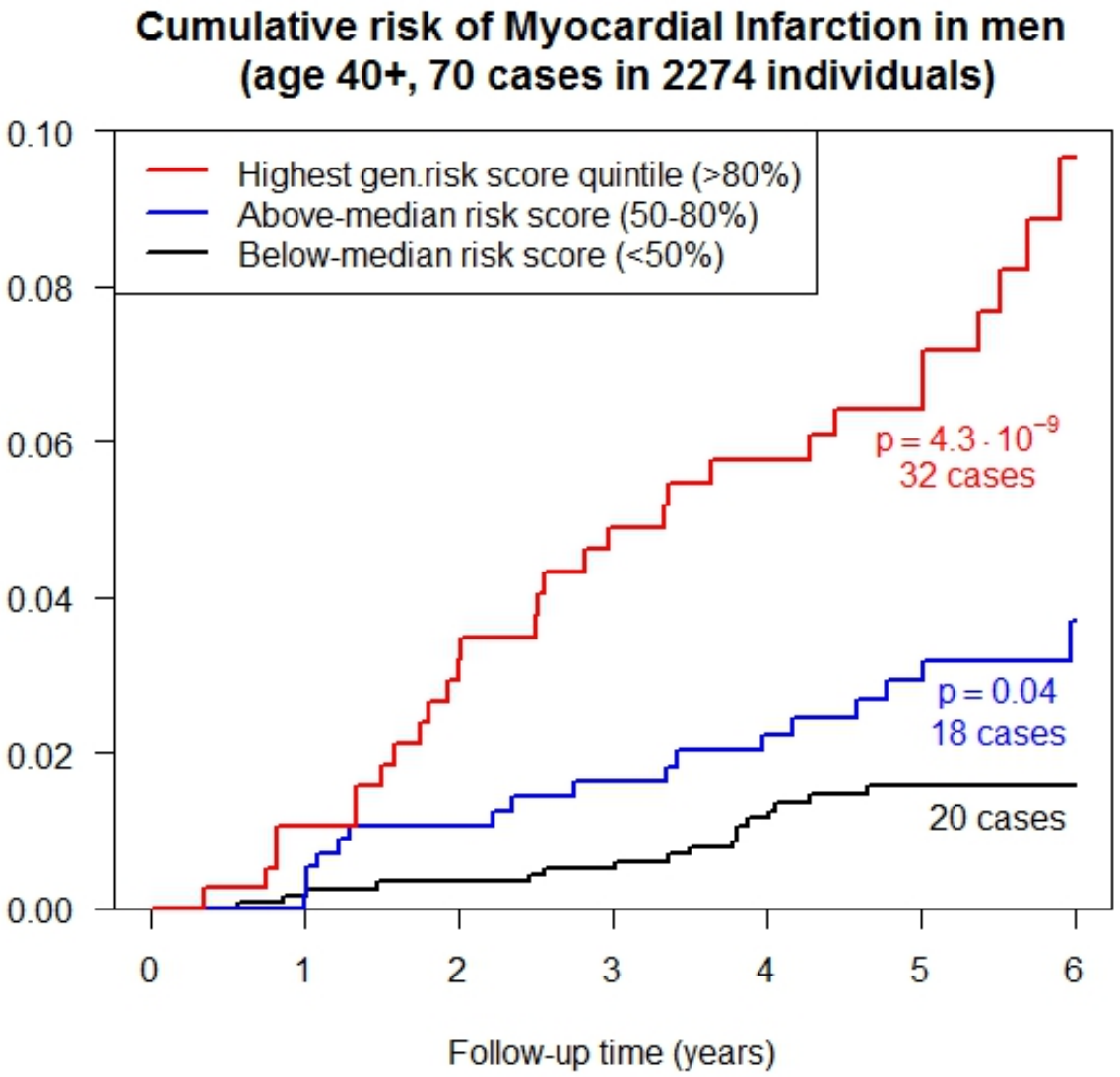
$X_2,\ldots, X_k$ - allele dosages for k independent markers (SNP-s), typically the ones with strongest effect

$\beta_1, \beta_2, \ldots, \beta_k$ – effect estimates (logistic regression parameters, ln OR) from a GWAS meta-analysis

Polygenic risk score for type II diabetes: histogram of the score in 7462 individuals (Estonian Biobank)

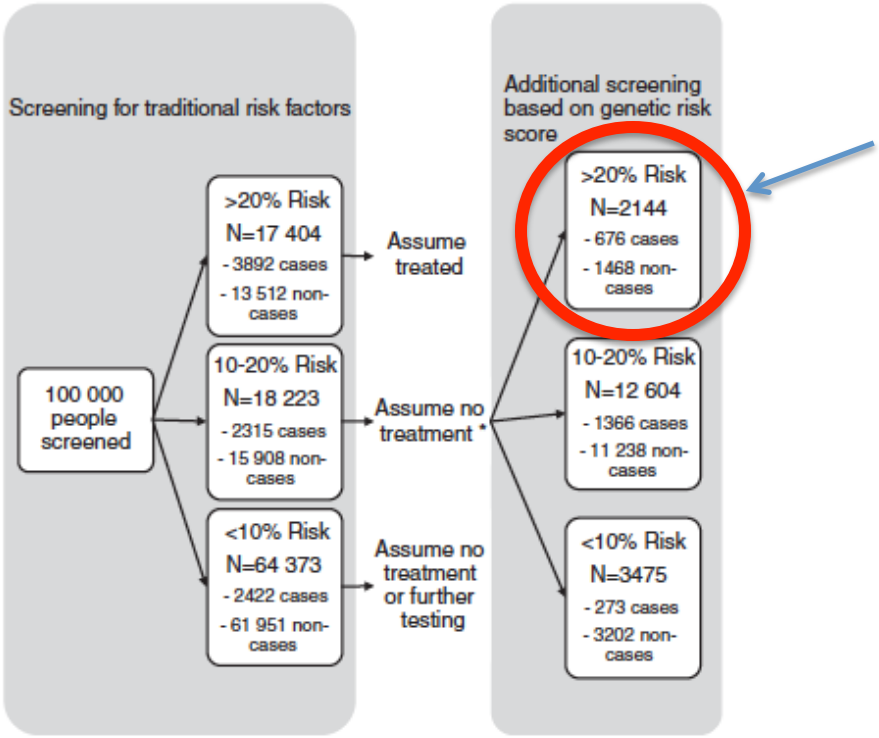


Incident Myocardial Infarction



A weaker, but still significant effect seen in women: p=0.005

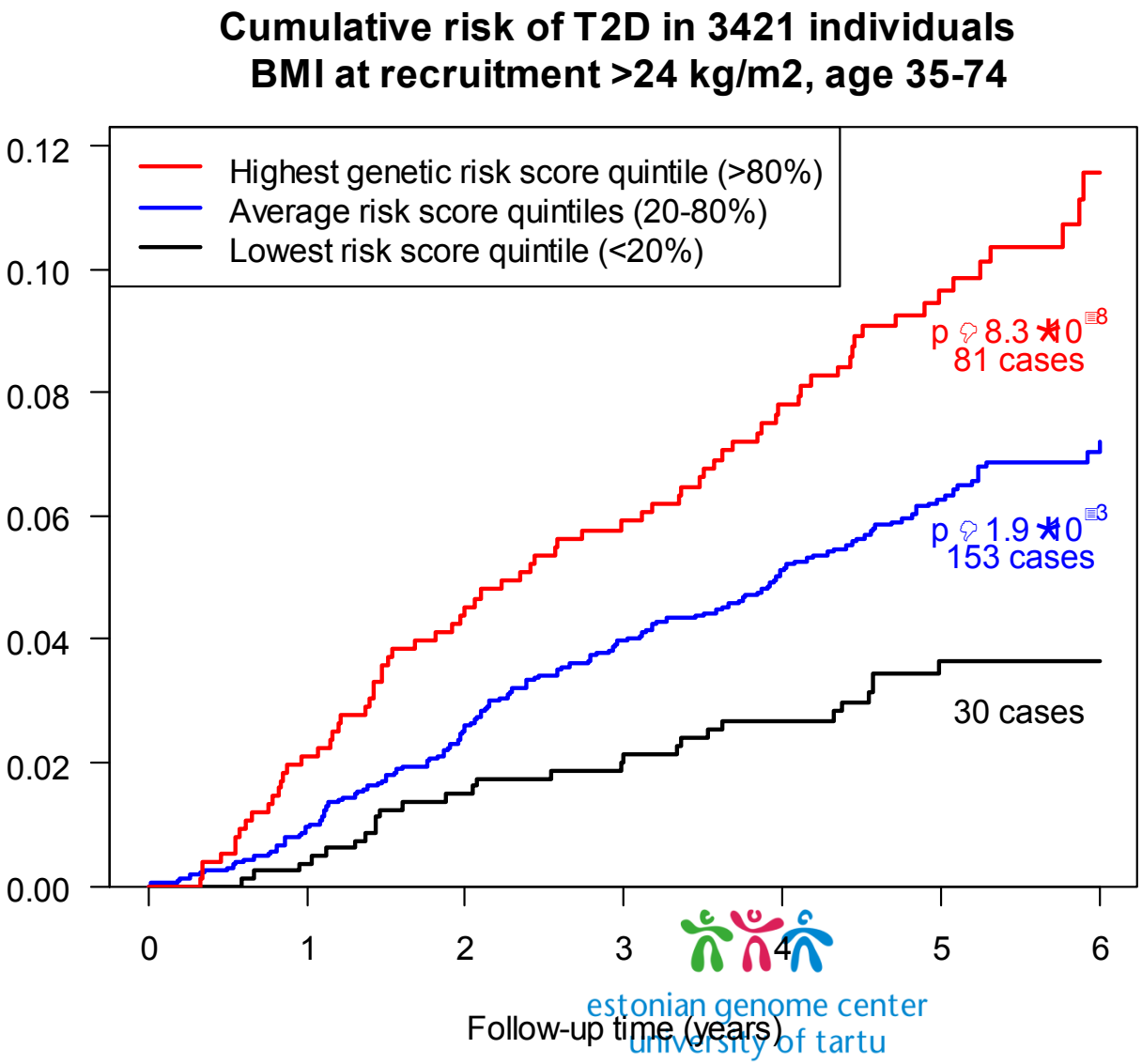
Prevented deaths of CHD in Finland



By treating 2144 persons who have >20% risk when the genetic information is known 135 deaths would be prevented in 10 years!

Tikkanen, E. 2013. Genetic risk profiles for coronary heart disease

Incident T2D: analysis of 264 incident cases in overweight individuals free of T2D at recruitment



No significant sex difference,
genetic risk score is the strongest predictor after BMI

(fasting glycose and insulin measurements are not available for this cohort)

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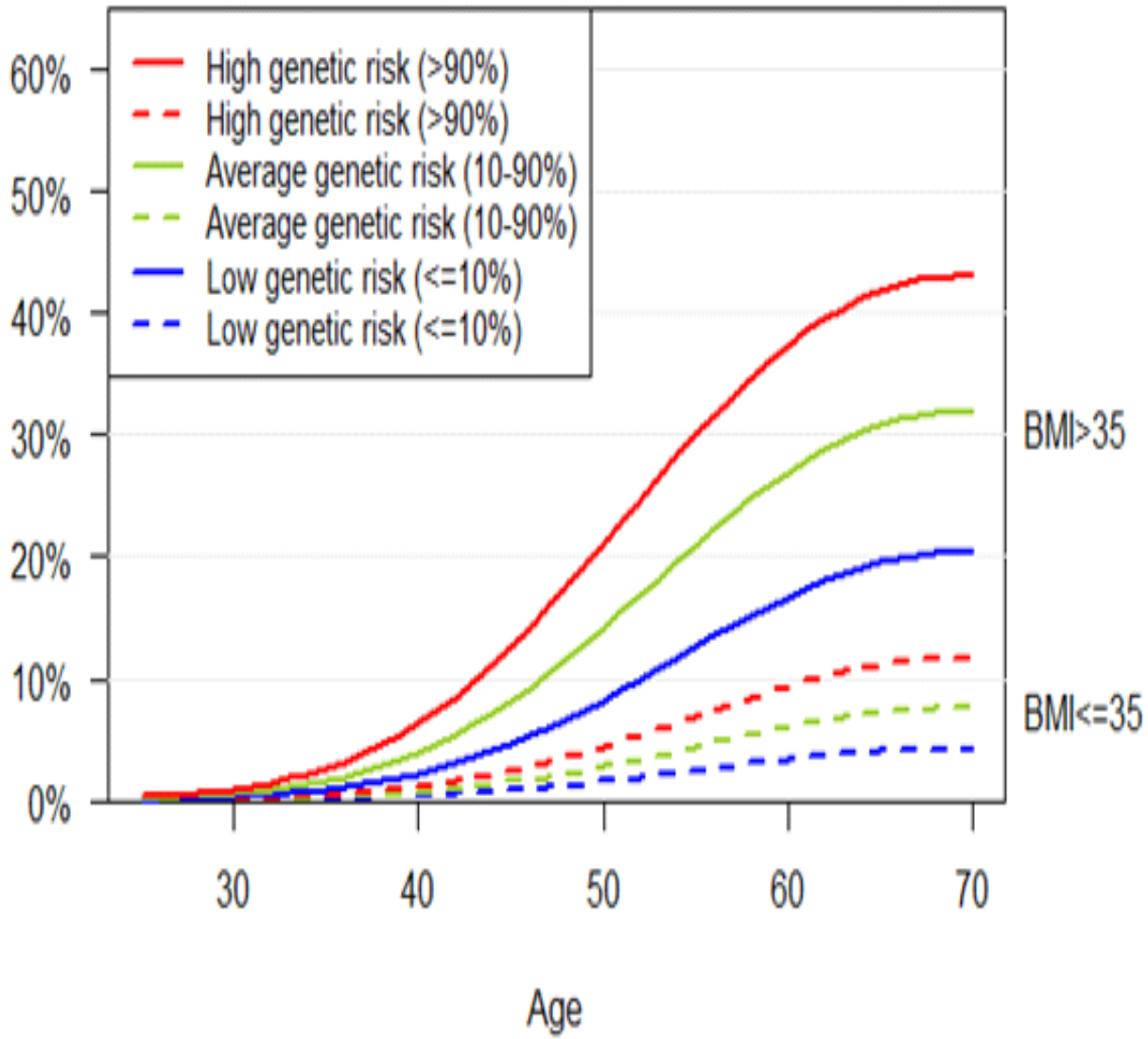
Type II diabetes risk for men depending on age and BMI



What is Clinical Decision Support Software (CDSS)?

- CDSS provides clinicians with knowledge presented at appropriate times
- It encompasses a variety of tools such as computerized alerts, clinical guidelines, and order sets
- CDSS has the potential provide the necessary level of personalized guidance to providers at the point of care that will be necessary in the era of genomic medicine
- This is a tool to advise PCP (like radiology report)

Economic burden of T2 diabetes (GER) 2000-2007

- Prevalence of treated diabetes rose continuously from 6.5 to 8.9% (+36.8%)
- Direct costs per patient with diabetes rose from € 5 197 to € 5 726 (+10.2%)
- Total direct cost burden of diabetes in Germany grew from € 27.8 billion to € 42.0 billion (+51.1%)
- per-capita costs were € 2 400 in 2000 and € 2 605 in 2007 (+8.5%)

Exp Clin Endocrinol Diabetes 2011; 119(6): 377-385

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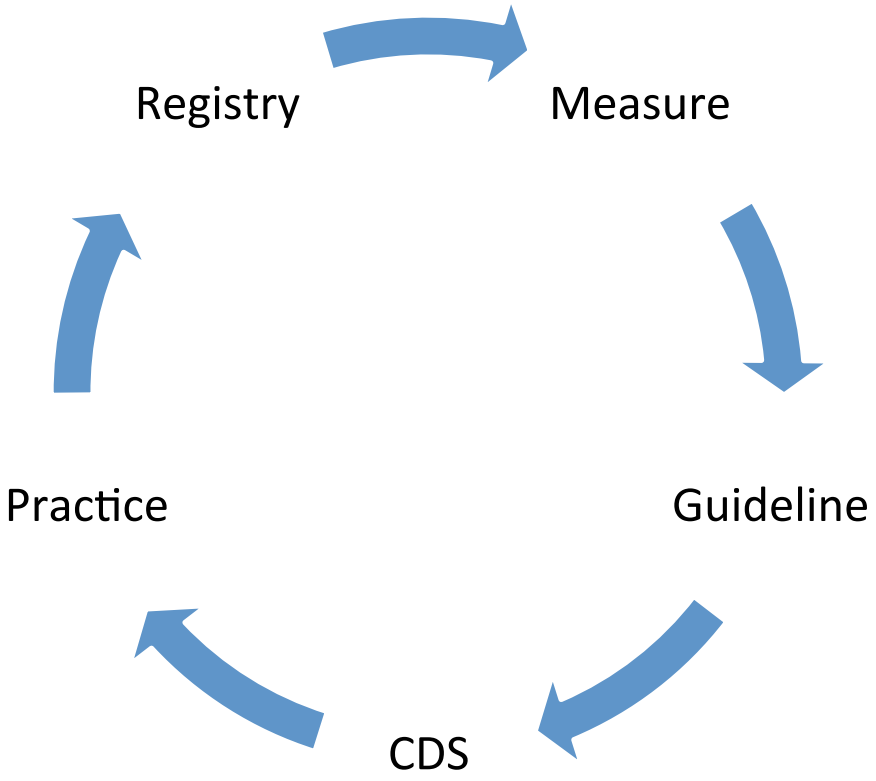
Virtuous Cycle of Clinical Decision Support



http://www2.eerp.usp.br/Nepien/DisponibilizarArquivos/tomada_de_decis%C3%A3o.pdf

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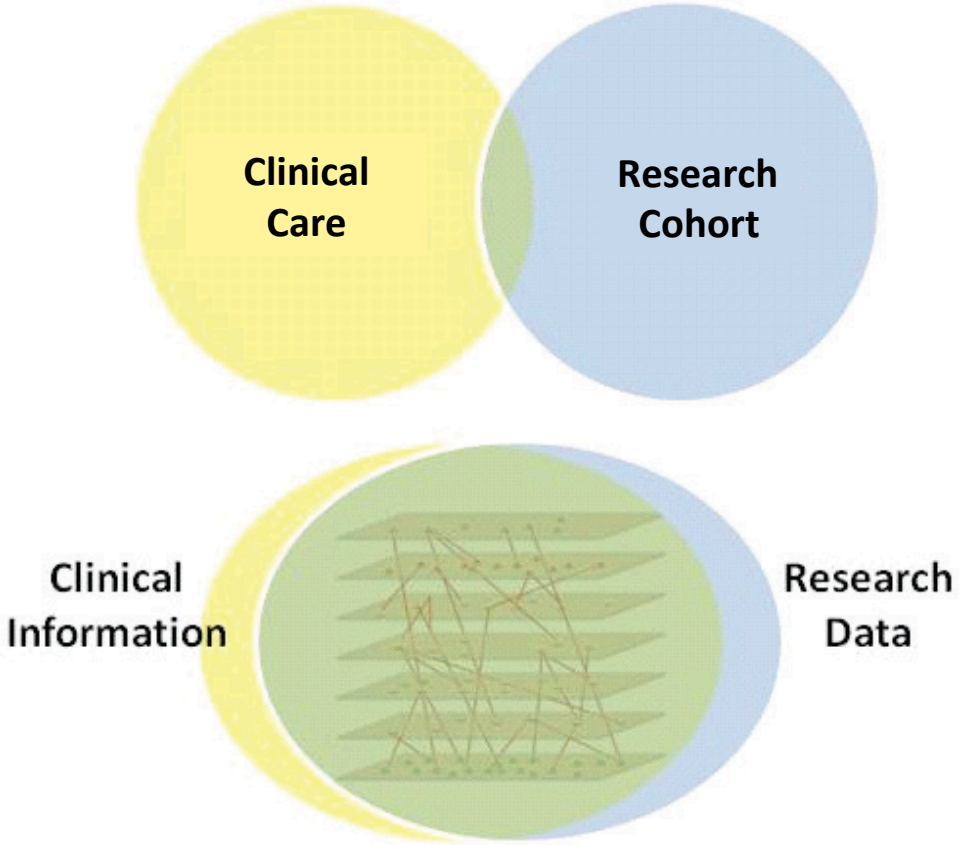
Future of the biobanking



*Committee on a Framework for Developing a New Taxonomy of Disease; 'Towards Precision Medicine', National Research Council November 2011

REPUBLIC OF ESTONIA
GOVERNMENT

Government

- 16.12. 2014. the Cabinet approved the Pilot Program of Personalized Medicine"
- Current government has "Personalized Medicine" as one of its activities for the next period
- From 1.03.15. the Ministry of Social Affairs has a new position "*Deputy Secretary General for E-services and Innovation*"
- Feasibility study has finished and next step, 3 pilot projects, are in preparations

Challenges and issues

- Awareness executives, doctors and patients
- New technologies and data empower patient with more possibilities to manage own health
- Ethical issues
  - Right to know and right not to know
  - Treatable and non-treatable conditions
  - Big data, cloud
- Not enough knowledge about associations between DNA variants and diseases, but improving
- Large work-load to keep database of known risk variance updated

Conclusions

- Estonia has great potential to plan and implement personalized medicine solutions for the whole country, starting with the pilot project for 50 000 gene donors
  - Genetic research with 5% of population genetic and continuously updated phenotype information
  - Nation wide Health Information Exchange platform
  - 10 years of experience of national level e-services (PKI, X-Road, ID-card, security framework)
  - High level public trust and acceptance

Thank you!
www.biobank.ee

Estonia.eu
Positively surprising

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European Union
Regional Development Fund

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